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Selexipag for the Treatment of Pulmonary Arterial Hypertension

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Selexipag for the Treatment of Pulmonary Arterial Hypertension

This document contains the following information

GRIPHON study original protocol	Pages 2-109
GRIPHON study final protocol	Pages 110-227
Summary of changes to GRIPHON study protocol	Pages 228-236
GRIPHON study original statistical analysis plan	Pages 237-372
GRIPHON study final statistical analysis plan	Pages 373-597
Summary changes to GRIPHON statistical analysis plan	Pages 374-383



ACT-293987

Pulmonary Arterial Hypertension

Protocol AC-065A302

GRIPHON

A multicenter, double-blind, placebo-controlled Phase 3 study to demonstrate the efficacy and safety of ACT-293987 in patients with pulmonary arterial hypertension

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SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called Actelion

Drug name / number

ACT-293987

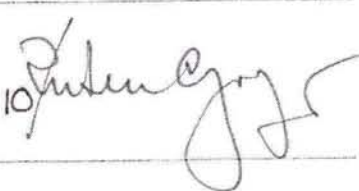
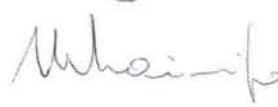
Disease

Pulmonary arterial hypertension.

Protocol number and acronym

AC-065A302 / GRIPHON

A multicenter, double-blind, placebo-controlled Phase 3 study to demonstrate the efficacy and safety of ACT-293987 in patients with pulmonary arterial hypertension

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SIGNATURE PAGE FOR INVESTIGATOR(S)

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Disease

Pulmonary arterial hypertension.

Protocol number and acronym

AC-065A302 / GRIPHON

A multicenter, double-blind, placebo-controlled Phase 3 study to demonstrate the efficacy and safety of ACT-293987 in patients with pulmonary arterial hypertension

I agree to the terms and conditions relating to this study as defined in this protocol, Case Report Form (CRF) and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on study patients (other than those procedures necessary for the well being of the patients).

I agree to conduct this study in accordance with the Declaration of Helsinki and its amendments, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and applicable regulations and laws. In particular, I will obtain approval by an Ethics Committee or Institutional Review Board (EC/IRB) prior to study start and signed informed consent from all patients included in this study. In addition, I will allow direct access to source documents and agree to inspection by auditors from the sponsor and Health Authorities. I will ensure that the study drug(s) supplied by the sponsor are being used only as described in this protocol. Furthermore, I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to worldwide Health Authorities worldwide.

Name	Country	Center number	Town	Date	Signature
Country					
Coordinating Investigator					
Center Principal Investigator					

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-minute walk distance
6MWT	6-minute walk test
ACT-293987	Actelion's investigational drug, formerly known as NS-304
ACT-333679	The active metabolite of ACT-293987
AE	Adverse event
ALT	Alanine aminotransferase / serum glutamic pyruvic transaminase (SGPT)
APAH	Pulmonary arterial hypertension associated with other diseases, e.g., scleroderma
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase / serum glutamic oxaloacetic transaminase (SGOT)
ATC	Anatomic Therapeutic Chemical
AUC	Area under the concentration-time curve
b.i.d.	<i>Bis in die</i> / twice a day
BL	Baseline, Day 1
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
cAMP	Cyclic adenosine monophosphate
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CEC	Critical Event Committee
CK	Creatine kinase
C _{max}	Maximal plasma concentration
CRF	Case Report Form
CRO	Contract Research Organization
CTx	Carboxy-terminal telopeptide

DMC	Data Monitoring Committee
DP receptor	Prostaglandin D ₂ receptor
dyn	Dyne (1 g·cm/s ²)
EC	Ethics Committee
ECG	Electrocardiogram
EDTA	Ethylene diamine tetra-acetic acid
EMA	European Medicines Agency
EOS	End of study
EOTE	End of treatment extension
EP receptor	Prostaglandin E ₂ receptor
ERA	Endothelin receptor antagonist
FDA	Food and Drug Administration
FEV ₁	Forced expiratory volume in 1 second
FP receptor	Prostaglandin F ₂ receptor
FPFV	First Patient First Visit
FVC	Forced vital capacity
GCP	Good Clinical Practice
GPCR	G-protein coupled receptor
GRIPHON	Prostacyclin (PGI ₂) receptor agonist in pulmonary arterial hypertension
HIV	Human Immunodeficiency Virus
HPAH	Heritable pulmonary arterial hypertension (formerly familial PAH)
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
INR	International Normalized Ratio
IP receptor	Prostacyclin receptor, PGI ₂ receptor

IPAH	Idiopathic pulmonary arterial hypertension
IRB	Institutional Review Board
ITT	Intention-to-treat
i.v.	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LC-MS/MS	Liquid chromatography with tandem mass spectrometry detection
LOQ	Limit of quantification
LVEDP	Left ventricular end diastolic pressure
MedDRA	Medical Dictionary for Regulatory Activities
MLA	Marked laboratory abnormality
mPAP	Mean pulmonary arterial pressure
MTD	Maximum tolerated dose
NDA	New drug application
NS-304	Previous name of the investigational drug AC-293987
NT pro-BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
p.o.	<i>Per os</i> / orally
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic(s)
PDE-5	Phosphodiesterase type-5
PE	Pharmacoeconomic(s)
PGI ₂	Prostacyclin (Prostaglandin I ₂)
PH	Pulmonary hypertension

PI	Package Insert
PK	Pharmacokinetic(s)
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
RVH	Right ventricular hypertrophy
RVSP	Right ventricular systolic pressure
s.c.	Subcutaneous
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
SVR	Systemic vascular resistance
$t_{1/2}$	Elimination half-life
$t_{\max}$	Time to maximum plasma concentration
TP receptor	Thromboxane A ₂ (TXA ₂) receptor
TXA ₂	Thromboxane A ₂
ULN	Upper limit of normal
UV	Ultraviolet
WHO	World Health Organization

PROTOCOL SYNOPSIS AC-065A302

TITLE	A multicenter, double-blind, placebo-controlled Phase 3 study to demonstrate the efficacy and safety of ACT-293987 in patients with pulmonary arterial hypertension					
ACRONYM	GRIPHON (Prostacyclin (PGI ₂) Receptor agonist In Pulmonary arterial HypertensiON)					
OBJECTIVES	Primary objective To demonstrate the effect of ACT-293987 on time to first clinical worsening in patients with pulmonary arterial hypertension (PAH). Secondary objective To evaluate the effect of ACT-293987 on exercise capacity and other secondary and exploratory efficacy endpoints in patients with PAH. To evaluate the safety and tolerability of ACT-293987 in patients with PAH.					
DESIGN / PHASE	Prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study.					
STUDY PLANNED DURATION	First Patient First Visit	Q4 2009	Last Patient First Visit	Q4 2011	Last Patient Last Visit	Q2 2013
CENTER(S) / COUNTRIES	Approximately 190 centers in approximately 44 countries (planned).					
PATIENTS / GROUPS	670 patients randomized into two groups, placebo: active 1:1, 335 patients per group.					

INCLUSION CRITERIA	1. Signed informed consent prior to initiation of any study-mandated procedure. 2. Male and female^{1,2} patients 18 years of age or older with symptomatic PAH 3. Patients with PAH belonging to one of the following subgroups of the updated Dana Point Clinical Classification Group 1: • Idiopathic (IPAH)³, or • Heritable (HPAH)³, or • Drug or toxin induced, or • Associated (APAH) with one of the following: – Connective tissue disease – Congenital heart disease with simple systemic-to-pulmonary shunt at least 1 year after surgical repair – HIV infection 4. Documented hemodynamic diagnosis of PAH by right heart catheterization – performed at any time <u>prior to Screening</u> showing: • Resting mean pulmonary arterial pressure (mPAP) > 25 mmHg and • Resting pulmonary vascular resistance (PVR) > 240 dyn·s·cm⁻⁵ and • Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) ≤ 15 mmHg

¹ Women of childbearing potential² must use a reliable method of contraception (failure rate less than 1% per year) from screening until 1 month after end of study drug treatment.

² A woman is considered to have childbearing potential unless she meets at least one of the following criteria:

- previous bilateral salpingo-oophorectomy or hysterectomy
- premature ovarian failure confirmed by a specialist gynecologist
- pre-pubescence, XY genotype, Turner syndrome, uterine agenesis
- age > 50 years and not treated with any kind of hormone replacement therapy for at least 2 years prior to screening, with amenorrhea for at least 24 consecutive months prior to screening.

³ If patient is > 50 years of age, results of recent pulmonary function tests ventilation/perfusion lung scan and an echocardiogram should be available to support PAH.

	5. 6-minute walk distance (6MWD) between 50 and 450 m (inclusive) at Screening (within 2 weeks prior to the Baseline Visit and on a different day than this visit). This distance must be confirmed by a second 6-six minute walk test (6MWT) at the Baseline Visit. The value of the second 6MWD should be within $\pm 10\%$ of the first assessment. 6. Patients who are able and willing to refrain from sunbathing, prolonged sun exposure, and artificial sunlight exposure like solarium use or UVA/UVB treatment, and to limit skin and eye exposure to sunlight using appropriate precautions (clothing, sunscreen, and sunglasses) from the first dose until 14 days after study drug discontinuation.
EXCLUSION CRITERIA	Patients will not be entered into the study if they meet any of the following criteria: 1. Patients with pulmonary hypertension (PH) in the Updated Dana Point Classification Groups 2–5, and PAH Group 1 subgroups that are not covered by the inclusion criteria. 2. Patients who have received prostacyclin (epoprostenol) or prostacyclin analogs (i.e., treprostinil, iloprost, beraprost) within 1 month before Baseline Visit, or are scheduled to receive any of these compounds during the trial. 3. Patients with moderate or severe obstructive lung disease: $FEV_1/FVC < 70\%$ and $FEV_1 < 65\%$ of predicted value after bronchodilator administration. 4. Patients with moderate or severe restrictive lung disease: Total Lung Capacity $< 60\%$ of predicted value. 5. Patients with moderate or severe hepatic impairment (Child-Pugh B and C). 6. Patients with documented left ventricular dysfunction (e.g., ejection fraction $< 35\%$). 7. Patients with clinically-significant chronic renal insufficiency (estimated creatinine clearance < 30 mL/min, or serum creatinine > 2.5 mg/dL). 8. Patients with BMI < 18.5 Kg/m².

	9. Patients who are receiving or have been receiving any investigational drugs within 1 month before the Baseline Visit. 10. Acute or chronic impairment (other than dyspnea), limiting the ability to comply with study requirements, in particular with 6MWT (e.g., angina pectoris, claudication, musculoskeletal disorder, need of walking aids). 11. Recently conducted (the program must be completed at least 8 weeks prior to screening) or planned cardio-pulmonary rehabilitation program based on exercise training. 12. Psychotic, addictive or other disorder limiting the ability to provide informed consent or to comply with study requirements. 13. Life expectancy less than 12 months. 14. Females who are lactating or pregnant (positive pre-randomization serum pregnancy test) or plan to become pregnant during the study. 15. Known hypersensitivity to any of the excipients of the drug formulations.
CONCOMITANT MEDICATIONS	Endothelin receptor antagonists (ERAs) and/or phosphodiesterase-5 (PDE-5) inhibitors are allowed. The dose must be stable for at least 1 month prior to Baseline Visit and until Week 16. Introduction of new treatment for PAH (or increasing the dose) without documented worsening of pulmonary arterial hypertension is strongly discouraged during the study period. Prostacyclin (epoprostenol) and prostacyclin analogs (i.e., treprostinil, iloprost, beraprost) and any investigational drug are prohibited (from 1 month prior to Baseline Visit until end of study)

STUDY PERIODS	Screening: Up to 28 days prior to Baseline Visit Treatment period: From Baseline Visit to EOS visit (included) - For an individual patient the EOS visit may occur before Study Closure (in the case of premature study drug discontinuation) or shortly after Study Closure (within 14 days). Patients who discontinue study drug must have an EOS Visit and a Post-treatment safety follow-up phone call. - Study Closure will be announced by the sponsor when the target number of clinical worsening events has been reached. All patients still on study drug at Study Closure must have an EOS Visit shortly thereafter (within 14 days). Patients who have prematurely discontinued study drug must be called at the time of study closure to ascertain vital status. Treatment Extension period: After Study Closure, from the EOS visit until the End-of-Treatment-Extension (EOTE) visit following unblinding of the database. The unblinding of the database will be announced by the sponsor, and the patient must have an EOTE visit shortly thereafter (within 14 days). Patients who had an EOS visit following a clinical worsening confirmed by the Critical Event Committee (CEC), or an EOTE visit, will be eligible to enter the open-label study AC-065A303/GRIPHON OL. Observation period: From Baseline Visit to Study Closure Post-treatment safety follow-up for serious adverse events (SAEs): SAEs must be reported until 30 days after study drug discontinuation or until the first dose of ACT-293987 in the open-label study, whichever comes first.

INVESTIGATIONAL DRUG	During the Baseline Visit (Day 1) patients will be randomized to the starting dose of 200 µg ACT-293987 b.i.d. or matching placebo. Patients will take the first dose of study drug in the evening of Day 1, and continue thereafter with twice daily dosing, in the morning and in the evening. At weekly intervals (scheduled phone calls or visits), patients will be up-titrated in increments of 200 µg b.i.d. until reaching their individual maximum tolerated dose (MTD) within a dose range of up to maximally 1,600 µg b.i.d. If the investigator identifies a tolerability concern for a patient, the patient's dose will be reduced to the previous dose level. At Week 12 (scheduled phone call), the MTD for each patient should be finally determined and this dose must then be kept unchanged for the next 4 weeks (from Week 12 on) until the Week 16 (Visit 4) assessment of the secondary endpoint, change in 6MWD. After Week 16, the investigator will be allowed to further increase the dose if needed (only at scheduled visits and up to the maximum of 1,600 µg b.i.d.) by 200 µg b.i.d. increments. Dose reduction may occur at anytime if the investigator identifies a tolerability concern for a patient. From Visit 2, and at each visit thereafter, patients must not take the morning dose before the completion of the CAMPHOR questionnaire (when applicable), 6MWT (when applicable) and the blood sampling. In addition, at Week 16 a post-dose blood sampling will be taken for pharmacokinetic (PK) analysis.
REFERENCE DRUG	Placebo matching ACT-293987
TREATMENT DURATION	Until the pre-specified number of 202 events has been reached (within a maximum of 3.5 years)
FORMULATIONS	Tablets of 200 µg ACT-293987 or matching placebo

EFFICACY ENDPOINTS	Primary endpoint Time to first clinical worsening up to 7 days after last study drug intake defined as: • Death (all-cause mortality) or • Hospitalization for worsening of PAH or • Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy or • Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH or • Disease progression (patients in modified NYHA/WHO functional class II-III at baseline) confirmed by : – decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by two tests on different days within 2 weeks) and – worsening of NYHA/WHO functional class or • Disease progression (patients in modified NYHA/WHO functional class III-IV at baseline) confirmed by : – decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) and – need for additional PAH specific therapy. Clinical worsening will be adjudicated by an independent Critical Event Committee. The date of the “last study drug intake” refers to the date of the actual last study drug intake reported in the Case Report Form (CRF) during the Treatment period. Hazards in the two treatment groups are expected to be proportional over time and censoring is expected to be 5%. A risk reduction of 40% on active is to be detected, assuming that placebo has an event rate of 20% / year, constant over time.

	Secondary endpoints • Change from Baseline to Week 16 in 6MWD measured at trough • Absence of worsening from Baseline to Week 16 in modified NYHA/WHO functional class • Change from Baseline to Week 16 in Borg dyspnea index • Time to death up to Study Closure • Change from Baseline to Week 16 in the sub-scale “Breathlessness” of the “Symptoms” score in the CAMPHOR questionnaire (at selected centers) • Change from Baseline to Week 16 in the “Symptoms” score of the CAMPHOR questionnaire (at selected centers) Exploratory endpoints • Time to death and to selected combinations of the components of clinical worsening up to 7 days after last study drug intake, • Change from Baseline to EOS in 6MWD measured at through • Change from Baseline to EOS in modified NYHA/WHO functional class • Change from Baseline to EOS in Borg dyspnea index • Change from Baseline to EOS in plasma N-terminal pro-brain natriuretic peptide (NT pro-BNP) • Change from Baseline to EOS in the sub-scale “Breathlessness” of the “Symptoms” score in the CAMPHOR questionnaire (at selected centers) • Change from Baseline to EOS in the “Symptoms” score of the CAMPHOR questionnaire (at selected centers) The date of the “last study drug intake” refers to the date of the actual last study drug intake reported in the CRF during the Treatment period.

TOLERABILITY / SAFETY ENDPOINTS	Safety and tolerability of ACT-293987 assessed as: • Treatment-emergent adverse events (AEs) until 7 days after last study drug intake • AEs leading to permanent discontinuation of study drug • Treatment-emergent SAEs until 7 days after last study drug intake* • Treatment-emergent ECG abnormalities until 7 days after last study drug intake. • Treatment-emergent marked laboratory abnormalities until 7 days after last study drug intake. • Change from Baseline to EOS in vital signs • Change from Baseline to EOS in bone turnover markers *SAEs during the Treatment Extension period will only be listed The date of the “last study drug intake” refers to the date of the actual last study drug intake reported in the CRF during the Treatment period.
PHARMACOKINETIC / PHARMACODYNAMIC EVALUATIONS	• Pharmacokinetic sampling for trough plasma concentrations of ACT-293987, ACT-333679, and other potential metabolites, at Baseline, Week 4, Week 8, Week 16, Week 26 (Month 6), Week 52 (Month 12), and EOS. • PK sampling after drug administration at Week 16. • Relationship between ACT-293987/ACT-333679 plasma levels and clinical endpoints and plasma NT pro-BNP levels
PHARMACOECONOMIC ENDPOINTS	• Number per year of all-cause and PAH-related hospitalizations from Baseline to EOS • Number per year of in-hospital patient days for all causes and PAH-related causes from Baseline to EOS
STATISTICAL METHODOLOGY	Analysis strategy Study AC-065A302 is designed to be analyzed for the time to first clinical worsening endpoint up to 7 days after last study drug intake. It is assumed that the study adequately supports a New Drug Application (NDA) submission if the null hypothesis of no difference from placebo for the time to event is rejected.

Hypotheses and methods

The primary endpoint, time to first clinical worsening up to 7 days after last study drug intake, will be analyzed as a time-to-event variable; hazards in the two treatment groups are expected to be proportional over time and the censoring rate is expected to be 5%. The difference to be detected is a hazard ratio of 0.5729 when the active group is compared to placebo (which is expected to have an event rate of 20%/year constant over time).

The null hypothesis of no difference between the treatment groups will be tested by means of the log-rank test. Supportive analyses will be conducted using appropriate covariates in a Cox regression model.

Type-I error

The overall type-I error for the study is set to 0.01.

Power estimation

- Time to first clinical worsening
Two hundred and two (202) events need to be observed to detect with 90% power the above-mentioned hazard ratio, at a two-sided 0.01 significance level, by means of the log-rank test. With the recruitment of 670 patients, randomized 1:1 to active treatment or placebo, over a period of 2 years (150 patients/1st year and 520 patients/2nd year), 202 events could be reached within a maximum of 3.5 years.

Sample size adaptation

The overall event rate (blinded) and the censoring rate will be continuously monitored. A blinded adaptation to the sample size might be implemented up to a maximum of 1,150 patients, if required to keep the expected duration and power of the study within acceptable ranges.

Analysis sets

The primary analysis set for this study is the All-randomized set including all patients who have received at least one dose of study drug treatment, and have at least one post-baseline value.

	All-treated and per-protocol sets will be used for supportive/exploratory analyses. Secondary efficacy endpoints Each secondary endpoint can then be analyzed in the sequence provided in the endpoints section, if the null-hypotheses of no difference from placebo were rejected for all the endpoints preceding in the sequence including the primary endpoint; each at the 0.05 two-sided level.
STUDY COMMITTEES	An independent Data Monitoring Committee (DMC) will review unblinded safety and tolerability data at regular intervals according to the DMC charter. An independent Critical Event Committee will review and confirm all clinical worsening events in a blinded fashion. A Steering Committee is involved in the study design and will provide guidance on the study conduct and study publications.

Table 1 Visit and assessment schedule

	Screening	Visit 1	Tel. ^a W1	Tel. ^a W2	Tel. ^a W3	Visit 2	Tel. ^a W5	Tel. ^a W6	Tel. ^a W7	Visit 3	Tel. ^a W12	Visit 4	Visit 5 and on-wards	Tel. ^a	Clinical Worsening Event	EOS Visit ^k	Safety Follow-up ^a	Sur-vival Follow-up	End of Treatment extension visit ^m
	≤ 28 days before Day 1	Base-line Day 1 Randomization	Day 8 ± 3 days	Day 15 ± 3 days	Day 22 ± 3 days	Week 4 ± 3 days	Week 5 ± 3 days	Week 6 ± 3 days	Week 7 ± 3 days	Week 8 ± 3 days	Week 12 ± 3 days	Week 16 ± 3 days	Month 6 and every 6 months ± 7 days	Month 9 and every 6 months ± 7 days			30 days after study drug discontinuation ^o		
Written informed consent	X																		
Inclusion/exclusion criteria	X	Re-confirm																	
Medical history incl. PAH	X	X																	
Concomitant medications	X	X				X				X		X	X	X	X	X			
Mod. NYHA/WHO functional class	X	X				X				X		X	X		X	X			
Physical examination	X	X				X				X		X	X		X	X			
Weight and height ^h	X	X				X				X		X	X		X	X			
Vital signs	X	X				X				X		X	X		X	X			
12-lead ECG		X				X				X		X	X		X	X			
6-minute walk test	X ^c	X								X		X	X		X	X			
Borg dyspnea score	X ^c	X								X		X	X		X	X			
CAMPBOR questionnaire (subset)		X										X	X ^f			X			
Pregnancy test (if appl.) ⁱ	X	X				X				X	X	X	X			X			
Laboratory test ^d	X	X				X				X		X	X		X	X			
Plasma NT pro-BNP		X				X				X		X	X			X			
PK sampling		X				X				X		X ⁿ	X ^e			X			
Study drug dispensing		X				X				X		X	X						
First dose of study drug		X (p.m.)																	
Dose titration			X	X	X	X	X	X	X		X ^g								
Drug accountability						X				X		X	X			X			X
(Serious) adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital status																		X	

a: Tel. = Scheduled telephone call b: In case of suspected clinical worsening c: Conducted ≤ 14 days before Day 1 d: Laboratory test (hematology and blood chemistry) e: On Visit 5 (Month 6) and Visit 6 (Month 12) only f: On Visit 6 (Month 12) and Visit 8 (Month 24) only g: Confirmation of MTD h: Height measured only at screening i: Serum pregnancy test to be performed at screening and urine pregnancy tests monthly until 1 month after study drug discontinuation k: In case of premature discontinuation of study drug and for all patients on study drug at Study Closure l: Telephone call at Study Closure for patients with premature EOS or to be performed at EOS visit for patients still under treatment m: the the End of Treatment Extension visit must be performed only for the patient still on study drug at Study Closure and who wish to enter the study AC-065A303/GRIPHON OL (* 6 months correspond to 26 weeks) n: Two PK samplings will be taken at this visit, one pre-dose and one post-dose. o: For patients who will enter the OL, the SAEs must be followed-up until the first dose of ACT-293987 in the Open-Label.

1 BACKGROUND AND RATIONALE

1.1 Pulmonary arterial hypertension

The most serious chronic disorder of the pulmonary circulation is pulmonary arterial hypertension (PAH). PAH is characterized by pulmonary arterial vasoconstriction and vascular remodeling resulting in a progressive increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), ultimately leading to right ventricular failure and death. PAH is defined as a sustained elevation of mean pulmonary arterial pressure (mPAP) > 25 mmHg at rest (or > 30 mmHg with exercise), with a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg and PVR > 3 Wood units ($> 240 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$) [Rubin 2004].

The Updated Clinical Classification of Pulmonary Hypertension (Dana Point 2008) [Simonneau 2009] classifies the numerous conditions that are known to lead to, or to be associated with, the development of PAH into five groups, based on their similar clinical presentation, pathology, pathophysiology, prognosis, and, most of all, similar therapeutic approach. PAH may occur in the absence of a demonstrable cause (idiopathic or heritable), as the result of the use of drugs and toxins, or as a complication of congenital heart disease, systemic conditions such as connective tissue disease, particularly scleroderma, HIV infection, portal hypertension, schistosomiasis, or chronic hemolytic anemia.

The pathophysiology of PAH involves multiple pathways, which are influenced by many overlapping secondary messenger systems. Vasoconstriction, obstructive remodeling of the pulmonary vessel wall caused by extensive cell proliferation and reduced rates of apoptosis, inflammation, and thrombosis within the pulmonary arteries are promoted by activation of these pathways, and lead to elevated PAP and PVR, and eventually right ventricular failure.

Currently, there is no cure for PAH. However, improved understanding of the pathogenic factors of the disease has led to the development of new therapies targeting specific pathways (the prostacyclin pathway; the endothelin pathway; and the nitric oxide pathway) [Humbert 2004, Farber 2004] that are believed to play an important role in the pathogenesis of PAH.

Today, a total of eight agents are currently approved for the treatment of PAH in the United States and/or in Europe: intravenous prostacyclin (epoprostenol), other prostanoid analogs, i.e., treprostinil (intravenous, subcutaneous and inhaled), and iloprost (inhaled), endothelin receptor antagonists (bosentan, sitaxsentan, and ambrisentan) and phosphodiesterase type-5 (PDE-5) inhibitors (sildenafil, tadalafil). All of these agents have been shown to improve exercise capacity as assessed by 6-minute walk test (6MWT) in short-term randomized placebo-controlled trials.

Pure vasodilators, such as calcium channel blockers, are effective only in a minority of patients who have an acute response to vasodilator testing [Rich 1992, Sitbon 2005].

The available therapies have positive effects in PAH, but in many patients the disease will progress and PAH remains a serious life-threatening condition.

Early recognition and an understanding of the selection and timing of therapeutic options remain critical elements in the optimal management of patients with this disorder.

Before the development of recent therapeutic options, idiopathic PAH was rapidly progressive and led to right heart failure and death. In the early 1990s, it was reported that the median survival of patients was 2.8 years after diagnosis [D'Alonzo 1991]. The first large prospective studies showed an actuarial survival rate of 68 to 77%, 40 to 56%, and 22 to 38% at 1, 3, and 5 years respectively [D'Alonzo 1991, Galie 2009].

1.2 Prostacyclin (PGI₂) and pulmonary hypertension

Prostacyclin (Prostaglandin I₂, PGI₂), a metabolite of arachidonic acid, is formed via the cyclooxygenase pathway. Endothelial cells are the main source of prostacyclin and its action is directed to both the local vascular wall and to blood cells, particularly those that adhere to the endothelium. It is a potent endogenous vasodilator, inhibitor of platelet aggregation and smooth muscle cell proliferation through its activity at the prostacyclin (IP) receptor [O'Grady 1980].

The IP receptor is a G protein-coupled receptor (GPCR) that activates adenylate cyclase, leading to increased cyclic adenosine monophosphate (cAMP) levels in the target cells. cAMP has been widely implicated in the control of pulmonary vascular tone and inhibition of mitogenic pathways in vascular smooth muscle cells.

Patients with PAH have been shown to have a deficiency of prostacyclin [Christman 1998] and of PGI₂ synthase [Tuder 1999] causing an imbalance in prostacyclin (PGI₂) and thromboxane A₂ (TXA₂), its physiological antagonist. These findings led to the rationale that targeting the PGI₂ pathway with IP receptor agonists could be beneficial.

The first, epoprostenol, the chemical analog of prostacyclin, was approved in 1996 for NYHA/WHO functional class III–IV idiopathic PAH (IPAH) and PAH associated with scleroderma, and showed to improve exercise tolerance and survival in patients with IPAH [Barst 1996]. Since continuous intravenous epoprostenol became available, the prognosis for patients suffering from PAH has significantly improved. However, due to its short half-life and chemical instability, long-term epoprostenol therapy requires a permanently implanted central venous catheter and a portable infusion pump, exposing patients to a series of complications including catheter-related embolism or thrombosis, infection, and delivery system malfunctions resulting in poorly tolerated overdosing or underdosing.

The complexity of epoprostenol therapy has led to attempts to develop other prostanoids with simpler modes of delivery. Treprostinil, a stable prostacyclin analog with a half-life of 3 h, has been developed for intravenous, subcutaneous delivery, and inhalation. It has beneficial effects on exercise and hemodynamics, which depend on the dose achieved. This, in turn, is determined by the patient's ability to tolerate the drug's side effects. Iloprost, another prostacyclin analog, has been approved for intravenous delivery and inhalation. Inhaled iloprost shows some selectivity of the hemodynamic effects to the lung vasculature, thus reducing systemic side effects, but has to be inhaled between 6 to 9 times per day, which may limit compliance.

The inconveniences of the administration routes of the above-mentioned drugs, such as injection site pain and reaction (redness and swelling) for subcutaneous administrations, or line infections, sepsis, hematoma, and local pain for intravenous infusions, are another factor influencing the patient's benefit from these treatments.

1.3 ACT-293987 – a non-prostanoid IP receptor agonist

ACT-293987 is an orally-available drug that is readily hydrolyzed to the active metabolite ACT-333679. Both ACT-293987 and ACT-333679 are potent and selective agonists at the human IP receptor.

ACT-333679 has a 13-fold higher affinity for the human IP receptor [[ACT-293987 IB](#)] and is 15-fold more potent than ACT-293987 in activating the human IP receptor. *In vitro* studies showed that ACT-333679 has at least 130-fold lower affinity for other human prostanoid receptors such as the prostaglandin E₁₋₄, D₂, and F₂ receptors, as well as the thromboxane A₂.

ACT-293987 has been selected for further clinical development based on its pharmacokinetic (PK) profile observed in Phase 1 studies and the results from the Phase 2 study [Section [1.3.2](#)].

1.3.1 Preclinical information

In vivo pharmacology studies demonstrated that orally administered ACT-293987 significantly reduced right ventricular systolic pressure (RVSP) and right ventricular hypertrophy (RVH) in a rat model of PAH. ACT-293987 also ameliorated the impaired relaxant response of the pulmonary artery from these animals.

Furthermore, ACT-293987 significantly increased survival of rats with monocrotaline-induced PAH [[Kuwano 2008](#)].

In normotensive rats prolonged administration of ACT-293987 did not attenuate the acute increase in femoral skin blood flow induced by the compound, suggesting lack of desensitization of the IP receptor [[Kuwano 2007](#)].

1.3.2 Clinical information

1.3.2.1 Phase 1 studies in healthy subjects

A total of five Phase 1 studies have been performed to date (studies PS003, QGUY/2006/NS304/-01, AC-065-101, 186933, and NS304/P1/01).

During the Phase 1 program, a total of 187 healthy male subjects have been exposed to ACT-293987 (n = 150) or placebo (n = 37). In these studies ACT-293987 was well tolerated after single and multiple daily oral doses of up to and including 1,600 µg b.i.d. No serious adverse events (SAEs) were reported in any of the Phase 1 studies and the majority of the AEs were of mild intensity. The most frequently reported adverse events (AEs) were headache, myalgia, jaw pain, dizziness, nausea, vomiting, arthralgia, diarrhea, and abdominal pain. No clear dose relationship could be established for the above- mentioned AEs.

Multiple doses of ACT-293987 up to 1,600 µg b.i.d (study AC-065-101), starting with 400 µg b.i.d. and up-titrated in increments of 200 µg every 3rd day, were well tolerated. Most AEs were mild or moderate in intensity. The incidence of AEs was similar for all treatment groups, which suggests improved tolerability after repeated dosing. Tolerability decreased at a dose of 1800 µg ACT-293987 b.i.d. and led to an increase in moderate AEs (headache, myalgia, and nausea) that required concomitant medication. The maximum dose tested in Japanese subjects was 600 µg b.i.d. There were no consistent differences in the number and type of AEs with increasing dose of ACT-293987.

Treatment with ACT-293987 up-titrated in increments of 200 µg to 1800 µg (the highest dose tested in Caucasian subjects) or 600 µg (the highest dose tested in Japanese subjects) (study AC-065-101 and NS304/P1/01), were not associated with clinically relevant changes in systolic and diastolic blood pressures, heart rate, electrocardiogram (ECG) intervals and morphology, vital signs and laboratory tests. In addition, in the AC-065-101 study, no changes were observed in thyroid markers, orthostatic hypotension, platelet aggregation test, bone formation, bone resorption markers, and coagulation markers.

Plasma concentration-time profiles and PK parameters of ACT-293987 and ACT-333679 were comparable across the studies performed in healthy subjects. The plasma concentration-time profiles of ACT-293987 revealed that, in general, maximum plasma concentrations were achieved in about 1–2 h after single-dose and multiple-dose administration. Thereafter, plasma concentrations of ACT-293987 decreased quickly. The plasma concentration-time profiles of ACT-333679 showed that, in general, maximum plasma concentrations were achieved in about 3–4 h after single- and multiple-dose administration. Thereafter, plasma concentrations of ACT-333679 compared to ACT-293987 decreased more slowly. In the study AC-065-101 the exposure (AUC) to ACT-333679 is approximately four times higher than to ACT-293987.

Following multiple oral administrations of ACT 293987, the apparent elimination half-lives of ACT 293987 and its active metabolite ACT 333679 were between 0.9 and 1.9 hours and between 7.9–14.5 h, respectively, which supports twice daily oral administration. The PK of ACT-293987, after both single- and multiple-dose administration, were approximately dose-proportional over the tested dose range, i.e., up to a single dose of 800 µg and multiple doses of 1800 µg b.i.d. of ACT-293987. After multiple-dose administration, steady-state conditions of ACT-293987 and ACT-333679 were reached on Day 3. No relevant accumulation in plasma either of ACT-293987 or ACT-333679 occurred after multiple-dose administrations.

Results from study QGUY/2006/NS304/-01 indicate that food intake delayed the exposure to ACT-333679, as the median $t_{\max}$ increased from 2.5 hours during fasting to 4 hours in fed state, and decreased the exposure to ACT-333679 by 27%.

More subjects reported AEs in the fasted period than in the fed period. These results may indicate better tolerability of ACT 293987 when administered with food.

ACT-293987 did not influence the PK or pharmacodynamics (PD) of warfarin. Similarly, co-administration of warfarin with ACT-293987 did not have an impact on the exposure to ACT-293987 or its active metabolite ACT-333679.

The metabolism and excretion of ACT 293987 were studied following a single dose administration of radioactively labeled ACT 293987A (400 µg) (study 186933). 105% of the radioactivity was excreted primarily via feces (93%) and urine (12%). Excretion was complete after 5 days indicating no relevant retention of drug-related material in man.

When comparing the PK of ACT-293987 and ACT-333679 from study QGUY/2006/NS30/-01, which mainly included Caucasian subjects, to those of study NS304/P1/01, which included only Japanese subjects, the concentrations of both ACT-293987 and ACT-333679 were higher in Japanese subjects. The difference in the PK was mainly due to the difference in body weight. When corrected for body weight a small residual difference was observed, however this difference was within one standard deviation of the mean and not consistent between the different dose levels. The clinical relevance of this observation is currently unknown.

For more detailed information please refer to the Investigator's Brochure [[ACT-293987 IB](#)].

1.3.2.2 Phase 2 studies in patients with pulmonary arterial hypertension

A Phase 2a proof-of-concept study in PAH (NS-304/-02) was completed in July 2009.

The study NS-304/-02 was conducted in seven European centers and enrolled 43 patients with PAH, who were randomized in a 3:1 ratio to ACT-293987 (n = 33) or placebo (n = 10). All enrolled patients received double-blind study treatment, which was prematurely discontinued in three patients (two on ACT-293987 and one on placebo). Median exposure to study treatment was 146 days in the placebo group and 149 days in the ACT-293987 group. For most patients, PAH was idiopathic (70% and 73% of patients in the placebo and ACT-293987 groups, respectively). At baseline, all patients were receiving either an ERA (bosentan, 70% and 61% of patients in the placebo and the ACT-293987 group, respectively), or sitaxentan in four patients in the ACT-293987 group only) or a PDE-5 inhibitor (sildenafil 60% and 64% of patients in the placebo and the ACT-293987 group, respectively). Three patients in the placebo group (30%) and 12 patients in the ACT-293987 (36%) were receiving both an ERA and a PDE-5 inhibitor.

After 17 weeks of treatment, mean PVR was decreased from baseline in the ACT-293987 group (-168 ± 45 dyn·sec/cm⁵) and increased in the placebo group (137 ± 35 dyn·sec/cm⁵). Values at Week 17 expressed as a percent of baseline values showed a significant 30.3% reduction in PVR with ACT-293987 compared with placebo (P = 0.0045, Wilcoxon rank sum test). Similar improvements in PVR were observed in the All-randomized analysis set.

After 17 weeks of treatment, the mean 6-minute walk distance (6MWD) increased from baseline in the ACT-293987 group ($+24.7 \pm 12.9$ meters) and was unchanged in the placebo group ($+0.4 \pm 8.9$ meters), which resulted in a mean treatment effect of 24.2 ± 23.7 meters (P = 0.2218, Wilcoxon rank sum test). Three subjects showed aggravation of PAH during the double blind study, two patients in the placebo group (20%) and one (3.3%) patient in the ACT-293987 group. All three patients were in NYHA/WHO functional class III at baseline. A statistically significant increase of Cardiac Index was observed in the ACT-293987 group when compared to a decrease in the placebo group, which resulted in a mean treatment effect: 0.48 ± 0.17 L/min/m², ($\pm$ standard error) (P = 0.0137, Wilcoxon rank sum test). A statistically significant decrease of SVR was observed in the ACT-293987 group when compared to an increase in the placebo group, which resulted in a mean treatment effect: -407.8 ± 164.2 dyn·sec/cm⁵, ($\pm$ standard error) (P = 0.0071, Wilcoxon rank sum test).

Ten (100%) patients in the placebo group reported a total of 39 treatment-emergent adverse events, whilst 31 (93.9%) patients in the ACT-293987 group reported a total of 182 adverse events (AE). The most frequently reported AE in the active group was

headache, reported in 22 patients (66.7%) in the ACT-293987 group compared with two patients (20%) in the placebo group. In the ACT-293987 group, pain in jaw, pain in extremity, nausea, diarrhea, flushing, dizziness, cough, and myalgia were reported in 12 patients (36.4%), 10 patients (30.3%), nine patients (27.3%), six patients (18.2%), six patients (18.2%), five patients (15.2%), four patients (12.1%), and four patients (12.1%) respectively. Most AEs in both treatment groups were of mild or moderate intensity, but a severe event was experienced by a larger proportion of patients on placebo (40%) than in the ACT-293987 group (18.2%). Seven serious adverse events (SAEs) were reported in four patients (40%) in the placebo group. Fourteen SAEs were reported in six patients (18.2%) in the ACT-293987 group. There were no changes from baseline to the end of treatment in either systolic or diastolic blood pressure, or in heart rate in the placebo group and in the ACT-293987 group. The analysis of marked laboratory abnormalities (MLA) in the ACT-293987 compared to the placebo group did not reveal any relevant increase of the incidence of MLA after ACT-293987 treatment. No clinically relevant ECG changes were observed in either treatment groups.

The open-label extension study (NS-304/-03) with 39 patients enrolled is ongoing and will continue in order to gather long-term safety information.

1.4 Study rationale

1.4.1 Medical and regulatory background

ACT-293987 is a new, selective, orally active non-prostanoid IP-receptor agonist selected for clinical development in PAH.

Prostacyclin (epoprostenol) and analogs like treprostinil (intravenous, subcutaneous, and inhaled) and iloprost (inhaled) have been approved for PAH. However, the administration routes are not always convenient. For subcutaneous administrations, injection site pain and reaction (redness and swelling) occur in the majority of patients. For intravenous infusions, line infections, sepsis, hematoma, and local pain are most common. Inhaled iloprost has to be given between 6 to 9 times per day, which may limit compliance. An orally available medicinal product, such as ACT-293987, which, by targeting the prostacyclin pathway, could affect the progressive course of PAH would represent an important advancement in the clinical management of PAH patients, and provide a significant contribution in the treatment options for these patients

To date, several medicinal products have been approved for the treatment of pulmonary hypertension (PH), specifically PAH. The majority of controlled trials performed in PAH have been relatively short-term studies in selected populations.

This Phase 3 study will be event-driven and will aim at comparing ACT-293987 (at the maximal tolerated dose of 200–1,600 µg b.i.d.) with placebo in patients with PAH. The main objective in this study will be to demonstrate prolongation of time to the first clinical worsening event.

This Phase 3 study is considered pivotal for the registration of ACT-293987 for the indication pulmonary arterial hypertension.

1.4.2 Patient population

The target population will be patients with PAH (groups 1.1 to 1.4 of the updated Dana Point classification [[Simonneau 2009](#)]) occurring in the absence of a demonstrable cause (idiopathic or heritable), or associated with collagen vascular disease, congenital heart disease with simple systemic-to-pulmonary shunts surgically corrected (at least 1 year post-surgical), HIV infection, or drugs and toxins.

Patients will not be eligible for the study if they have PAH associated with portal hypertension, or if their PAH is associated with significant venous or capillary involvement, or has other causes than those mentioned above.

The study will enroll males and females aged 18 years or older with symptomatic PAH, who will receive ACT-293987 or placebo. Background therapy with existing PAH therapies, except for prostacyclin and prostacyclin analogs, will be allowed.

1.4.3 Study design

The study is designed as a multicenter, randomized, double-blind, parallel-group, placebo-controlled Phase 3 study to compare ACT-293987 (at the maximal tolerated dose of 200–1,600 µg b.i.d.) with placebo.

It is planned to randomize 670 evaluable patients (335 patients per group) in approximately 190 centers in 44 countries.

1.4.4 Comparative drug(s) and/or placebo

Patients participating in this study will receive ACT-293987 or matching placebo. Study medication can be given on top of a stable dose of endothelin receptor antagonists (ERAs) and/or phosphodiesterase-5 (PDE-5) inhibitors.

1.4.5 Dose selection

Uptitration to the individual patient's highest tolerated dose appears to be the most adequate treatment regimen for prostacyclin receptor (IP receptor) agonists, including epoprostenol (i.v.), treprostinil (i.v., s.c., and inhaled) and iloprost (inhaled). Starting with high doses of these compounds is associated with poor tolerability due to typical prostanoid-associated pharmacological effects such as headache, myalgia, flushing,

nausea, and vomiting. Clinical experience with IP receptor agonists has shown that it is important to start at lower doses and up-titrate in order to improve tolerability.

ACT-293987 and its active metabolite ACT-333679 are potent and selective agonists at the human IP receptor. The pharmacological profile suggests that similar pharmacological and clinical effects as seen with other chronic-use IP receptor agonists can be expected, and therefore, a similar dosing regimen is recommended.

Results from Phase 1 studies with ACT-293987 have shown the occurrence of typical PGI₂-related AEs such as headache, nausea, flushing, leg pain, and jaw pain. The data indicate that an up-titration regimen improves tolerability. The findings from the completed Phase 1 study (AC-065-101), and from study NS-304/-02 support a titration regimen starting with a low dose (200 µg b.i.d.) and up-titration in increments of 200 µg up to a maximum of 1,600 µg b.i.d.

This approach, using gradually up-titration to each individual patient's highest tolerated dose is therefore expected to increase the potential of reaching an efficacious dose for each patient.

1.4.6 Treatment duration

The treatment duration for this study is expected to be up to 3.5 years.

The study will be event-driven and, by definition will be terminated as soon as the targeted overall number of 202 clinical worsening events (defined in the primary endpoint) has been reached. With the recruitment of 670 patients randomized 1:1 to active treatment and placebo, over a period of 2 years (150 patients/1st year and 520 patients/2nd year), this number of events is expected within a maximum of 3.5 years.

1.4.7 Primary endpoints

To date, most clinical studies have assessed exercise capacity in patients with PAH by measuring the 6MWD, used as primary surrogate endpoint.

However, PAH is a serious and progressive life-threatening disease with a life expectancy of 2.8 years from the time of diagnosis, if not treated [[D'Alonzo 1991](#)]. The goal of PAH therapy is to prolong survival of patients while improving symptoms and preventing disease progression [[Barst 2009](#)]. Thus, the time to clinical worsening is considered to be a hard and more clinically relevant endpoint.

In this study, the primary endpoint will be the time to first clinical worsening, up to 7 days after last study drug intake, defined as:

- Death (all-cause mortality)
or
- Hospitalization for worsening of PAH based on predefined criteria
or
- Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy
or
- Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to PAH worsening
or
- Disease progression (patients in NYHA/WHO functional class II-III at baseline) confirmed by :
 - decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) **and**
 - worsening of NYHA/WHO functional class**or**
- Disease progression (patients in NYHA/WHO functional class III-IV at baseline) confirmed by :
 - decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) and
 - need for additional PAH specific therapy.

Clinical worsening will be adjudicated in a blinded fashion by an independent Critical Event Committee (CEC).

1.4.8 Statistical hypotheses and sample size

For the statistical analysis of the primary endpoint, the null hypothesis is that there is no difference between the active group and placebo for the distribution of time to clinical worsening. The difference to be detected is a hazard ratio of 0.5729 when the active group is compared to placebo (which is expected to have an event rate of 20%/year constant over time), corresponding to a risk reduction of 40%. Hazards in the two treatment groups are expected to be proportional over time and censoring is expected to be 5%. The null hypothesis will be tested by means of the log-rank test at two-sided 0.01 significance level.

Two hundred and two (202) events need to be observed to detect with 90% power the above-mentioned hazard ratio. With the recruitment of 670 patients, randomized 1:1 to active treatment or placebo, over a period of 2 years (150 patients/1st year and 520 patients/2nd year), 202 events could be reached within a maximum of 3.5 years.

The overall type-I error is set to 0.01.

2 STUDY OBJECTIVES

2.1 Primary objective

To demonstrate the effect of ACT-293987 on time to first clinical worsening in patients with PAH.

2.2 Secondary objectives

To evaluate the effects of ACT-293987 on exercise capacity and other secondary and exploratory efficacy endpoints in patients with PAH.

To evaluate the safety and tolerability of ACT-293987 in patients with PAH.

3 INVESTIGATIONAL PLAN

3.1 Overall study design and plan

The study is designed as a multicenter, randomized, double-blind, parallel-group, placebo-controlled, prospective Phase 3 study to compare the effects (defined as efficacy, safety, tolerability, PK/PD) of ACT-293987 (at the maximal tolerated dose of 200–1,600 µg b.i.d.) versus placebo over a period of up to 3.5 years.

Patients will be up-titrated with weekly increments of 200 µg b.i.d. until reaching the individual maximum tolerated dose (MTD) [Section 3.3.2].

The study consists of the following periods:

- The **Screening period** will be completed within a maximum of 28 days before Baseline
 - The Screening period ends with the Baseline Visit at which randomization (1:1) will take place.
- **Treatment period:** From Baseline Visit to end of study (EOS) visit
 - Due to the fact that patients will take their first dose of study medication on the evening of the **Baseline Visit**, this day is called **Day 1**.
 - For an individual patient, the EOS visit may occur before the Study Closure (in the case of premature study drug discontinuation) or shortly after Study Closure (within 14 days). Patients who discontinue study drug must have an EOS visit and a post-treatment safety follow-up phone call.
 - Study Closure will be announced by the sponsor when the overall target number of 202 clinical worsening events has been reached. All patients still on study drug at Study Closure must have an EOS Visit shortly thereafter (within 14 days). Patients who have prematurely discontinued study drug must be called at the time of Study Closure to ascertain vital status.
- **Treatment Extension period:** from the EOS visit following the Study Closure, until the End-Of-Treatment-Extension (EOTE) visit following unblinding of the database. The unblinding of the database will be announced by the sponsor, and the patient must have the EOTE visit shortly thereafter (within 14 days)

Patients who had an EOS visit following a clinical worsening confirmed by the CEC, or an EOTE visit, are eligible to enter the Open-label study AC-065A303/GRIPHON OL.

- **Observation period:** From Baseline Visit to Study Closure.
- **Post-treatment safety follow-up for SAEs:** SAEs must be reported up to 30 days after last study drug intake or until administration of the first dose of ACT 293987 in the open-label study, whichever comes first.

Anticipating a recruiting rate of 670 randomized patients over a period of 2 years (150 patients/1st year and 520 patients/2nd year), it is expected that the treatment period at individual patient level will range between approximately 1.5 and 3.5 years for patients who are on treatment until Study Closure.

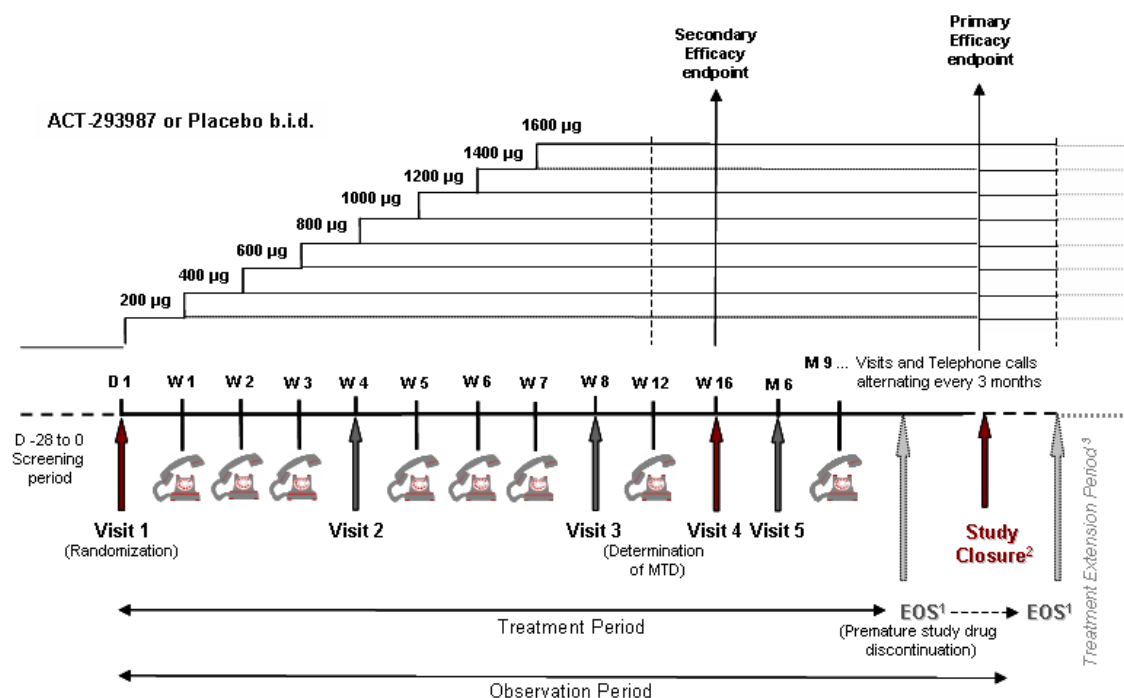
An independent **Data Monitoring Committee (DMC)** will review unblinded safety and tolerability data at regular intervals to ensure patient safety.

An independent **Critical Event Committee** will review and confirm all clinical worsening events in a blinded fashion.

A **Steering Committee** is involved in the study design and will provide guidance on the study conduct and study publications.

No interim analyses are planned in this study.

Figure 1 Study design



1. EOS visit for an individual patient may occur before Study Closure (in the case of premature study drug discontinuation) or shortly after Study Closure (within 14 days). Patients who discontinue study drug before Study Closure must have an EOS Visit and a Post-treatment safety follow-up phone call.
2. Study Closure will be announced when the target number of clinical worsening events has been reached. Patients who have prematurely discontinued study drug must be called at the time of Study Closure to ascertain vital status.
3. Patients who are on study drug after Study Closure and who wish to enter the open-label study AC-065A303/GRIPHON OL must enter the Treatment Extension period.

3.2 Study population

3.2.1 Patient population

Patients participating in this study are adult males and females with symptomatic PAH as defined in the inclusion criteria in Section 3.2.2 below.

3.2.2 Inclusion criteria

Eligible patients must meet all of the following inclusion criteria:

1. Signed informed consent prior to initiation of any study-mandated procedure.
2. Male and female^{4,5} patients 18 years of age or older with symptomatic PAH.
3. Patients with PAH belonging to one of the following subgroups of the Updated Clinical Classification Group 1 (Dana Point, 2008):
 - Idiopathic (IPAH)⁶, or
 - Heritable (HPAH)³, or
 - Drug or toxin induced, or
 - Associated (APAH) with one of the following:
 - Connective tissue disease
 - Congenital heart disease with simple systemic-to-pulmonary shunt at least 1 year after surgical repair
 - HIV infection

⁴ Women of child-bearing potential² must use a reliable method of contraception with a failure rate less than 1% per year (oral hormonal contraceptive, implant, vaginal hormone ring, or intrauterine system [IUS], (abstinence will not be considered as a reliable method of contraception) from screening until one month after end of study drug treatment.

⁵ A woman is considered to have childbearing potential unless she meets at least one of the following criteria:

- previous bilateral salpingo-oophorectomy or hysterectomy
- premature ovarian failure confirmed by a specialist gynecologist
- pre-pubescence, XY genotype, Turner syndrome, uterine agenesis
- age > 50 years and not treated with any kind of hormone replacement therapy for at least 2 years prior to screening, with amenorrhea for at least 24 consecutive months prior to screening.

⁶ If patient is > 50 years of age, results of recent pulmonary function tests ventilation/perfusion lung scan and an echocardiogram should be available to support IPAH/HPAH diagnosis

4. Documented hemodynamic diagnosis of PAH by right heart catheterization – performed at any time prior to Screening showing:
 - Resting mean pulmonary arterial pressure (mPAP) > 25 mmHg
and
 - Resting pulmonary vascular resistance (PVR) > 240 dyn·s·cm⁻⁵
and
 - Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVDEP) ≤ 15 mmHg (if available).
5. 6-minute walk distance between 50 and 450 m (inclusive) at Screening (within 2 weeks prior to the Baseline Visit and on a different day than this visit). This distance must be confirmed by a second 6MWT at the Baseline Visit. The value of the second 6MWD should be within ± 10% of the first assessment at Screening.
6. Patients who are able and willing to refrain from sunbathing, prolonged sun exposure and artificial sunlight exposure like solarium use or UVA/UVB treatment, and to limit skin and eye exposure to sunlight using appropriate precautions (clothing, sunscreen and sunglasses) from the first dose until 14 days after study drug discontinuation.

3.2.3 Exclusion criteria

Patients will not be entered into the study if they meet any of the following criteria:

1. Patients with pulmonary hypertension (PH) in the updated Dana Point Clinical Classification Groups 2–5, and PAH Group 1 subgroups that are not covered by the inclusion criteria.
2. Patients who have received prostacyclin (epoprostenol) or prostacyclin analogs (i.e., treprostinil, iloprost, beraprost) within one month before Baseline Visit, or are scheduled to receive any of these compounds during the trial.
3. Patients with moderate or severe obstructive lung disease: FEV₁/FVC < 70% and FEV₁ < 65% of predicted value after bronchodilator administration.
4. Patients with moderate or severe restrictive lung disease: Total Lung Capacity < 60% of predicted value.
5. Patients with moderate or severe hepatic impairment (Child-Pugh B and C).
6. Patients with documented left ventricular dysfunction (e.g., ejection fraction < 35%)
7. Patients with severe renal insufficiency (estimated creatinine clearance < 30 mL/min, or serum creatinine > 2.5 mg/dL).
8. Patients with BMI < 18.5 kg/m².
9. Patients who are receiving or have been receiving any investigational drugs within 1 month before the Baseline Visit.

10. Acute or chronic impairment (other than dyspnea), limiting the ability to comply with study requirements, in particular with 6MWT (e.g., angina pectoris, claudication, musculoskeletal disorder, need for walking aids).
11. Recently conducted (the program must be completed at least 8 weeks prior to screening) or planned cardio-pulmonary rehabilitation program based on exercise training
12. Psychotic, addictive or other disorder limiting the ability to provide informed consent or to comply with study requirements.
13. Life expectancy less than 12 months.
14. Females who are lactating or pregnant (positive pre-randomization serum pregnancy test) or plan to become pregnant during the study.
15. Known hypersensitivity to any of the excipients of the drug formulations.

3.2.4 Concomitant medications

3.2.4.1 Allowed concomitant medications

Approved endothelin receptor antagonists (ERAs) and/or phosphodiesterase type-5 (PDE-5) inhibitors are permitted for the treatment of PAH. The dose must be stable for at least 1 month prior to Baseline Visit and until Week 16. After Week 16, any change of dose must be recorded in the Case Report Form (CRF).

3.2.4.2 Prohibited concomitant medications

- Due to the fact that ACT-293987 and its active metabolite, ACT-333679, are IP receptor agonists, prostacyclin (epoprostenol) and prostacyclin analogs (i.e., treprostinil, iloprost, beraprost) are prohibited from 1 month prior to Baseline until EOS visit.
- Any investigational drug other than the study drug is prohibited from 1 month prior to Baseline until EOS or EOTE.

Introduction of new treatment for PAH (or increasing the dose) without adjudicated clinical worsening of PAH is strongly discouraged during the study period.

3.3 Study drugs

The study drugs are the investigational drug ACT-293987, and matching placebo.

3.3.1 Investigational drug and matching placebo

Patients who meet all inclusion criteria and none of the exclusion criteria will receive ACT-293987 or matching placebo.

- The study drug will be provided by the sponsor in child-proof bottles containing 120 tablets which must not be stored above 25 °C and must be protected from moisture.
- The study drug is to be administered orally (p.o.) in tablets of 200 µg ACT-293987 or matching placebo.
- The dose regimen is b.i.d. (twice daily) with an interval of approximately 12 hours.
- Depending on the MTD of the patient, a single dose will consist of 1 to 8 tablets (200 to 1,600 µg) of investigational drug or placebo.
- The MTD of an individual patient will be determined after a 12 weeks up-titration phase, and kept stable at least until the Week 16 assessment of the secondary endpoint [as described in Section 3.3.2]. After Week 16, the investigator will be allowed to further increase the dose if needed (only at scheduled visits and up to the maximum of 1,600 µg b.i.d.) by 200 µg b.i.d. increments. Dose reduction may occur at anytime if the investigator identifies a tolerability concern for a patient
- Due to the fact that this study drug must be up-titrated in order to reach an individual MTD, any interruption of study drug intake of 3 days or more will require a new up-titration [see Section 3.4.1].

3.3.2 Study drug up-titration

The study drug must be up-titrated to each individual patient's MTD in the range of 200 µg to 1,600 µg b.i.d.

Patients will start with one tablet of ACT-293987 (200 µg) in the evening of Day 1 and with 200 µg b.i.d. on Day 2. If this dose is well tolerated, the dose will be up-titrated by the investigator in 200 µg b.i.d. increments at weekly intervals during scheduled telephone calls or visits until reaching the patient's MTD.

The decision to not further up-titrate the dose will be based on the investigator's medical judgment based on the occurrence and severity of typical pharmacological effects of IP-receptor agonists, such as headache, jaw pain, myalgia, flushing and nausea, that cannot be tolerated by the patient.

The dose will then be reduced by 200 µg b.i.d., and this adjusted dose will be defined as the MTD.

At Week 12 (scheduled phone call), the MTD for each patient will be determined: this dose must be kept stable for the next 4 weeks (from Week 12 on) until the Week 16 (Visit 4) assessment of the secondary endpoint, change in 6MWD.

After Week 16, investigators will be allowed to titrate the dose of the patient further if needed (up to the maximum of 1,600 µg b.i.d.) by 200 µg b.i.d., and only at scheduled visits. All titrations must be documented in the CRF.

3.3.3 Study drug dosing scheme

Table 2 Dosing scheme

Period	Duration	Dose regimen	
First dose	Day 1 in the evening (p.m.)	200 µg	1 tablet
Up-titration	Day 2 a.m. to Day 8 a.m.	200 µg b.i.d.	1 tablet b.i.d.
	Day 8 p.m. to Day 15 a.m.	400 µg b.i.d.*	2 tablets b.i.d.
	Day 15 p.m. to Day 22 a.m.	600 µg b.i.d. *	3 tablets b.i.d.
	Day 22 p.m. to Week 4 p.m.	800 µg b.i.d. *	4 tablets b.i.d.
	Week 4 p.m. to Week 5 a.m.	1000 µg b.i.d. *	5 tablets b.i.d.
	Week 5 p.m. to Week 6 a.m.	1200 µg b.i.d. *	6 tablets b.i.d.
	Week 6 p.m. to Week 7 a.m.	1400 µg b.i.d. *	7 tablets b.i.d.
	Week 7 p.m. to Week 12 a.m.	1,600 µg b.i.d. *	8 tablets b.i.d.
Maintenance	From Week 12 throughout the study	Max. tolerated dose: 200–1,600 µg b.i.d.	1–8 tablets b.i.d.

* Or the highest tolerated dose until Week 12.

At the beginning of each up-titration phase, patients will be recommended to take the first dose in the evening in order to reduce the likelihood of the occurrence of headache, jaw pain, flushing, and nausea. The study drug should be taken with food.

Beginning with the morning of Visit 2, and at each visit thereafter, patients must not take the morning dose before completion of the CAMPHOR questionnaire (when applicable), the 6MWT (when applicable) and the blood samplings. In addition, at Week 16 a post-dose blood sampling will be taken for PK analysis.

3.4 Study drug discontinuation and study withdrawal

3.4.1 Study drug interruption or discontinuation

The investigator must interrupt or permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the patient.

The interruption or premature discontinuation of study drug might be triggered by an AE, a diagnostic or therapeutic procedure, an abnormal assessment (e.g., ECG or laboratory abnormalities), or for administrative reasons (in particular withdrawal of the patient's consent). The reason for study drug interruption or premature discontinuation must be documented in the CRF.

Study drug must be permanently discontinued when a clinical worsening event is adjudicated by the CEC. The patient must perform the EOS visit and will be called at Study Closure for ascertaining vital status.

Any study drug interruption of 3 days or more will require new up-titration. Patients will start with one tablet of ACT-293987 (200 µg) b.i.d. If this dose is well tolerated, the dose will be up-titrated by the investigator in 200 µg increments up to the patient's maximum dose achieved before study drug interruption. The frequency of dose increment will be based on the medical judgment of the investigator, considering patient's tolerability to study drug prior to its interruption.

Interruptions of 1 day or more must be recorded on the study drug log in the CRF.

3.4.2 Patient's follow-up after study drug discontinuation

In the event of premature permanent discontinuation of study drug, patients must have an EOS visit. Patients will be followed up for SAEs for 30 days after study drug discontinuation or until the first dose of ACT-293987 in the open-label study. In addition, patients will be contacted at the time of Study Closure (approximately 3.5 years after study initiation) for vital status assessment.

3.4.3 Study withdrawal

A patient will be considered as withdrawn from the study if, and only if, he/she is lost to follow-up after exhausting all means of contact.

The potential follow-up of patients after their withdrawal of consent will depend upon local regulations or specific agreement with the patients.

3.4.4 Replacement policy

3.4.4.1 Patients

Patients who prematurely discontinue from the study drug for any reason will not be replaced.

3.4.4.2 Centers

To ensure the successful completion of the study, the sponsor may wish to replace centers which have no patient enrollment. Centers not able to recruit any patients within 3 months of study initiation will be considered for closure.

3.5 Treatment exposure and compliance

Records of study drug used, dosages administered, and intervals between visits are to be kept during the study. Study drug accountability is to be performed on an ongoing basis by the study staff and checked by the monitor during site visits and at the completion of the study. Patients are to be asked to return all unused study drug at each visit.

3.6 Treatment assignment and blinding

3.6.1 Treatment assignment

Both randomization and drug packaging are performed by independent Contract Research Organizations (CROs) ICON (see contact details on page 2) and Creapharm, respectively.

Patients will be randomized to one of the treatment groups using a centralized randomization system via the Interactive Web/Voice Response System (IWRS/IVRS). A unique randomization number will be assigned to each patient (patient randomization number). Further details are provided in the IWRS/IVRS specification document and study-specific IWRS/IVRS user manual.

The randomization code must be kept strictly confidential, and accessible only to authorized persons who are not involved in the conduct and analysis of the study, until time of unblinding. A sealed randomization code is kept by Actelion Global Quality Management in a safe cabinet. A second set will be provided to the statistician of the DMC.

The randomization code will be unblinded/broken and made available for data analysis only after Study Closure, i.e., when the study has been completed, the protocol deviations determined and the clinical database declared complete, accurate and locked.

3.6.2 Blinding

This study is performed in a double-blind fashion. The investigator and study staff, the patients, the monitors, and the sponsor staff will remain blinded to the treatment until study closure. The investigational drug and its matching placebo are indistinguishable and all patient kits will be packaged in the same way.

At regular intervals an independent DMC will review unblinded safety and tolerability data to ensure patient safety. In order not to unblind data for the above individuals, an independent statistician will prepare data tables for the DMC.

3.6.3 Emergency procedure for unblinding

The investigator and the study staff must remain blinded to the patient's treatment assignment, even if the patient refuses to participate in any study procedures or experiences an AE, or if the patient dies. The identity of the study drug may be revealed only if the patient experiences a medical emergency whose management would be improved by the knowledge of the blinded treatment assignment. In this case, emergency unblinding will be performed via IWRS/IVRS. A back-up system for code breaking will be put in place to ensure that this procedure remains possible, even if the IWRS fails.

The occurrence of any code break during the study must be clearly justified and explained by the investigator. Before breaking the code via the IWRS, every attempt must be made by the investigator to discuss the intended code break with the sponsor. In all cases, the sponsor must be informed as soon as possible before or after the code break.

Any code break must be documented in a detailed report with the date and time of the code break, and signed by the investigator. This report is to be attached to the CRF.

3.7 Study drug packaging and labeling

3.7.1 Study drug packaging

The sponsor will provide study drug or matching placebo as tablets in child-proof bottles containing 120 tablets.

3.7.2 Study drug labeling

The labeling and packaging of ACT-293987 and matching placebo will be conducted according to Good Manufacturing Practice, Good Clinical Practice, and any local or national regulatory requirements.

3.7.3 Study drug storage and dispensing

The investigator is responsible for safe and proper handling and storage of the study drug at the investigational site, and for ensuring that the study drug is administered only to patients enrolled in the study and in accordance with the protocol.

Study drug must be kept in a locked cabinet or room, which can be accessed only by the pharmacist, the investigator, or another duly designated person. The study drug must not be stored above 25 °C and must be protected from moisture. The study centers will be supplied with study drug according to each center's needs, depending on the rate of patient enrollment. Each center will have an individual stock of study drug, which will be re-supplied continuously as soon as a predefined minimum level of study drug has been reached.

Patients will receive child-proof bottles with 120 tablets each at Visit 1 (Randomization, Day 1), Visit 2 (Week 4), Visit 3 (Week 8), Visit 4 (Week 16), Visit 5 (Month 6) and at the 6-monthly visits thereafter up to the EOS visit. The patient will receive the amount of study medication at each of these visits needed to supply enough medication for the time interval between the visits.

Each bottle will have a label with a tear-off part specifying the study protocol number and the bottle number. When the medication is issued to the patient, the investigator or pharmacist (if applicable) must remove the tear-off part and attach it to the Drug Dispensing Log.

3.8 Study endpoints

3.8.1 Efficacy endpoints

3.8.1.1 *Primary efficacy endpoints*

The primary endpoint in this study is time to first clinical worsening up to 7 days after last study drug intake, defined as time from Baseline to the first of the following events:

- Death (all-cause mortality)
or
- Hospitalization for worsening of PAH based on predefined criteria
or
- Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy
or
- Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH
or

- Disease progression (patients in modified NYHA/WHO functional class II-III at baseline) confirmed by :
 - decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) **and**
 - worsening of NYHA/WHO functional class**or**
- Disease progression (patients in NYHA/WHO functional class III-IV at baseline) confirmed by :
 - decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) **and**
 - need for additional PAH specific therapy.

The endpoint “Time to first clinical worsening up to 7 days after last study drug intake” is derived from the date of the clinical worsening event up to 7 days after the actual last study drug intake reported in the CRF during the Treatment period.

Clinical worsening events will be adjudicated in a blinded fashion by an independent CEC.

3.8.1.2 Secondary efficacy endpoints

- Change from Baseline to Week 16 in 6MWD at trough.
- Absence of worsening from Baseline to Week 16 in modified NYHA/WHO functional class.
- Change from Baseline to Week 16 in Borg dyspnea index.
- Time to death up to Study Closure.
- Change from Baseline to Week 16 in the sub-scale ‘Breathlessness’ of the ‘Symptoms’ score in the CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) questionnaire (at selected centers).
- Change from Baseline to Week 16 in the ‘Symptoms’ score of the CAMPHOR questionnaire (at selected centers).

The endpoints “Change from Baseline to Week 16 in 6MWD”, “Absence of worsening from Baseline to Week 16 in modified NYHA/WHO functional class” and “Change from Baseline to Week 16 in Borg dyspnea index” are derived from the assessments at Baseline and at Week 16.

The endpoints “Change from Baseline to Week 16 in the sub-scale ‘Breathlessness’ of the ‘Symptoms score’ in the CAMPHOR questionnaire” and “Change from Baseline to Week 16 in the ‘Symptoms’ score of the CAMPHOR questionnaire” are derived from the assessments of the CAMPHOR questionnaire at Baseline and at Week 16 evaluated at selected centers.

3.8.1.3 Exploratory efficacy endpoints

- Time to death and to selected combinations of the adjudicated components of clinical worsening up to 7 days after the day of the last study drug intake:
 - Death
 - Death, or hospitalization for worsening of PAH
 - Death, or hospitalization for worsening of PAH, or worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy
 - Death, or hospitalization for worsening of PAH, or worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy, or worsening of PAH resulting in initiating parenteral prostanoid therapy or chronic oxygen therapy
 - Death, or hospitalization for worsening of PAH, or worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy, or worsening of PAH resulting in initiating parenteral prostanoid therapy or chronic oxygen therapy, or disease progression

The date of the “last study drug intake” refers to the date of the actual last study drug intake reported in the CRF during the Treatment period.

- Change from Baseline to EOS in 6MWD measured at trough.
- Change from Baseline to EOS in Borg dyspnea index.
- Change from Baseline to EOS in modified NYHA/WHO functional class.
- Change from Baseline to EOS in plasma NT pro-brain natriuretic peptide (NT pro-BNP).
- Change from Baseline to EOS in the sub-scale ‘Breathlessness’ of the ‘Symptoms’ score in the CAMPHOR questionnaire (at selected centers).
- Change from Baseline to EOS in the ‘Symptoms’ score of the CAMPHOR questionnaire (at selected centers).

The endpoint “Time to death and to selected combinations of the adjudicated components of clinical worsening up to 7 days after the last study drug intake” is derived from the date of the clinical worsening event up to 7 days after the actual last study drug intake reported in the CRF during the Treatment period. For each component, the first adjudicated clinical worsening event of the patient will be considered for the analysis.

3.8.1.4 Imputation methods for efficacy endpoints

No imputation method will be used for the primary endpoint, due to its nature.

If there is a missing assessment (e.g., no confirmatory 6MWT, modified NYHA/WHO functional class) for a clinical worsening event, the CEC will be responsible for qualifying or disqualifying this event for the analysis of the primary endpoint.

Patients without a clinical worsening event will be censored 7 days after study treatment discontinuation.

3.8.1.4.1 Imputation methods for the secondary efficacy endpoints

If there are missing values at Week 16 for 6MWD, modified NYHA/WHO functional class, Borg dyspnea index, or CAMPHOR scores, the last valid post-baseline value before Week 16 is carried forward in substitution of the missing values unless one of the following applies:

- If the patient experiences a mortality event before Week 16: “0” meters for the 6MWD or the worst value⁵ for the other parameters are used to replace the missing values.
- If the patient is alive but otherwise experienced clinical worsening adjudicated by the CEC before Week 16 (as defined in Section 3.8.1.1), the worst value⁵ is used to replace the missing values.

Patients for whom no post-Baseline value is available after applying these substitution rules will be excluded from the analysis of this endpoint, assuming that the unavailability of the data can be attributed to a random unknown mechanism that is independent of the treatment.

For time to death up to Study Closure, patients without the event will be censored at the last available date, either the date of last contact or the date of the EOS visit.

⁵For the 6MWD, the patient’s worst value is his/her Baseline value corrected with the highest change of worsening from Baseline observed between all patients belonging to the relevant analysis set for the 6MWD. If the result is smaller than “0”, “0” meters is substituted. For the modified NYHA/WHO functional class or Borg dyspnea index, the worst value between all patients belonging to the relevant analysis set is substituted for the missing values.

If there are missing scores at Week 16 for the CAMPHOR questionnaire, the worst value for the scores is substituted for the missing values. The patient’s worst value is his/her Baseline value corrected with the highest change of worsening from Baseline observed between all patients belonging to the relevant analysis set. If the result is smaller than “0”, “0” is substituted

3.8.1.4.2 Imputation methods for the exploratory efficacy endpoints

If there are missing values at EOS for 6MWD, modified NYHA/WHO functional class, or Borg dyspnea index or CAMPHOR scores, the last valid post-baseline value before EOS is carried forward in substitution of the missing values unless one of the following applies:

- If the patient experiences a mortality event before EOS: “0” meters for the 6MWD or the worst value⁵ for the other parameters are used to replace the missing values.
- If the patient is alive but otherwise experienced clinical worsening adjudicated by the CEC before EOS (as defined in Section 3.8.1.1), the worst value⁵ is used to replace the missing values.

If there are missing plasma NT pro-BNP values, the last valid post-baseline value before EOS is carried forward.

For the time to death and to selected combinations of the adjudicated components of clinical worsening up to EOS, patients without an event will be censored 7 days after study treatment discontinuation.

3.8.2 Safety and tolerability endpoints

Except where otherwise specified, the last valid post-baseline value is carried forward in substitution for the missing values.

- Treatment-emergent AEs up to 7 days after last study drug intake.
- Adverse events leading to premature discontinuation of study drug.
- Treatment-emergent SAEs until 7 days after last study drug intake.
- Treatment-emergent ECG abnormalities up to 7 days after last study drug intake
- Treatment-emergent marked laboratory abnormalities up to 7 days after last study drug intake. Marked laboratory abnormalities are defined in the sponsor’s internal guidelines and will be assessed for the laboratory parameters described in Section 3.9.2.5.
- Change from Baseline to EOS in vital signs.
- Change from Baseline to EOS in bone turnover markers.
- For patients who prematurely discontinue due to an adjudicated clinical worsening event, and who continue in the open-label study, the treatment-emergent AEs, ECGs and marked laboratory abnormalities will be counted until last study drug intake during the Treatment period.
- EOS will be derived from the date of EOS visit as recorded in the CRF.

3.8.3 Pharmacoeconomic endpoints

- Number per year of all-cause and PAH-related hospitalizations from Baseline to EOS.
- Number per year of in-patient hospital days for all causes and PAH-related causes from Baseline to EOS.

3.8.4 Pharmacokinetic and pharmacodynamic endpoints

- Trough plasma concentrations of ACT-293987, ACT-333679 and other potential metabolites at Baseline, Week 4, Week 8, Week 16, Week 26 (Month 6), Week 52 (Month 12), and EOS.
- Plasma concentrations of ACT-293987, ACT-333679 and other potential metabolites will be evaluated by PK sampling at specific time intervals after drug administration at Week 16.
- The relationship between ACT-293987/ACT-333679 plasma levels and clinical endpoints and the effects of ACT-293987 on plasma NT pro-BNP levels.

3.9 Study assessments

When applicable, the patient must perform the specified assessments in the following order:

1. CAMPHOR questionnaire (at selected sites)
2. 6MWT / Borg dyspnea index

Beginning with the morning of Visit 2, and at each visit thereafter, patients must not take the morning dose before the completion of the CAMPHOR questionnaire (when applicable), the 6MWT (when applicable) and the blood samplings. In addition, at Week 16 a post-dose blood sampling will be taken for PK analysis.

3.9.1 Efficacy assessments

3.9.1.1 6MWT and Borg dyspnea index

The 6MWT is recorded at Screening, Baseline, Week 8, Week 16, Month 6, and every 6 months thereafter, at EOS visit, and also if there is a suspected clinical worsening event. It is a non-encouraged test, which measures the distance covered by the patient during a 6-minute walk [[Appendix 1](#)]. After Baseline, the 6MWT must be performed at trough (i.e., 12 h post dose).

The Borg dyspnea index is recorded after each 6MWT. The index rates dyspnea severity on a scale from '0' to '10' [[Appendix 2](#)].

3.9.1.2 Clinical worsening events

Clinical worsening events are recorded for the premature discontinuations, up to 7 days after the day of the last study drug intake during the treatment period, or up to 7 days after the EOS visit for patients still on study drug at study closure.

3.9.1.3 Modified NYHA/WHO functional class

Modified NYHA/WHO functional class [\[Appendix 3\]](#) is recorded at Screening, Baseline, Week 4, Week 8, Week 16, Month 6, and every 6 months thereafter, at EOS and if there is a clinical worsening event.

3.9.1.4 Vital status

Vital status is recorded at Study Closure regardless of whether the patient has prematurely discontinued study drug or not.

3.9.2 Safety and tolerability assessments

The definitions, reporting, and follow-up of AEs, SAEs, and potential pregnancies are described in Section [4](#).

3.9.2.1 CAMPHOR questionnaire

At selected sites, the CAMPHOR questionnaire is completed by the patient at Baseline, Week 16, Month 12, Month 24, and EOS [\[Appendix 4\]](#).

The questionnaire consists of three domains (Symptoms, Activities and Quality of Life) with 25, 15 and 25 negatively-weighted items respectively. The 25-item Symptoms score includes the Energy, Breathlessness, and Mood subscales, with 10, 8 and 7 items, respectively [\[McKenna 2006\]](#).

Details about self-administration of the CAMPHOR questionnaire can be found in the CAMPHOR manual provided to the investigator.

3.9.2.2 Vital signs

Vital signs (blood pressure and heart rate) are recorded at Screening, Baseline, Week 4, Week 8, Week 16, Month 6 and every 6 months thereafter, and at EOS. Vital signs are also recorded if there is a suspected clinical worsening event.

Blood pressure (systolic and diastolic) and heart rate will be measured non-invasively in a sitting position. The patient should rest for 5 minutes before measurement of blood pressure and heart rate. The right or the left arm may be used. However, the arm used for measurement should be kept constant throughout the study for an individual patient.

3.9.2.3 Weight and height

Height is recorded at Screening only and weight is measured and recorded at every visit until EOS, and if there is a suspected clinical worsening event.

3.9.2.4 Physical examination

Physical examination (i.e., inspection, percussion, palpation and auscultation) is performed at Screening, Baseline Visit, Week 4, Week 8, Week 16, Month 6 and every 6 months thereafter, at EOS, and if there is a suspected clinical worsening event. Clinically-relevant findings that are present prior to study drug initiation must be recorded on the relevant Medical History CRF page. Clinically-relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be documented in the patient's medical records and recorded on an AE page of the CRF.

3.9.2.5 Laboratory assessments**□ Type of laboratory**

A central laboratory (see contact details on [page 2](#)) will be used for blood chemistry and hematology tests. Pregnancy tests (serum and urine) will be performed locally, and serum pregnancy test will also be performed centrally. The screening laboratory tests may be performed locally to assess patient eligibility.

Laboratory reports will be available to the investigator. Clinically significant marked laboratory abnormalities must be reported by the investigator as an AE/SAE, as appropriate.

Details about collection and shipment of samples, and the reporting of results and abnormalities, can be found in the laboratory manual provided to the investigator.

□ Laboratory parameters**• Hematology and blood chemistry**

Hematology and blood chemistry tests are performed at Screening, Baseline, Week 4, Week 8, Week 16, Month 6 and every 6 months thereafter, EOS, and if there is a suspected clinical worsening event. They include hemoglobin, hematocrit, counts of platelets, leukocytes and erythrocytes, liver aminotransferases (AST/ALT), alkaline phosphatase, total and direct bilirubin, creatinine, urea, glucose, sodium, potassium and albumin, bone markers (bone alkaline phosphatase and carboxy-terminal telopeptide (CTx)).

- **Pregnancy test**

A serum pregnancy test for women of childbearing potential must be performed at Screening. Thereafter, urine pregnancy tests should be performed monthly up to at least 1 month after study drug discontinuation. Urine pregnancy tests are either performed during a scheduled visit or at home with the pregnancy test kit provided to the patient from Visit 3 onwards.

Results of pregnancy tests will not be recorded in the CRF but must be recorded in the patient's records.

3.9.2.6 ECG

A standard 12-lead ECG is performed at Baseline, Week 4, Week 8, Week 16, Month 6 and every 6 months thereafter, EOS and if there is a suspected clinical worsening event. The patient should rest for at least 5 minutes prior to the recording, and should be in a supine position during the recording.

Clinically-relevant ECG findings that are present prior to the initiation of study drug must be documented in the Medical History section of the CRF.

Clinically-relevant ECG findings found after the study drug initiation that were not present at Screening or that worsened during the study must be reported as an AE [see Section 4.2] as appropriate.

A central ECG service (see contact details on page 2) will be used for ECG evaluation.

Details about collection of ECG data, and the reporting of results and abnormalities, can be found in the ECG manual provided to the investigator.

3.9.3 Pharmacokinetic and pharmacodynamic assessments

3.9.3.1 Pharmacokinetic assessments

Pharmacokinetic samples will be collected during this study for all patients, in order to provide information about the concentration of the drug and the active metabolite over time in the target population. Trough plasma concentrations of ACT-293987, ACT-333679, and other potential metabolites will be measured at Visit 1 (Baseline) and before the morning dose at Visits 2–6, and at EOS. One additional PK sample will be taken from each patient at Visit 4 (Week 16) within a defined time-window. This will allow characterization of the time-course of ACT-293987 and ACT-333679. Further, the relationships between plasma concentrations of ACT-293987 and ACT-333679 and changes in efficacy and safety parameters will be evaluated.

□ **Timing for sampling**

For each patient, eight blood samples will be drawn: trough plasma concentrations of ACT-293987, ACT-333679 and other metabolites will be evaluated by PK sampling at Baseline, Weeks 4, 8, and 16, Month 6, Month 12, and EOS, and at specified time intervals after drug administration of either 0.5 to 1h, 1 to 2h, 2 to 4h, 4 to 6h, 6 to 8h, and at 8 to 12h (due to b.i.d. dosing) during the dosing interval at Week 16. If for any reason the blood sample cannot be taken as recommended, the sample should be taken pre-dose in the morning within 1 week after the scheduled visit.

If the 8 to 12h time-window falls too late in the evening, the patient can come 1–2 days later 8–12 hours after the morning dose; however the blood sample must be taken before the evening dose.

□ **Procedures for sampling**

For the PK sample at Visit 1 and the PK samples at trough at Visits 2–6, about 5 mL of blood will be collected in lithium heparin vacutainers, via either direct venipuncture or an indwelling cannula. For the additional post-dose PK samples at Visit 4, about 5 mL of blood will be collected in lithium heparin vacutainers, via either direct venipuncture or an indwelling cannula. Detailed instructions for the collection, preparation, labeling, storage, and shipment of the plasma samples can be found in the laboratory manual provided to the investigator. The samples must be stored at $-25\text{ }^{\circ}\text{C} \pm 5\text{ }^{\circ}\text{C}$ or $-80\text{ }^{\circ}\text{C}$, and need to be analyzed before the 210-day expiry period.

Importantly, blood samples should be drawn before the morning dose of study drug is administered.

The actual date and clock times of drug intake and withdrawal of each blood sample are to be entered in the CRF.

Details on the assignment of the patient to a defined time-window are described in the site-guideline provided to the investigator.

□ **Bioanalysis**

The concentrations of ACT-293987, ACT-333679 and other potential metabolites will be determined using a validated LC-MS/MS assay. The foreseen limit of quantification (LOQ) for both analytes is 0.01 ng/mL. Concentrations will be calculated by interpolation from a calibration curve. Quality control (QC) samples will be used to determine between-run and overall precision and accuracy of the analysis.

□ Shipping procedures

The site staff will be responsible for the shipment of the samples. Samples must be sent to the central laboratory, Quest (see contact details page 2) at time intervals as defined in the laboratory manual. The samples, together with the completed shipment forms, must be packed securely in polystyrene insulated shipping containers containing enough dry ice to last for 48 h. The central laboratory will ensure subsequent shipment of the PK samples to SwissBioQuant AG.

3.9.3.2 Pharmacodynamic assessment (Plasma NT pro-BNP)

Plasma NT pro-BNP samples will be collected at Baseline, Week 4, Week 8, Week 16, Month 6 and every 6 months thereafter, and at EOS.

□ Procedures for sampling

About 6 mL of venous blood will be collected into chilled lithium heparin vacutainers, via either direct venipuncture or an indwelling cannula. Detailed instructions for the preparation, labeling, storage, and shipment of the plasma samples can be found in the laboratory manual provided to the investigator. The samples must be stored at -20 °C or -80 °C.

The actual date and clock time of withdrawal of each blood sample is to be entered in the CRF.

□ Shipping procedures

The site staff will be responsible for the shipment of the samples. Samples must be sent to the central laboratory, Quest (see contact details page 2) at time intervals as defined in the laboratory manual. The samples, together with the completed shipment forms, must be packed securely in polystyrene insulated shipping containers containing enough dry ice to last for 48 h.

3.9.4 Baseline parameters and concomitant medications**3.9.4.1 Baseline demographics and disease characteristics**

The following characteristics are to be recorded in the CRF at the Screening Visit:

- Medical history (previous and ongoing clinically-significant diseases).
- Etiology of PAH, date of diagnosis of PAH by right heart catheterization, modified NYHA/WHO functional class, 6MWD and Borg dyspnea index.
- Age, gender, race, height, and weight.
- Vital signs (blood pressure and heart rate).

3.9.4.2 Concomitant medications

PAH therapy (ongoing, initiated, discontinued) and diuretic therapy taken in the period between 3 months prior to Randomization (Baseline Visit) and up to EOS will be recorded on the Concomitant Medication pages of the CRF. Any dose changes on PAH therapy must be recorded in the CRF.

All other concomitant medications taken in the period between Randomization and EOS will also be recorded on the Concomitant Medication pages of the CRF.

3.10 Visit and assessment schedule

For a tabulated summary of all visits and assessments described in the following section, see [Table 1](#).

3.10.1 Screening period

3.10.1.1 Screening visit

The Screening Visit should be performed no more than 28 days prior to Randomization.

It is the responsibility of the investigator to obtain written informed consent from each patient participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

The informed consent form (ICF) must be signed and dated at the latest during the Screening Visit prior to the execution of any study assessment or procedure.

The Screening Visit includes:

- Patient information and consent form signature
- Demographics
- Medical history
- Concomitant medications
- Vital signs
- Height and body weight
- Physical examination
- NYHA/WHO functional class
- 6MWT and Borg dyspnea index (within 14 days prior to Visit 1)
- Complete laboratory tests including:
 - Hematology
 - Blood chemistry
 - Serum pregnancy test (for women of childbearing potential)

The investigator must check all the inclusion/exclusion criteria and decide on the patient's eligibility for the study.

3.10.2 Treatment period

From the start of treatment up to 7 days after the last study drug intake during the treatment period, clinical worsening events will be reported in the event pages of the CRF and as SAEs, if applicable.

For women of childbearing potential, a urine pregnancy test will be assessed monthly after initiation of study medication.

Beginning with the morning of Visit 2, and at each visit thereafter, patients must not take the morning dose before completion of the CAMPHOR questionnaire (when applicable), the 6MWT (when applicable) and the blood samplings. In addition, at Week 16 a post-dose blood sampling will be taken for PK analysis.

3.10.2.1 Baseline/Randomization Visit (Visit 1)

Visit 1 is the start of the observation and treatment period for patients who are eligible.

- Medical history
- CAMPHOR questionnaire (at selected sites)
- Concomitant medications
- Weight
- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG
- 6MWT and Borg dyspnea index
- Pregnancy test for women of childbearing potential
- Blood sampling for hematology, biochemistry and plasma NT pro-BNP
- Blood sampling for PK
- SAEs, only if related to study-mandated procedures
- Randomization and dispensing of study drug (ACT-293987 or matching placebo tablets) for 4 weeks

3.10.2.2 Week 1 (telephone call)

- Recording of AEs/SAEs
- Titration to next dose (2 tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.3 Week 2 (telephone call)

- Recording of AEs/SAEs
- Titration to next dose (3 tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.4 Week 3 (telephone call)

- Recording of AEs/SAEs
- Titration to next dose (4 tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.5 Visit 2 (Week 4)

- Concomitant medications
- Weight
- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG
- Pregnancy test for women of childbearing potential
- Blood sampling for hematology, biochemistry and plasma NT pro-BNP
- Blood trough sampling for PK
- AEs/SAEs
- Return of unused medications including empty bottles, drug accountability
- Dispensing of study drug (ACT-293987 or matching placebo tablets) for 4 weeks
- Titration to next dose (five tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.6 Week 5 (telephone call)

- Recording of AEs/SAEs
- Titration to next dose (six tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.7 Week 6 (telephone call)

- Recording of AEs/SAEs
- Titration to next dose (seven tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.8 Week 7 (telephone call)

- Recording of AEs/SAEs
- Titration to next dose (eight tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.9 Visit 3 (Week 8)

- Concomitant medications
- Weight
- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG
- 6MWT measured at trough and Borg dyspnea index
- Pregnancy test for women of childbearing potential
- Blood sampling for hematology, biochemistry and plasma NT-pro-BNP
- Blood trough sampling for PK
- AEs/SAEs
- Return of unused medications including empty bottles, drug accountability
- Dispensing of study drug (ACT-293987 or matching placebo tablets) for 8 weeks

3.10.2.10 Week 12 (telephone call)

- Recording of AEs/SAEs
- Confirmation of MTD
- Pregnancy test result for women of childbearing potential (patient to perform pregnancy test at home with validated kit provided by the site)

3.10.2.11 Visit 4 (Week 16)

- CAMPHOR questionnaire (at selected sites)
- Concomitant medications
- Weight
- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG
- 6MWT measured at trough (i.e., 12 hours post dose) and Borg dyspnea index
- Pregnancy test for women of childbearing potential
- Blood sampling for hematology, biochemistry and plasma NT pro-BNP
- Blood trough sampling for PK
- Recording of AEs/SAEs
- Blood post-dose sampling for PK within a defined time-window
- Return of unused medications including empty bottles, drug accountability
- Dispensing of study drug (ACT-293987 or matching placebo tablets) for 10 weeks

3.10.2.12 Visit 5 (Week 26)

- Concomitant medications
- Weight
- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG
- 6MWT measured at trough (i.e., 12 hours post dose) and Borg dyspnea index
- Pregnancy test for women of childbearing potential (patient to perform pregnancy test at home with validated kit provided by the site)
- Blood sampling for hematology, biochemistry and plasma NT pro-BNP
- Blood trough sampling for PK
- Recording of AEs/SAEs
- Return of unused medications including empty bottles, drug accountability
- Dispensing of study drug for 6 months

3.10.2.13 Visit 6 (and every 6 months thereafter)

- CAMPHOR questionnaire (at selected sites), only at Visit 6 (Month 12) and Visit 8 (Month 24)
- Concomitant medications
- Weight
- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG
- 6MWT measured at trough (i.e., 12 hours post dose) and Borg dyspnea index
- Pregnancy test for women of childbearing potential (patient to perform pregnancy test at home with validated kit provided by the site)
- Blood sampling for hematology, biochemistry and plasma NT pro-BNP
- Blood trough sampling for PK, at Visit 6 (Month 12) only
- Recording of AEs/SAEs
- Return of unused medications including empty bottles, drug accountability
- Dispensing of study drug (ACT-293987 or matching placebo tablets) for 6 months

3.10.2.14 Telephone call Month 9 (and every 6 months thereafter)

- Concomitant medications
- Recording of AEs/SAEs

3.10.2.15 Clinical Worsening Event (in case of suspected clinical worsening)

In the case of a suspected clinical worsening, the Clinical Worsening Event and corresponding AE pages in the CRF must be completed.

For a suspected clinical worsening, the assessments include:

- Concomitant medications
- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- Weight
- 12-lead ECG
- 6MWT, Borg dyspnea index
- Recording of AEs/SAEs

If there is an adjudicated clinical worsening of PAH (as defined in the primary endpoint of the study) by the CEC, the study medication must be permanently discontinued and the patient must have the EOS Visit. These patients will be offered entry into the open-label study AC-065A303/GRIPHON OL.

3.10.2.16 EOS Visit

The EOS Visit is performed in the case of a permanent discontinuation of study drug due to an AE, withdrawal of consent, or the clinical worsening of PAH, and for all patients still on study drug at the Study Closure [see Section [3.10.4](#)].

The EOS Visit assessments include:

- CAMPHOR questionnaire (at selected sites)
- Concomitant medications
- Blood trough sampling for PK
- Vital signs (blood pressure and heart rate)
- Weight
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG
- 6MWT measured at trough (i.e. 12h post dose) and Borg dyspnea index
- Pregnancy test (urine dipstick) for women of childbearing potential
- Blood sampling for hematology, biochemistry and plasma NT pro-BNP
- Recording of AEs/SAEs
- Return of unused medications including empty bottles, drug accountability

3.10.3 Follow-up period

3.10.3.1 30-day follow-up

All patients will be contacted by telephone 30 days after study drug discontinuation (Safety follow-up call).

An AE (whether serious or not) occurring up to 7 days after last study drug intake, should be reported in the CRF and in a SAE form, if applicable. The date of the “last study drug intake” refers, in case of premature discontinuation to the date of the actual last study drug intake reported in the CRF during the treatment period, or at study closure to the date of the EOS visit following the study closure..

All SAEs occurring up to 30 days after study drug discontinuation or until first dose of ACT 293987 in the open-label study must be reported in a SAE form.

Adverse events still ongoing 7 days after the study drug discontinuation must be followed up for 30 days after study drug discontinuation or until resolution or stabilization or until the event is otherwise explained.

Serious adverse events still ongoing at the End-of-Study visit must be followed up until resolution or stabilization, or until the event is otherwise explained.

3.10.4 Study closure

The Study Closure will be communicated by the sponsor once the overall target number of 202 clinical worsening events is achieved.

All patients on study drug should perform their EOS Visit assessments for this study within 2 weeks after Study Closure is communicated by the sponsor.

Patients who are on study drug at Study Closure will be offered entry into the open-label extension study AC-065A303/ GRIPHON OL.

For these patients, the treatment period will be extended from the EOS Visit until the sponsor is able to analyze the study results (database lock and unblinding). Then the End of Treatment Extension Visit will be performed and the patient transferred into the open-label study.

All patients who prematurely discontinue from the study and have their EOS Visit before Study Closure should be contacted by phone within 2 weeks of the Study Closure to assess their vital status. The potential follow-up of patients after their withdrawal of consent will depend on local regulations or specific agreement with the patients.

3.10.4.1 End of Treatment Extension Visit

Patients who are on study drug at Study Closure and are eligible to enter the open-label extension study AC-065A303/GRIPHON OL will be allowed to extend their double-blind treatment period after the EOS Visit until the study is unblinded. After unblinding, patients will perform the End of Treatment Extension Visit and then be transferred into the open-label study and can either continue taking active treatment on their individual MTD or start up-titration of active treatment if the assigned treatment in this study was placebo.

The End of Treatment Extension Visit assessments includes:

- Recording of new AEs/SAEs experienced since last visit (if applicable)
- Recording of the outcome and the resolution date of ongoing AEs at EOS visit, on specific CRF pages.
- Return of unused medications including empty bottles, drug accountability

4 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

4.1 Summary table

Periods	Screening	Treatment	Follow-up	After follow-up
Time frame	From signature of informed consent to study drug initiation	During study drug administration and until 3 days after last study drug administration	From 7 days to 30 days after study drug discontinuation or until the first dose of ACT-293987 in the open-label study.	After 30 days
AE/SAE reporting on CRF AE page	None	All AEs/SAEs (treatment-emergent ¹)	None	None
SAE reporting on SAE form	Only if related to study-mandated procedures	All SAEs (treatment-emergent ¹)	All SAEs	If felt appropriate by investigator
Clinical study report	Not applicable	Analyzed	Described	Might be described

¹ A treatment-emergent AE is any AE temporally associated with the use of study drug (from study drug initiation until 3 days after study drug discontinuation), whether or not considered related to the study drug.

The resolution date and outcome of all AEs that occurred during the double-blind study and are ongoing when the patient is entering the Treatment extension period must be recorded on specific CRF pages. If the AE is worsening, a new AE must be recorded on specific CRF pages of the treatment extension with the onset date equal to the date of worsening.

4.2 Adverse events

4.2.1 Definitions of adverse events

An AE is any adverse change from the patient's baseline condition, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease, that occurs during the course of the study, whether or not considered related to the study drug.

A treatment-emergent AE is any AE temporally associated with the use of a study drug (from study drug initiation until at 7 days after study drug discontinuation), whether or not considered related to the study drug.

Adverse events include:

- Exacerbation of a pre-existing disease
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study
- Lack of efficacy in the acute treatment of a life-threatening disease
- Events considered by the investigator to be related to study-mandated procedures
- Abnormal assessments, e.g., incident physical examination abnormalities, ECG findings, if they represent a clinically significant finding that was not present at baseline or worsened during the course of the study
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug

Adverse events do not include:

- Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
- Overdose of either study drug or concomitant medication without any signs or symptoms. However, overdose of study medication must be mentioned in the Study Drug Log.

4.2.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is reported on specific AE pages of the CRF.

If the intensity of an AE worsens during study drug administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

The three categories of intensity are defined as follows:

□ Mild

The event may be noticeable to the patient. It does not influence daily activities, and usually does not require intervention.

□ Moderate

The event may make the patient uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

□ Severe

The event may cause noticeable discomfort, and usually interferes with daily activities. The patient may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious [see Section 4.3.1]. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event (such as severe headache) may be of relatively minor medical significance and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39 °C that is not considered severe may become serious if it prolongs hospital discharge by a day [see Section 4.3.1.2]. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

These definitions do not apply to clinically significant and asymptomatic laboratory test abnormalities or abnormal assessments (e.g., ECG findings) considered as AEs. The investigator should tick “non-applicable” on the AE page of the CRF to qualify the intensity of the AE.

4.2.3 Relationship to study drug

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study drug, and reported as either related or unrelated.

□ Related to study drug

This category applies to any AE (whether serious or not) that appears to have a reasonable possibility of causal relationship to the use of the study drug (i.e., a relationship cannot be ruled out).

Guidelines to determine whether an event might be considered related include (but are not limited to) the following:

- The event occurred in close temporal relationship to study drug administration.
- The event abated (diminished) or disappeared when treatment with the study drug was down-titrated, interrupted, or discontinued.
- The event reoccurred when treatment was reintroduced.
- Environmental factors such as clinical state and other treatments could equally have caused the event.

□ Unrelated to study drug

This category applies to any AE (whether serious or not) that does not appear to have a reasonable relationship to the use of study drug (see above guidelines).

4.2.4 Reporting of adverse events

All AEs occurring after study drug initiation and up to 7 days after study drug discontinuation must be recorded on specific AE pages of the CRF.

4.2.5 Follow-up of adverse events

Adverse events still ongoing 7 days after study drug discontinuation for a given patient must be followed up for 30 days after study drug discontinuation or until resolution or stabilization or until the event is otherwise explained.

4.3 Serious adverse events

4.3.1 Definitions

4.3.1.1 Serious adverse events

An SAE is defined by the International Conference on Harmonisation (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Fatal
- Life-threatening
- Requiring patient's hospitalization, or prolongation of existing hospitalization
- Resulting in persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Medically significant, or requires intervention to prevent at least one of the outcomes listed above

Life-threatening refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.

Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the patient, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The reference safety document to assess whether or not an SAE should be reported by the sponsor to Health Authorities, ECs/IRBs and investigators in an expedited fashion is the Investigator's Brochure [[ACT-293987 IB](#), see also Section [4.3.2.4](#)].

4.3.1.2 Hospitalization – prolongation of existing hospitalization

The following reasons for hospitalizations are not considered AEs, and are therefore also not SAEs:

- Hospitalizations for cosmetic elective surgery, or social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., elective hip replacement for arthritis. Complications that occur during hospitalization are AEs or SAEs (for example if a complication prolongs hospitalization).

4.3.1.3 Serious adverse events related to study-mandated procedures

An SAE is defined as related to study-mandated procedures if it appears to have a reasonable possibility of a causal relationship (i.e., a relationship cannot be ruled out) to such a procedures (other than administration of study drug). Examples of study-mandated procedures include discontinuation of a patient's previous treatment during a washout period, complication of a mandated invasive procedure such as blood sampling or heart catheterization, car accident on the way to the hospital for a study visit, etc.

4.3.2 Reporting of serious adverse events

4.3.2.1 Screening period

Serious adverse events occurring between signing the Informed Consent Form and study drug initiation are only required to be reported if they are considered by the investigator to be related to study-mandated procedures.

As these SAEs are not reported as AEs in the CRF, they are collected only on an SAE form, and entered only into the drug safety database.

4.3.2.2 Treatment period

All SAEs, regardless of causal relationship, must be reported, including those related to study-mandated procedures. Those SAEs occurring during study drug administration, i.e., between study drug initiation and 7 days after study drug discontinuation or until the first dose of ACT 293987 in the open-label study (if applicable), are defined as treatment-emergent SAEs.

These SAEs are reported on SAE forms and also on AE pages in the CRF. They are therefore entered into both the drug safety and clinical databases, and must be reconciled before study closure.

4.3.2.3 Follow-up period

All SAEs regardless of causal relationship occurring from 7 days after study drug discontinuation up to 30 days after study drug discontinuation or until the first dose of ACT 293987 in the open label study (if applicable) must be reported.

All SAEs occurring during the follow-up period must be recorded on an SAE form. These SAEs are therefore entered only into the drug safety database.

4.3.2.4 Reporting procedures

All SAEs must be reported by the investigator to the Actelion drug safety department within 24 hours of the investigator's first knowledge of the event.

All SAEs must be recorded on SAE forms, irrespective of the study drug received by the patient, and whether or not this event is considered by the investigator to be related to study drug. These SAE forms must be faxed to the Actelion drug safety department (contact details for which are provided at the beginning of this protocol). The investigator must complete the SAE form in English (unless otherwise specified), and must assess the relationship of the event to study drug.

Such preliminary reports will be followed by detailed descriptions that may include copies of hospital case reports, autopsy reports, hospital discharge summaries and other documents when requested and applicable. Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Actelion drug safety department may contact the investigator to obtain further information.

Suspected (considered related to the study drug) and unexpected (not previously described in the reference safety document) serious adverse reactions (SUSARs) will be expedited by Actelion to Health Authorities, ECs/IRBs and investigators, as appropriate. Unblinding of SUSARs will be performed as appropriate.

The SAEs listed below are due to the underlying disease and are therefore expected to occur in this patient population. For expedited reporting, these SAEs will be treated as “disease-related” and expected. They therefore do not require systematic unblinding and do not require expedited reporting to Health Authorities, ECs/IRBs, and investigators. However, these events, as with all safety data, will be monitored during the study by the DMC.

The events to be treated as expected are listed in the Investigator’s Brochure.

4.3.3 Follow-up of serious adverse events

Serious adverse events still ongoing at the EOS Visit must be followed up until resolution or stabilization, or until the event is otherwise explained.

4.3.4 After the 30-day follow-up period

New SAEs occurring at any time after the 30-day follow-up period following study drug discontinuation may be reported to the sponsor’s drug safety department within 24 hours of the investigator’s knowledge of the event, if felt appropriate by the investigator. These SAEs are only entered in the drug safety database.

4.4 Pregnancy

4.4.1 Teratogenicity

In the reproduction toxicity studies performed so far, no changes were observed in fertility and teratogenicity. (A pre- and postnatal development study in the rat is ongoing).

However, appropriate precautions must be taken by women of childbearing potential. Women must not become pregnant during the study and for up to 1 month after study drug discontinuation.

If a woman becomes pregnant while on study drug, permanent discontinuation of study drug must be considered. The investigator must counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

4.4.2 Reporting of pregnancy

Irrespective of the treatment received by the patient, any pregnancy occurring during study drug administration or during the first month following study drug discontinuation, must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the sponsor's Pregnancy form, which is to be faxed to the sponsor's drug safety department (see contact details provided on the Pregnancy form), and on an AE page of the CRF, as applicable.

4.4.3 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion and its outcome must be reported to the sponsor's drug safety department.

Such follow-up information will only be entered in the drug safety database, and hence will not affect study closure.

5 STATISTICAL METHODOLOGY AND ANALYSES

5.1 Analysis strategy

Study AC-065A302 is designed to be analyzed for the time to first clinical worsening endpoint up to 7 days after last study drug intake as defined in Section 3.8.1. It is assumed that the study can adequately support a New Drug Application (NDA) submission if the null hypothesis of no difference from placebo for time to event is rejected

5.2 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be written and finalized before the study closure, i.e., database closure and unblinding of the randomization code. The SAP will provide full details of the analyses, the data displays, and the algorithms to be used for data derivations.

The SAP will include the definition of protocol deviations and the link between major and minor protocol deviations and the analysis sets.

Protocol deviations will be identified by medically-trained staff before the Study Closure.

5.3 Analysis sets

Four analysis sets are defined.

Patients without a valid or substituted [see Section 3.8] post-baseline value for a particular endpoint will be excluded from the relevant analysis.

□ All-randomized set

This analysis set includes all randomized patients, whether or not they received study drug.

□ All-treated set

This analysis set includes all randomized patients who received at least one dose of the study drug.

□ Safety set

This analysis set includes patients who were randomized, received at least one dose of the study drug, and had at least one safety assessment post-baseline.

□ Per-protocol set

This analysis set comprises all patients included in the All-treated set who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug on the primary endpoint, i.e., without major protocol violations.

5.4 Statistical analysis

5.4.1 Primary endpoint.

Time to first clinical worsening up to 7 days after last study drug intake as defined in Section 3.8.1.

The date of the “last study drug intake” refers to the date of the actual last study drug intake reported in the CRF during the Treatment period.

5.4.1.1 Statistical model

The risk of occurrence of a clinical worsening event in one group relative to the other is not expected to change with time. Therefore, the use of methods requiring proportional hazards is considered appropriate.

5.4.1.2 Hypotheses and statistical inference

The following hypothesis will be tested:

Null hypothesis (H_0): The distribution of the primary endpoint is the same in the treatment groups.

Alternative hypothesis (H_1): The distribution of the primary endpoint in the placebo group differs from the distribution in the active group.

The difference to be detected is a hazard ratio test treatment / placebo of 0.5729 when the active group is compared to placebo (which is expected to have an event rate of 20%/year constant over time).

Type I error: $\alpha = 0.0100$ (2-sided)

Type II error: $\beta = 0.0100$ (power = 90%)

5.4.1.3 Primary endpoint analysis

5.4.1.3.1 Main analysis

The null hypothesis will be tested by means of the log-rank test.

No adjustment for covariates is planned for the primary analysis.

Clinical worsening up to 7 days after last study drug intake will be counted for the analysis of the primary endpoint. Patients without clinical worsening event permanently discontinuing treatment will be censored 7 days after study treatment discontinuation. Their number is expected to be 5% per year in all treatment groups.

The primary analysis set will be the All-randomized set.

5.4.1.3.2 *Supportive analyses*

Supportive analyses will be conducted using appropriate covariates (e.g., the start date of concomitant PAH medications) in a Cox regression model.

In order to evaluate the robustness of results, the primary endpoint will be analyzed on the Per-protocol set.

Additional supplementary analyses will be performed censoring patients receiving additional medication for PAH without having reached the endpoint; censoring will be at the initiation of the additional medication.

While exploratory, all supplementary statistical analyses carried out on the primary endpoint will be conducted at the same nominal significance level as the main analysis.

5.4.1.4 *Primary endpoint display*

The time to occurrence of the first clinical worsening event up to 7 days after the last study drug intake will be described by Kaplan Meier estimates. 95% confidence intervals of the event-free proportion estimates at relevant time-points will be presented for each treatment group in graphical and tabular form. The hazard ratio of test treatment/placebo with its 95% two-sided confidence limits will also be computed.

5.4.1.5 *Power estimation*

Observing 202 events will provide 90% power to detect the above-mentioned hazard ratio, at two-sided 0.01 significance level, by means of the log-rank test. With the recruitment of 670 patients, randomized 1:1 to active treatment or placebo, over a period of 2 years (150 patients/1st year and 520 patients/2nd year), 202 events could be reached within a maximum of 3.5 years.

Power considerations are determined using the East[®] software version 5.0.

5.4.1.6 *Sample size adaptation*

The overall event rate (blinded) and the censoring rate will be continuously monitored. A blinded adaptation to the sample size might be implemented, up to a maximum of 1,150 patients, if required to keep the expected duration and the power of the study within acceptable ranges.

5.4.2 Secondary efficacy endpoints

5.4.2.1 Secondary efficacy endpoints analysis

Each secondary endpoint can then be analyzed in the sequence provided in the endpoints section, if the null-hypotheses of no difference from placebo were rejected for all the endpoints preceding in the sequence including the primary endpoint; each at the 0.05 two-sided level.

The null hypothesis of no difference between test treatment and placebo for the distribution of the secondary endpoints will be tested as follows:

- Change from Baseline to Week 16 in 6MWD at trough – Wilcoxon rank-sum test
- Absence of worsening from Baseline to Week 16 in modified NYHA/WHO functional class – Fisher’s exact test
- Change from Baseline to Week 16 in Borg dyspnea index – Wilcoxon rank-sum test
- Time to death up to Study Closure – log-rank test
- Change from Baseline to Week 16 in the sub-scale ‘Breathlessness’ of the ‘Symptoms’ score in the CAMPHOR questionnaire (at selected centers) – Wilcoxon rank-sum test
- Change from Baseline to Week 16 in the ‘Symptoms’ score of the CAMPHOR questionnaire (at selected centers) – Wilcoxon rank-sum test

Imputation methods for the substitution of incomplete, missing, or potentially biased data are defined in Section 3.8.1.4.

5.4.2.2 Secondary efficacy endpoints display

The change from Baseline to Week 16 in 6MWD will be displayed using descriptive statistics by treatment group and placebo-corrected for the active treatment group, including the usual location and scale statistics (mean, median, standard deviation, standard error, first and third quartiles, minimum and maximum) and 95% two-sided confidence limits of means and medians.

For the Absence of worsening from Baseline to Week 16 in modified NYHA/WHO functional class the transition table from the baseline score to the Week 16 score will be computed and displayed. For each treatment group, the proportions of patients in each category at Baseline and at Week 16 will be displayed, as well as the proportion of patients having a worsening from Baseline to Week 16 (i.e., shifted to a higher class) together with the 95% confidence limits. The relative risk of worsening (ACT-293987/placebo) will be displayed with 95% confidence intervals.

The change from Baseline to Week 16 in Borg dyspnea index will be displayed similarly to the change from Baseline to Week 16 in 6MWD.

Time to death up to Study Closure will be displayed similarly to the primary endpoint.

The change from Baseline to Week 16 in CAMPHOR questionnaire scores will be displayed similarly to the change from Baseline to Week 16 in Borg dyspnea index.

5.4.3 Exploratory efficacy endpoints

5.4.3.1 Exploratory efficacy endpoints display

The time to death and to the selected combinations of components of first clinical worsening will be displayed similarly to the primary endpoint for each component.

The changes from Baseline to EOS in 6MWD, Borg-dyspnea index, and modified NYHA/WHO functional class will be displayed similarly to the corresponding secondary endpoints.

For the changes from Baseline to Week 16 in modified NYHA/WHO functional class the transition table from the baseline score to the EOS score will be computed and displayed. For each treatment group, the proportions of patients in each category at Baseline and at EOS will be displayed, as well as the proportion of patients having an improvement/worsening from baseline to EOS (i.e., shifted to a lower/higher class) together with the 95% confidence limits. The relative risk of improvement and worsening (ACT-293987/placebo) will be displayed with 95% confidence intervals.

The changes from Baseline to EOS in plasma NT pro-brain natriuretic peptide (NT pro-BNP) will be displayed using descriptive statistics by treatment group and placebo-corrected for the active treatment group, including the usual location and scale statistics (mean, median, standard deviation, standard error, first and third quartiles, minimum and maximum) and 95% two-sided confidence limits of the mean and median.

EOS will be derived from the date of EOS visit as recorded in the CRF.

5.4.4 Safety and tolerability endpoints

The Safety set is used to perform all safety analyses.

For patients who prematurely discontinue due to a clinical worsening as adjudicated by the CEC, and who continue in the open-label study, the treatment-emergent AEs, ECGs and marked laboratory abnormalities will be counted until last study drug intake. The date of the “last study drug intake” refers to the date of the actual last study drug intake reported in the CRF during the Treatment period.

5.4.4.1 *Adverse events, serious adverse events, deaths and premature discontinuation of study treatment*

All AEs and SAEs are coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA dictionary).

Individual patient listings of all collected AEs will be provided by treatment group.

The frequency and the crude incidence of patients who experienced treatment-emergent AEs until 7 days after last study drug intake will be tabulated by system organ class (SOC), individual preferred terms within each SOC, and by treatment group (in descending order according to the incidence in the investigational study drug group, i.e., ACT-293987).

The frequency and the crude incidence of patients who experienced treatment-emergent AEs until 7 days after last study drug intake coded with the same preferred term will be tabulated by treatment group (in descending order according to the incidence in the investigational study drug group, i.e., ACT-293987).

Treatment-emergent AEs until 7 days after last study drug intake will also be tabulated by severity and by relationship to study drug.

Adverse events leading to permanent discontinuation of study drug will be listed and summarized similarly to AEs.

Treatment-emergent SAEs until 7 days after last study drug intake will be listed and summarized similarly to AEs, separately for treatment-emergent SAEs and SAEs occurring before study drug initiation (only those related to study-mandated procedures) and after 3 days from the study drug discontinuation.

Reasons for treatment-emergent deaths until 7 days after last study drug intake will be listed and summarized similarly to AEs. Deaths occurring before study drug initiation (only those related to study mandated procedures) and after 7 days since last study drug intake will be listed separately by treatment group.

Reasons for premature discontinuation of study drug will be listed and summarized by frequency tables. Individual patient listing will be provided by treatment group.

5.4.4.2 12-lead ECG

Treatment-emergent ECG abnormalities until 7 days after last study drug intake coded with the same preferred term will be summarized by treatment group and presented similarly to the AEs.

Absolute values and changes from baseline of ECG numeric parameters will be summarized by tabulating mean, median, standard deviation, first and third quartiles, minimum and maximum by treatment group.

Individual patient listing of ECG data will be provided by treatment group.

5.4.4.3 Laboratory and bone turnover markers

The frequency and the crude incidence of patients who experienced treatment-emergent marked laboratory abnormalities until 7 days after last study drug intake will be tabulated for each laboratory parameter by treatment group.

Numeric laboratory parameters will be transformed to standard units. Laboratory parameter values converted to standard units will be summarized by tabulating mean, median, standard deviation, first and third quartiles, minimum and maximum by treatment group for both the absolute values and the changes from baseline.

Individual patient listings will be provided by treatment group.

The sponsor's internal guidelines will be used for definition of marked laboratory abnormalities, and for the standardization of numeric values obtained from different laboratories and/or using different normal ranges.

5.4.4.4 Vital signs and body weight

Vital signs (blood pressures and heart rate) and body weight will be summarized by tabulating mean, median, standard deviation, first and third quartiles, minimum and maximum by treatment group for the absolute values and for the changes from baseline.

Individual patient listings will be provided by treatment group.

5.4.5 Pharmacokinetic and pharmacodynamic endpoints

- Trough plasma concentrations of ACT-293987, ACT-333679 and other potential metabolites at Baseline, Week 4, Week 8, Week 16, Week 26 (Month 6), Week 52 (Month 12), and EOS.
- Plasma concentrations of ACT-293987, ACT-333679 and other potential metabolites will be evaluated by PK sampling at specific time intervals after drug administration at Week 16
- The relationship between ACT-293987/ACT-333679 plasma levels and clinical endpoints and on plasma NT pro-BNP levels.

A supplemental PK/PD analysis plan will be written and finalized before the study closure, i.e., database closure and unblinding of the randomization code, to provide full details of the analyses, the data displays and the algorithms to be used for data derivations. All analyses will be exploratory in nature.

5.4.6 PK and PK/PD analyses

The PK and PD analyses will use mixed-effects population PK modeling with the software NONMEM, Version 6 or later. Details will be defined in a separate SAP.

5.4.7 Pharmacoeconomic endpoints

- Number per year of all-cause and PAH-related hospitalizations from Baseline to EOS.
- Number per year of in-patient hospital days for all causes and PAH-related causes from Baseline to EOS.

They will be summarized by the usual location and scale statistics. A PE-SAP will be prepared, describing the details of the PE analyses, the data displays, and the algorithms to be used for data derivations.

5.4.8 Exposure to study drug(s)

Exposure to study drug will be described in terms of duration, dose, and maximum tolerated dose. The duration of exposure is defined as the time elapsing between the study drug initiation and discontinuation, inclusive. The exposure time will be tabulated by treatment group using mean, median, standard deviation, first and third quartiles, minimum and maximum. The cumulative distribution of exposure time by different class intervals (i.e., at least 4 weeks, at least 8 weeks, at least 16 weeks, and at every interval of 26 weeks thereafter) will be tabulated to show the number and percentage of patients in each class interval. The maximum tolerated dose is tabulated by treatment group using mean, median, standard deviation, first and third quartiles, minimum and maximum.

5.4.9 Baseline parameters and concomitant medications

Continuous baseline parameters and disease characteristics (i.e., age, height, weight, BMI, blood pressure, heart rate, 6MWT, and Borg Dyspnea index and time from PAH diagnosis) will be summarized by treatment group using mean, median, standard deviation, first and third quartiles, minimum and maximum.

Qualitative baseline parameters and disease characteristics (i.e., gender and race, etiology of PAH, modified NYHA/WHO functional class, previous and concomitant medications) will be summarized by treatment group using counts and percentages.

Individual patient listings will be provided by treatment group.

Other baseline characteristics (e.g., medical history) will only be listed by treatment group.

Distributions of these parameters will only be compared between the treatment groups descriptively. No statistical inference will be performed.

Previous and concomitant medications will be coded according to the latest available version of the World Health Organization (WHO) drug code and the anatomic therapeutic chemical (ATC) class code. They will be summarized by type (i.e., previous and concomitant) and treatment group by tabulating the number and percentages of patients having received each treatment.

5.5 Exploratory analyses

Exploratory data-driven analyses can be performed, with the caveat that any statistical inference will not have any confirmatory value.

5.6 Interim analyses

No interim efficacy analyses are planned during the study.

The DMC is empowered to recommend modifications of the protocol (to enhance patient safety) or to recommend early termination of the study if major concerns arise about patient safety at any time during the course of this study or during any other study with the same investigational drug. There is no limit to the number and timing of interim analyses aimed at guaranteeing the safety of the patients.

6 PROCEDURES AND GOOD CLINICAL PRACTICE

6.1 Procedures

6.1.1 Protocol amendments

Any change to a protocol must be considered to be an amendment if the documents have already been submitted to ECs/IRBs or Health Authorities. An amendment could therefore occur before or after the approval of these documents by ECs/IRBs or Health Authorities. Each amendment must be documented in writing and approved by the sponsor, and must be reviewed by the Coordinating/Principal Investigator(s) or Steering Committee, as appropriate.

Changes to the Core Patient Information and Informed Consent requested by ECs/IRBs are not considered to be formal amendments, as long as they do not significantly change the core document or affect the protocol.

6.1.1.1 Non-substantial amendment

Purely administrative or minor logistical changes require only a non-substantial amendment. Such changes include but are not limited to changes in study staff or contact details (e.g., the sponsor instead of CRO monitors), or minor changes in the packaging or labeling of study drug.

The implementation of a non-substantial amendment may be undertaken with or without notification to the appropriate ECs/IRBs and Health Authorities (subject to national regulations).

6.1.1.2 Substantial amendment

A substantial amendment is required for significant changes. These include, but are not limited to, new data affecting the safety of patients, and changes to the objectives/ or endpoints of the study, eligibility criteria, dose regimen, study assessments/procedures, or treatment or study duration, with or without the need to modify the Core Patient Information and Informed Consent.

Substantial amendments must be approved by the appropriate ECs/IRBs, and in some jurisdictions by the Health Authorities. The implementation of a substantial amendment may only occur after formal approval by the appropriate ECs/IRBs and/or Health Authorities, and must be signed by the investigators.

6.1.1.3 Urgent amendment

An urgent amendment might become necessary to preserve the safety of the patients included in the study. The requirements for approval must not prevent any immediate action being taken by the investigators or the sponsor in the best interests of the patients.

If deemed necessary, an investigator may therefore implement an immediate change to the protocol for safety reasons, and in such exceptional cases the implementation of urgent amendments will occur before submission to, or approval by, ECs/IRBs and Health Authorities.

In such cases, the investigator must notify the sponsor within 24 hours. A related substantial amendment will be prepared and submitted by the sponsor to the appropriate ECs/IRBs and Health Authorities within 10 working days of receiving the notification.

6.1.2 Monitoring

The monitor will contact and visit the investigator regularly, and must be permitted to have access to all source documents needed to verify the entries on the CRF and other protocol-related documents on request, provided that patient confidentiality is maintained in accordance with local regulations. It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on the CRFs. The sponsor's monitoring standards require full verification that informed consent has been provided, and verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety and tolerability endpoints. Additional checks of the consistency of the source data with the CRFs will be performed according to the study-specific monitoring plan.

The rules regarding identification of any data recorded directly on the CRFs and considered to be source data are specified in the following document: "Site Guidelines". The investigator must ensure that patient anonymity is maintained. On CRFs or other documents submitted to the sponsor, patients must be identified only by number, and never by name. The investigator must keep a patient identification code list showing the randomization number, the patient's name, date of birth and address or any other locally accepted identifiers. Documents identifying the patients (e.g., signed informed consent forms) should not be sent to the sponsor, and must be kept in strict confidence by the investigator.

The investigator and co-investigators agree to cooperate with the monitor(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the patient is hospitalized or dies in a hospital other than the study center, the investigator is responsible for contacting that hospital in order to document the SAE.

The investigator must on request supply the sponsor with any required background data from the study documentation or clinical records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In the case of special problems and/or governmental queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

An initiation visit will be performed before the first patient is included in the study. Monitoring visits and contacts will occur at regular intervals thereafter, according to a frequency defined in the study-specific monitoring plan. A close-out visit will be performed after study closure.

6.1.3 Data management

6.1.3.1 Data collection

A Patient Screening and Enrollment Log will be completed for all patients, both eligible and non-eligible, with the reasons for exclusion where applicable.

For each patient enrolled, regardless of study drug initiation, a CRF must be completed and signed by the principal investigator or co-investigator. This also applies to those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the CRF. Case report forms are to be completed on an ongoing basis, and will be collected by the monitor(s).

All forms must be completed using a digital pen, and must be legible. Errors must be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the Principal Investigator, co-investigator, or study nurse.

6.1.3.2 Database management and quality control

All data from the CRF will be entered into the database twice, by two different individuals.

The entered data will be systematically checked by the sponsor or CRO staff, using error messages printed from validation programs and database listings. Errors with obvious corrections will be corrected and communicated to the site. Data clarification requests will be entered on Data Clarification Forms, which will be returned to the investigational site for resolution. A copy of the signed Data Clarification Form is to be kept with the CRFs, and, once received at the sponsor or CRO, the resolutions will be entered into the clinical database.

A second review of the data will be performed by medically trained staff.

Quality control audits of the database will be made before study closure.

Laboratory samples will be processed centrally through Quest and the results will be sent electronically to the sponsor.

After the database has been declared complete and accurate, the database will be locked. Any changes to the database after that time may only be made by joint written agreement between the Clinical Trial Leader and the Trial Statistician.

6.1.4 Recording of data and retention of documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, and the study data to be subsequently verified. These documents are to be classified into two different categories: investigator's file, and patient clinical source documents.

The investigator's file will contain the protocol/ and all protocol amendments, the FDA form 1572 for studies conducted under a US IND, a financial disclosure form, the CRFs and data clarification and query forms, EC/IRB and Health Authority approval with correspondence, informed consent, drug records, staff curricula vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence in accordance with ICH GCP and local regulations.

Patient clinical source documents include, but are not limited to, hospital/clinic records, physicians' and nurses' notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, etc.

These two categories of documents must be kept on file by the investigator for as long as is necessary to comply with national and international regulations (generally 2 years after either discontinuation of clinical development, or the last marketing approval, of the investigational drug). No study document should be destroyed without prior written approval from the sponsor. Should the investigator wish to assign the study records to another party, or move them to another location, the sponsor must be notified in advance.

When source documents are required for the continued care of the patient, appropriate copies should be made for storing off site.

6.1.5 Audit

The sponsor's Global Quality Management Department may conduct audits of clinical research activities in accordance with internal standard operating procedures (SOPs) to evaluate compliance with the principles of GCP- and ICH-related guidelines.

Health Authorities may also wish to conduct an inspection (during the study or after its completion). Should an inspection be requested by a Health Authority, the investigator must inform the sponsor immediately that such a request has been made.

The investigator must permit such audits by the sponsor or Health Authorities, and must facilitate them by providing access to the relevant source documents.

6.1.6 Handling of study drug(s)

The sponsor will supply all study drug(s) to the site according to local regulations. Drug supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the drug labels. The site must maintain an accurate record of the shipment and dispensing of study drug(s) on an accountability form, which must be given to the monitor at the end of the study. An accurate record of the date and amount of study drug(s) dispensed to each patient must be available for inspection at any time.

All drug supplies are to be used only in accordance with this protocol, and not for any other purpose. The responsible person must not destroy any drug labels, or unused drug supply. On termination of the study, the monitor will collect used and unused patient kits, which will be sent to the warehouse, where the sponsor or its deputy will check drug accountability. In certain circumstances, used and unused drug containers may be destroyed at the site once drug accountability is final and has been checked by the sponsor or its deputy, and written permission for destruction has been obtained from the sponsor.

6.1.7 Publication and reporting of study results

Study results will be documented in a clinical study report that will be signed by representatives of the sponsor and by the Coordinating Investigator.

In accordance with standard editorial and ethical practice, the results of the study will be published. Results from multicenter studies must be published or presented at congresses only in their entirety and not as individual center data, except for ancillary studies.

The Coordinating Investigator and the Steering Committee will have the opportunity to review the analysis of the data and to discuss with the sponsor the interpretation of the study results prior to publication.

Any study-related article or abstract written independently by investigators must be submitted to the sponsor for review at least 60 days prior to submission for publication or presentation.

The list of authors of any formal publication or presentation of study results may include, as appropriate, representatives of the sponsor, and will be determined by mutual agreement.

6.1.8 Disclosure and confidentiality

By signing this protocol, the investigator agrees to keep all information provided by the sponsor in strict confidence, and to request similar confidentiality from his or her staff and the EC/IRB. Study documents provided by the sponsor (including Investigator's Brochures, protocols, CRFs and other protocol-related documents) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorization from the sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

6.1.9 Premature termination or suspension of the study

Both the sponsor and the investigator reserve the right to terminate the study at any time.

If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators, the ECs/IRBs and Health Authorities, as appropriate, and provide the reasons for the termination or suspension.

If the study is prematurely terminated or suspended for any reason, the investigator in agreement with the sponsor must promptly inform all enrolled patients, and ensure their appropriate treatment and follow-up.

In addition, if the investigator terminates or suspends a study without prior agreement from the sponsor, the investigator must promptly inform the sponsor and the EC/IRB, and must provide the sponsor and the EC/IRB with a detailed written explanation of the termination or suspension.

If the EC/IRB terminates or suspends its approval/favorable opinion of a study, the investigator must promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

Any premature termination or suspension of the study must be discussed with the DMC, and Steering Committee, as appropriate.

6.2 Good Clinical Practice

6.2.1 Ethics and Good Clinical Practice

The investigator will ensure that this study is conducted in full compliance with the principles of the 'Declaration of Helsinki' (as amended in Tokyo, Venice, Hong Kong, Somerset West, Edinburgh and Seoul), and with the laws and regulations of the country in which the clinical research is conducted. A copy of the Declaration of Helsinki will be provided to each investigational site.

All studies must follow ICH GCP Guidelines and, if applicable, the US Code of Federal Regulations. In other jurisdictions in which GCP Guidelines exist, the investigators will ensure strict adherence to the stated provisions.

6.2.2 Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the patient (such as patient information used to obtain informed consent) to an EC or IRB. Approval from the committee must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval. A list of members participating in the meeting must be provided, including the functions of these members. If study staff were present, it must be clear that none of these persons voted.

Modifications made to the protocol after receipt of the EC/IRB approval must also be submitted as amendments by the investigator to the EC/IRB in accordance with local procedures and regulations (see Section [6.1.1](#)).

6.2.3 Informed consent

It is the responsibility of the investigator to obtain informed consent according to GCP and local regulations from each individual participating in this study, after adequate explanation of the aims, methods, objectives and potential hazards of the study. The investigator must also explain to the patients that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason. Appropriate forms for documenting informed consent will be provided to the sites prior to the study.

The Informed Consent and Patient Information will be provided in the local language.

6.2.4 Compensation to patients and investigators

The sponsor provides insurance in order to indemnify (with both legal and financial coverage) the investigator/center against claims arising from the study, except for claims that arise from malpractice and/or negligence.

Compensation of the patient in the event of study-related injuries will comply with applicable regulations.

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Appendix 1 Actelion Guidelines for 6MWT

1. 6-minute walk test (6MWT)

1.1. General procedures [ATS 2002]

- **The 6MWT is a non-encouraged test** the same tester at the same location and the same time of the day to minimize intraday variability throughout the study should administer it.
- **The 6MWT should be performed** along a long, flat, straight corridor that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The use of treadmill is forbidden.
- **The corridor used for the test should be 30 meters in length (100 feet).** The length of the corridor should be marked every 3 meters (10 feet). The turnaround point should be marked with a cone. A starting line, which marks the beginning and the end of each 60-m lap, should be marked on the floor using brightly colored tape.
- **The required equipment** is: a countdown timer (or stop watch), a mechanical lap counter, 2 small cones for the turnaround points, a chair (easily moved along the walking course), a worksheets on a clipboard, a sphygmomanometer, an automated electronic defibrillator and, a source of oxygen.
- **The tester** should stand near the starting line during the test. **Do not walk with the patient!** Intermittent rest periods are allowed if the patient can no longer continue. If the patient needs to rest briefly, he/she may stand or sit and resumes walking when he/she is sufficiently rested. But the clock must continue to run. The tester can at any moment immediately stop the 6MWT in case the patient complains of having chest pain, intolerable dyspnea, leg cramps, looking pale or ashen appearance...
- **Study specific requirements:**

The two qualifying 6MWTs at Screening and Baseline (Visit 1) must be performed within 14 days and on 2 separate days.

1.2 Instructions to the patient

Patients will be instructed that the preceding meal should be light, have rested at least 20 minutes before the test starts. Patients should receive their usual medication on the day of the test. If the patient is used to taking bronchodilators before a walk, he/she should take them 5-30 min before the test. Also if the patient is on chronic oxygen therapy, oxygen should be given at their standard rate during the test. Patients should be told to wear comfortable clothing and appropriate walking shoes. **Patients using walking aids (cane, walker, etc) should not be enrolled in the study.**

The person administering the test will use the following exact dialog with the patient:

“The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able to.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I’m going to show you. Please watch the way I turn without hesitation”. (*The tester demonstrates the walking and pivots around a cone briskly*).

“Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line.

Remember the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don’t run or jog. I will tell you when 2 minutes, 4 minutes have elapsed. Keep walking when I talk.”

After these instructions are given to the patient, the person administering the test will then ask:

“Do you have any questions about the test?”

“Please explain what you are going to do.”

“Are you ready?”

“Start now, or whenever you are ready”

The tester will then start the timer and write down the clock time of the test start.

The tester will tell the patient the time elapsed by saying:

“You have 4 minutes to go.”

“You have 2 minutes to go.”

When the timer is 15 seconds from completion, the tester says:

“In a moment I’m going to tell you to stop. When I do, just stop right where you are and I will come to you”.

When the timer alarm rings the tester says:

“Stop!”

The tester walks over to the patient, marks the spot where the patient stopped.

No other instruction or encouragement will be given during the test. Eye contact and body language signaling to the patient to speed up should be avoided during the test.

- Heart rate and blood pressure are checked **before** and **right after** the test.
- Total distance walked should be recorded in the worksheet at the end of 6MWT.

2. Borg dyspnea index

Following the walk test, the person administering the test will obtain a rating of dyspnea using the Borg Scale.

The tester will use the following dialog:

“I would like to use the following scale to indicate the maximal shortness of breath you had during the walk test (indicate the Borg scale). If there was no shortness of breath at all you would point to 0; if the shortness of breath was not very great you would choose from 0.5 to 2; if you were somewhat more short of breath you would select 3; and if the breathing was getting very difficult, you would choose 4 to 9, depending on just how hard it was; 10 represents the greatest shortness of breath you have ever experienced in your life.”

Appendix 2 Borg dyspnea index (Borg scale)

0	NOTHING AT ALL
0.5	VERY, VERY SLIGHT (just noticeable)
1	VERY SLIGHT
2	SLIGHT (light)
3	MODERATE
4	SOMEWHAT SEVERE
5	SEVERE (heavy)
6	
7	VERY SEVERE
8	
9	
10	VERY, VERY SEVERE (maximal)

Appendix 3 Modified NYHA/WHO classification of functional status of patients with PH

- Class I** Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
- Class II** Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
- Class III** Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
- Class IV** Patients with pulmonary hypertension who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

Adapted from [Rich 1998] Rich S. Primary pulmonary hypertension: executive summary. Evian, France. World Health Organization 1998.

ACT-293987

Pulmonary arterial hypertension

Protocol AC-065A302/GRIPHON

Version 1.US.A

5 January 2009, page 99/99

EudraCT 2009-014490-41

IND 104,504

Doc No D-10.023

Confidential

Appendix 4 CAMPHOR questionnaire

CAMPHOR

Cambridge Pulmonary Hypertension Outcome Review

Please read this carefully

On the following pages you will find some statements that have been made by people who have Pulmonary Arterial Hypertension.

Please read each statement carefully.

We would like you to put a tick in the box ☒ next to 'Yes' if you feel it applies to you and a tick in the box ☒ next to 'No' if it does not

Please choose the response that applies best to you
at the moment

© Galen Research & Papworth Hospital, 2004

Symptoms

Please read each statement carefully and decide whether it applies to you **at the moment**

1. My stamina levels are low	Yes ☐
	No ☐
2. I have to rest during the day	Yes ☐
	No ☐
3. I feel worn out	Yes ☐
	No ☐
4. I get tired very quickly	Yes ☐
	No ☐
5. I'm tired all the time	Yes ☐
	No ☐
6. I feel very weak	Yes ☐
	No ☐
7. I feel completely exhausted	Yes ☐
	No ☐
8. I want to sit down all the time	Yes ☐
	No ☐
9. I soon run out of energy	Yes ☐
	No ☐

10. Everything is an effort Yes ☐
No ☐

11. I get out of breath when I stand up Yes ☐
No ☐

12. When I talk I get out of breath Yes ☐
No ☐

Please read each statement carefully and decide whether it applies to you
at the moment

13. When I walk I get out of breath Yes ☐
No ☐

14. I get breathless if I bend Yes ☐
No ☐

15. I get breathless going up one step Yes ☐
No ☐

16. I get breathless walking up a slight slope Yes ☐
No ☐

17. I get breathless without doing anything Yes ☐
No ☐

18. I get breathless climbing a flight of stairs Yes ☐
No ☐

19. I have mood swings Yes ☐
No ☐

20. I get very down Yes ☐
No ☐

21. I seldom feel happy Yes ☐
No ☐

Please read each statement carefully and decide whether it applies to you
at the moment

22. I've forgotten what it's like to enjoy myself Yes ☐
No ☐

23. I feel hopeless Yes ☐
No ☐

24. It does get me down Yes ☐
No ☐

25. I often feel anxious Yes ☐
No ☐

please turn over

Activities

Please put a tick in the box ☒ under the response which best describes your abilities at the moment. Please respond to all 15 statements.

**Please describe your ability without the use of aids or assistance.
However, do describe your ability taking into account oxygen if you use it.**

Please mark only one box.

	Able to do on own without difficulty	Able to do on own with difficulty	Unable to do on own
1. Cut your toenails	☐	☐	☐
2. Have an all over wash	☐	☐	☐
3. Get dressed	☐	☐	☐
4. Walk around inside the house (not including climbing stairs)	☐	☐	☐
5. Walk short distances on level ground	☐	☐	☐
6. Walk longer distances on level ground	☐	☐	☐
7. Walk up a slight incline	☐	☐	☐
8. Climb a flight of stairs	☐	☐	☐
9. Bend down to pick objects up from the floor	☐	☐	☐
10. Stand for a short time	☐	☐	☐
11. Stand for a long time	☐	☐	☐
12. Lift heavy items	☐	☐	☐
13. Carry heavy items	☐	☐	☐
14. Do light jobs around the house or garden	☐	☐	☐
15. Do heavy jobs around the house or garden	☐	☐	☐

Quality of Life

Please read each statement carefully and put a tick ☒ next to the response that applies best to you *at the moment*

1. I have to talk very quietly	True	☐
	Not True	☐
2. I can't stay away from home	True	☐
	Not True	☐
3. I've lost interest in food	True	☐
	Not True	☐
4. I can't put energy into my close relationships	True	☐
	Not True	☐
5. Walking for pleasure is out of the question	True	☐
	Not True	☐
6. My condition puts a strain on my close relationships	True	☐
	Not True	☐
7. I feel very isolated	True	☐
	Not True	☐
8. I can't do things on the spur of the moment	True	☐
	Not True	☐
9. I feel vulnerable when I'm on my own	True	☐
	Not True	☐

10. It feels like my body has let me down	True	☐
	Not True	☐

11. I feel as if I'm not in control of my life	True	☐
	Not True	☐

12. I feel dependent on other people	True	☐
	Not True	☐

Please remember to put a tick in **only one** of the alternative responses for each of the statements

13. .Sometimes it's too much effort to speak	True	☐
	Not True	☐

14. I feel as if I am a burden to people	True	☐
	Not True	☐

15. Travelling distances is a problem	True	☐
	Not True	☐

16. I don't like to be seen like this	True	☐
	Not True	☐

17. I feel that I'm losing my role in life	True	☐
	Not True	☐

18. I worry that I neglect people close to me	True	☐
	Not True	☐

Please read each statement carefully and decide whether it applies to you **at the moment**

19. I feel guilty asking for help	True	☐
	Not True	☐
20. My condition limits the places I can go	True	☐
	Not True	☐
21. I dislike having to rely on other people	True	☐
	Not True	☐
22. I don't want to talk to anybody	True	☐
	Not True	☐
23. I feel as if I let people down	True	☐
	Not True	☐
24. I am reluctant to leave the house	True	☐
	Not True	☐
25. I'm unable to join in activities with my family and friends	True	☐
	Not True	☐

Thank you for taking the trouble to fill in this questionnaire.

Please check all the pages to make sure that you have
answered every statement.

Participant ID: _____

Date: _____



Selexipag / ACT-293987

Pulmonary Arterial Hypertension

Protocol AC-065A302

GRIPHON

A multicenter, double-blind, placebo-controlled Phase 3 study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with pulmonary arterial hypertension

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Confidentiality statement

The information contained in this document, especially unpublished data, is the property of the sponsor of this study, Actelion Pharmaceuticals Ltd. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from Actelion Pharmaceuticals Ltd, except to the extent necessary to obtain informed consent from those persons to whom the study drug may be administered.

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MEDICAL HOTLINE	Toll-free Hotline phone numbers for participating countries can be found in the site guidelines. For countries where no toll-free phone number is available, a toll phone number will be used

SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called Actelion

Drug name / number

Selexipag / ACT-293987

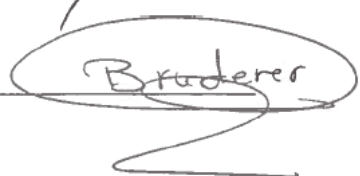
Indication

Pulmonary arterial hypertension.

Protocol number, acronym, title

AC-065A302 / GRIPHON

A multicenter, double-blind, placebo-controlled Phase 3 study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with pulmonary arterial hypertension.

	NAME (TITLE)	DATE	SIGNATURE
Clinical Project Team Leader	Aline Frey, PharmD	29/01/2013	
Clinical Project Physician	Alexis Rames, MD	29/01/2013	
Project Statistician	Peter Jakobs,	29/01/2013	
Clinical Pharmacologist	Shirin Bruderer; PhD	29/01/2013	

SIGNATURE PAGE FOR INVESTIGATOR(S)

Drug name / number

Selexipag / ACT-293987

Indication

Pulmonary arterial hypertension.

Protocol number, acronym, title

AC-065A302 / GRIPHON

A multicenter, double-blind, placebo-controlled Phase 3 study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with pulmonary arterial hypertension.

I agree to the terms and conditions relating to this study as defined in this protocol, Case Report Form (CRF) and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on study patients (other than those procedures necessary for the well being of the patients).

I agree to conduct this study in accordance with the Declaration of Helsinki and its amendments, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and applicable regulations and laws. In particular, I will obtain approval by an Ethics Committee or Institutional Review Board (EC/IRB) prior to study start and signed informed consent from all patients included in this study. In addition, I will allow direct access to source documents and agree to inspection by auditors from the sponsor and Health Authorities. I will ensure that the study drug(s) supplied by the sponsor are being used only as described in this protocol. Furthermore, I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to worldwide Health Authorities worldwide.

Name	Country	Center number	Town	Date	Signature

Center Principal
Investigator

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-minute walk distance
6MWT	6-minute walk test
ACT-293987	Actelion's investigational drug, formerly known as NS-304
ACT-333679	The active metabolite of ACT-293987
AE	Adverse event
ALT	Alanine aminotransferase / serum glutamic pyruvic transaminase (SGPT)
APAH	Pulmonary arterial hypertension associated with other diseases, e.g., scleroderma
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase / serum glutamic oxaloacetic transaminase (SGOT)
ATC	Anatomic Therapeutic Chemical
AUC	Area under the concentration-time curve
b.i.d.	<i>Bis in diem</i> / twice a day
BL	Baseline, Day 1
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
cAMP	Cyclic adenosine monophosphate
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CEC	Critical Event Committee
CL	Confidence limit

CK	Creatine kinase
C _{max}	Maximal plasma concentration
CRF	Case Report Form
CRO	Contract Research Organization
CTx	Carboxy-terminal telopeptide
DMC	Data Monitoring Committee
dPAP	Diastolic Pulmonary arterial pressure
DP receptor	Prostaglandin D ₂ receptor
dyn	Dyne (1 g·cm/s ²)
EC	Ethics Committee
ECG	Electrocardiogram
EDTA	Ethylene diamine tetra-acetic acid
EMA	European Medicines Agency
EOS	End of study
EOTE	End of treatment extension
EP receptor	Prostaglandin E ₂ receptor
ERA	Endothelin receptor antagonist
FDA	Food and Drug Administration
FEV ₁	Forced expiratory volume in 1 second
FP receptor	Prostaglandin F ₂ receptor
FPFV	First Patient First Visit
FVC	Forced vital capacity
GCP	Good Clinical Practice
GPCR	G-protein coupled receptor

GRIPHON	Prostacyclin (PGI ₂) receptor agonist in pulmonary arterial hypertension
HIV	Human Immunodeficiency Virus
HPAH	Heritable pulmonary arterial hypertension (formerly familial PAH)
<i>hr</i>	Hazard ratio
HR	Heart Rate
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IP receptor	Prostacyclin receptor, PGI ₂ receptor
IPAH	Idiopathic pulmonary arterial hypertension
IRB	Institutional Review Board
ITT	Intention-to-treat
i.v.	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LOQ	Limit of quantification
LVEDP	Left ventricular end diastolic pressure
MedDRA	Medical Dictionary for Regulatory Activities
MLA	Marked laboratory abnormality

mPAP	Mean pulmonary arterial pressure
MM	Morbidity and mortality event (previously referred to as clinical worsening event)
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
MVSO ₂	Mixed Venous Oxygen saturation
NDA	New drug application
NS-304	Previous name of the investigational drug AC-293987
NT pro-BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OL	Open label
p.o.	<i>Per os</i> / orally
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic(s)
PDE-5	Phosphodiesterase type-5
PGI ₂	Prostacyclin (Prostaglandin I ₂)
PH	Pulmonary hypertension
PI	Package Insert
PK	Pharmacokinetic(s)
PTOCV	Post-Treatment Observation Closure Visit
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization

RVH	Right ventricular hypertrophy
RVSP	Right ventricular systolic pressure
s.c.	Subcutaneous
SAC	Statistical Analysis Center
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SFU	Survival Follow-Up
SmPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard Operating Procedure
sPAP	Systolic Pulmonary arterial pressure
SUSAR	Suspected unexpected serious adverse reaction
SVR	Systemic vascular resistance
$t_{1/2}$	Elimination half-life
$t_{\max}$	Time to maximum plasma concentration
TP receptor	Thromboxane A ₂ (TXA ₂) receptor
TXA ₂	Thromboxane A ₂
ULN	Upper limit of normal

PROTOCOL SYNOPSIS AC-065A302

TITLE	A multicenter, double-blind, placebo-controlled Phase 3 study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with pulmonary arterial hypertension.					
ACRONYM	GRIPHON (Prostacyclin (PGI ₂) Receptor agonist In Pulmonary arterial HypertensiON)					
OBJECTIVES	Primary objective To demonstrate the effect of ACT-293987 on time to first morbidity and mortality (MM) event in patients with pulmonary arterial hypertension (PAH). Secondary objective To evaluate the effect of ACT-293987 on exercise capacity and other secondary and exploratory efficacy endpoints in patients with PAH. To evaluate the safety and tolerability of ACT-293987 in patients with PAH.					
DESIGN / PHASE	Prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study.					
STUDY PLANNED DURATION	First Patient First Visit	Q4 2009	Last Patient First Visit	Q1 2013	Last Patient Last Visit	Q1 2014
CENTER(S)/COUNTRIES	Approx. 190 centers in approximately 44 countries (planned).					
PATIENTS / GROUPS	1,150 patients randomized into two groups, placebo: active 1:1, 575 patients per group.					

INCLUSION CRITERIA	1. Signed informed consent prior to initiation of any study mandated procedure. 2. Male and female^{1,2} patients aged from 18 years to 75 years inclusive with symptomatic PAH 3. Patients with PAH belonging to one of the following subgroups of the updated Dana Point Clinical Classification Group 1: • Idiopathic (IPAH)³, or • Heritable (HPAH)³, or • Drug or toxin induced, or • Associated (APAH) with one of the following: – Connective tissue disease – Congenital heart disease with simple systemic-to-pulmonary shunt at least 1 year after surgical repair – HIV infection 4. Documented hemodynamic diagnosis of PAH by right heart catheterization – performed at any time <u>prior to Screening</u> showing: • Resting mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg and • Resting pulmonary vascular resistance (PVR) $\geq 400 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ and • Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) ≤ 15 mmHg 5. 6-minute walk distance (6MWD) between 50 and 450 m (inclusive) at Screening (within 2 weeks prior to the Baseline Visit and on a different day than this visit).

¹ Women of childbearing potential² must use a reliable method of contraception (failure rate less than 1% per year) from screening until 1 month after study drug discontinuation.

² A woman is considered to have childbearing potential unless she meets at least one of the following criteria:

- previous bilateral salpingo-oophorectomy or hysterectomy
- premature ovarian failure confirmed by a specialist gynecologist
- pre-pubescence, XY genotype, Turner syndrome, uterine agenesis
- age > 50 years with amenorrhea for at least 24 consecutive months prior to screening.

³ Other forms of PH must have been excluded and must be appropriately documented in the patient chart (e.g., results of pulmonary function tests, ventilation/perfusion lung scan, echocardiogram/or cardiac MRI, hospital summary from referred patients).

EXCLUSION CRITERIA	Patients will not be entered into the study if they meet any of the following criteria: 1. Patients with pulmonary hypertension (PH) in the Updated Dana Point Classification Groups 2–5, and PAH Group 1 subgroups that are not covered by the inclusion criteria. 2. Patients who have received prostacyclin (epoprostenol) or prostacyclin analogs⁴ (i.e., treprostinil, iloprost, beraprost) within 1 month before Baseline Visit, or are scheduled to receive any of these compounds during the trial. 3. Patients with moderate or severe obstructive lung disease: FEV₁/FVC < 70% and FEV₁ < 65% of predicted value after bronchodilator administration. 4. Patients with moderate or severe restrictive lung disease: Total Lung Capacity < 70% of predicted value. 5. Patients with moderate or severe hepatic impairment (Child-Pugh B and C). 6. Patients with documented left ventricular dysfunction (i.e. ejection fraction < 45%). 7. Patients with severe renal insufficiency (estimated creatinine clearance < 30 mL/min or serum creatinine > 2.5 mg/dL). 8. Patients with BMI < 18.5 Kg/m². 9. Patients who are receiving or have been receiving any investigational drugs within 1 month before the BL Visit. 10. Acute or chronic impairment (other than dyspnea), limiting the ability to comply with study requirements, in particular with 6MWT (e.g., angina pectoris, claudication, musculoskeletal disorder, need of walking aids). 11. Recently conducted (the program must be completed at least 8 weeks prior to screening) or planned cardio-pulmonary rehabilitation program based on exercise training. 12. Psychotic, addictive or other disorder limiting the ability to provide informed consent or to comply with study requirements. 13. Life expectancy less than 12 months. 14. Females who are lactating or pregnant (positive pre-

⁴ Single administration of drugs used for acute vasodilator testing during RHC procedure is allowed (e.g. i.v./inhaled prostacyclin or inhaled nitric oxide or oral sildenafil).

	randomization serum pregnancy test) or plan to become pregnant during the study. 15. Known hypersensitivity to any of the excipients of the drug formulations.
CONCOMITANT MEDICATIONS	Single administration of drugs (e.g. i.v./inhaled prostacyclin analogs or inhaled nitric oxide or oral sildenafil) for acute vasodilator testing during RHC procedure is accepted. Endothelin receptor antagonists (ERAs) and/or phosphodiesterase-5 (PDE-5) inhibitors are allowed. The dose must be stable for at least 3 months prior to Baseline Visit and until Week 26 (Visit 5). For diuretic therapy, the dose must be stable for at least 1 month prior to Baseline Visit and until Week 26. Introduction of new treatment for PAH (or increasing the dose) without MM event confirmed by the Critical Event Committee (CEC) is strongly discouraged during the study period. Prostacyclin (epoprostenol) and prostacyclin analogs⁵ (i.e., treprostinil, iloprost, beraprost) and any investigational drug are prohibited (from 1 month prior to Baseline Visit until end of study)
STUDY PERIODS	Screening: Up to 28 days prior to Baseline Visit Treatment period: From Baseline Visit to End Of Study (EOS) visit (included) - For an individual patient the EOS Visit may occur before Study Closure (in the case of premature study drug discontinuation) or shortly after Study Closure (within 4 weeks). Patients who discontinue study drug must have an EOS Visit and a Post-treatment safety follow-up phone call. - Study Closure will be announced by the sponsor when the target number of MM events has been reached. All patients still on study drug at Study Closure must have an EOS Visit shortly thereafter (within 4 weeks). Patients who have prematurely discontinued study drug will enter the post-treatment observation period and have a Post-Treatment Observation Closure Visit (PTOCV) at time of Study Closure.

⁵ except for acute vasodilator testing during RHC procedure

	Patients who did not give their consent to the post-treatment observation period must be called at the time of Study Closure to ascertain vital status assessment, as previously agreed. Treatment Extension period: After Study Closure, from the EOS Visit until the End-of-Treatment-Extension (EOTE) visit following unblinding of the database. The unblinding of the database will be announced by the sponsor, and the patient must have an EOTE visit shortly thereafter (within 4 weeks). Patients who had an EOS Visit following a MM event confirmed by the CEC, or an EOTE visit, will be eligible to enter the open-label study AC-065A303/GRIPHON OL (if approved by the national Health Authority in the country). Observation period: From Baseline Visit to EOS/PTOCV within 4 weeks after study closure announcement by the sponsor. Post-treatment observation period: After the EOS visit until the (PTOCV) After their EOS visit, all patients who prematurely discontinued study drug will enter the post-treatment observation period until the announcement of study closure by the sponsor. Then, the PTOCV will have to be scheduled shortly thereafter (within 4 weeks). During this period, clinic visits and telephone calls alternating every three months will be performed. Unscheduled clinic visits may also be performed if the patient's PAH condition deteriorates. Post-treatment safety follow-up for serious adverse events (SAEs): SAEs must be reported until 30 days after study drug discontinuation or until the first dose of ACT-293987 in the open-label study, whichever comes first.
INVESTIGATIONAL DRUG	During the Baseline Visit (Day 1) patients will be randomized to the starting dose of 200 µg ACT-293987 b.i.d. or matching placebo. Patients will take the first dose of study drug in the evening of Day 1, and continue thereafter with twice daily dosing, in the morning and in the evening.

	At weekly intervals (scheduled phone calls or visits), patients will be up-titrated in increments of 200 µg b.i.d. until reaching their individual maximum tolerated dose (MTD) within a dose range of up to maximally 1,600 µg b.i.d. If the investigator identifies a tolerability concern for a patient, the patient's dose will be reduced to the previous dose level. At Week 12 (scheduled phone call), the MTD for each patient should be finally determined and this dose must then be kept unchanged for the next 14 weeks (from Week 12 on) until the Week 26 (Visit 5) assessment of the secondary endpoint, change in 6MWD. After Week 26, the investigator will be allowed to further increase the dose if needed (only at scheduled visits and up to the maximum of 1,600 µg b.i.d.) by 200 µg b.i.d. increments. Dose reduction may occur at anytime if the investigator identifies a tolerability concern for a patient. From Visit 2, and at each visit thereafter, patients must not take the morning dose before the completion of the CAMPHOR questionnaire (when applicable), 6MWT (when applicable) and the blood sampling. In addition, at Week 16 a post-dose blood sampling will be taken for pharmacokinetic (PK) analysis. At Month 12 (Visit 6), two additional ECGs examination will be done 2 and 4 hours after study drug intake.
REFERENCE DRUG	Placebo matching ACT-293987
TREATMENT DURATION	Until the pre-specified number of 331 CEC-confirmed MM events has been reached (within a maximum of 4.3 years)
FORMULATIONS	Tablets of 200 µg ACT-293987 or matching placebo

EFFICACY ENDPOINTS	Primary endpoint Time to first MM event confirmed by the CEC up to 7 days after last study drug intake defined as: • Death (all-cause mortality) or • Hospitalization for worsening of PAH based on predefined criteria⁶ or • Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy or • Initiation of parenteral⁷ prostanoid therapy or chronic oxygen therapy due to worsening of PAH⁸ or • Disease progression (patients in modified NYHA/WHO functional class II-III at baseline) confirmed by : – decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by two tests on different days within 2 weeks) and – worsening of NYHA/WHO functional class or • Disease progression (patients in modified NYHA/WHO functional class III-IV at baseline) confirmed by : – decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) and – need for additional PAH specific therapy. MM events will be adjudicated in a blinded fashion by an independent CEC. Each individual component of the primary endpoint (and its associated date) will be adjudicated by the CEC. The cause of death (related to PAH vs. not related to PAH) will be assessed by the CEC. These new CEC responsibilities have been implemented in Version 3 of the GRIPHON CEC Charter and re-adjudication of all MM events previously submitted to CEC will be done. If there is a missing assessment (e.g. no confirmatory 6MWT, no modified NYHA/WHO functional class), the CEC will ultimately

⁶ See protocol section 3.8.1.1 for definition of hospitalization for worsening of PAH based on predefined criteria

⁷ Subcutaneous or intravenous

⁸ See protocol section 3.8.1.1 for definition of chronic oxygen therapy

	be responsible for qualifying or disqualifying the event and the date for the analysis of the primary endpoint using all available clinical data. Secondary endpoints • Change from Baseline to Week 26 in 6MWD measured at trough. • Absence of worsening from Baseline to Week 26 in modified NYHA/WHO functional class • Borg Dyspnea Index at Week 26 • Time to death up to Study Closure. • Change from Baseline to Week 26 in the sub-scale 'Breathlessness' of the 'Symptoms' score in the CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) questionnaire (at selected centers). • Change from Baseline to Week 26 in the 'Symptoms' score of the CAMPHOR questionnaire (at selected centers). Exploratory endpoints a. Time from randomization to first CEC-confirmed MM event (excluding disease progression) up to Study Closure b. Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the treatment period c. Time from randomization to CEC-confirmed death due to PAH up to 7days after last study drug intake in the treatment period d. Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study closure e. Time from randomization to first CEC-confirmed MM event up to Study Closure f. Time from randomization to CEC-confirmed death due to PAH up to Study Closure g. CEC-confirmed (potentially recurrent) hospitalizations due to

	worsening of PAH up to Study Closure h. Time course of CEC-confirmed (potentially recurrent) MM events hospitalization due to worsening of PAH, initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH, and death up to Study Closure i. Change from Baseline to Week 16 in 6MWD measured at trough j. Change from Baseline to EOS in 6MWD measured at trough k. Borg dyspnea index at Week 16 l. Borg dyspnea index at EOS m. Absence of worsening from Baseline to Week 16 in modified NYHA/WHO functional class n. Change from Baseline to EOS in modified NYHA/WHO functional class o. Change from Baseline to EOS in plasma NT pro-brain natriuretic peptide (NT pro-BNP) p. Change from Baseline to Week 16 in the sub-scale 'Breathlessness' of the 'Symptoms' score in the CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) questionnaire (at selected centers) q. Change from Baseline to Week 16 in the 'Symptoms' score of the CAMPHOR questionnaire (at selected centers) r. Change from Baseline to EOS in the sub-scale 'Breathlessness' of the 'Symptoms' score in the CAMPHOR questionnaire (at selected centers) s. Change from Baseline to EOS in the 'Symptoms' score of the CAMPHOR questionnaire (at selected centers)
TOLERABILITY / SAFETY ENDPOINTS	Safety and tolerability of ACT-293987 assessed as: • Treatment-emergent adverse events (AEs) until 7 days after last study drug intake* • AEs leading to permanent discontinuation of study drug • Treatment-emergent SAEs until 7 days after last study drug intake* • Treatment-emergent ECG abnormalities until 7 days after last study drug intake* • Treatment-emergent marked laboratory abnormalities until 7

	days after last study drug intake* • Change from Baseline to EOS in vital signs • Change from Baseline to EOS in bone turnover markers • Change from Baseline to EOS in retinal arterial tortuosity * The date of the “last study drug intake” refers to the date of the actual last study drug intake reported in the CRF during the treatment period.
PHARMACOKINETIC / PHARMACODYNAMIC EVALUATIONS	• Pharmacokinetic sampling for trough plasma concentrations of ACT-293987 and ACT-333679 at Baseline, Week 4, Week 8, Week 16, Week 26 (Month 6), Week 52 (Month 12), and EOS • PK sampling after drug administration at Week 16. • Relationship between ACT-293987/ACT-333679 plasma levels and clinical endpoints and plasma NT pro-BNP.
PHARMACOECONOMIC ENDPOINTS	• Number per year of all-cause and PAH-related hospitalizations from Baseline to EOS • Number per year of in-hospital patient days for all causes and PAH-related causes from Baseline to EOS
STATISTICAL METHODOLOGY	Hypotheses Hypotheses are formulated in terms of “survival” functions $S(t)$, <i>i.e.</i>, the probability that time to first MM event confirmed by the CEC is $\geq t$ for a day t (relative to the date of randomization). One-sided hypotheses are expressed in terms of the survival functions $S_{m/m,selexipag}(t)$ and $S_{m/m,placebo}(t)$. $H_{0,m/m}$: $S_{m/m,selexipag}(t) \leq S_{m/m,placebo}(t)$ for all $t \geq 0$ versus $H_{A,m/m}$: $S_{m/m,selexipag}(t) \geq S_{m/m,placebo}(t)$ for all $t \geq 0$ and $S_{m/m,selexipag}(t) > S_{m/m,placebo}(t)$ for some $t > 0$. Primary statistical analysis The primary statistical analysis will be performed on the Full Analysis Set by a one-sided unstratified log-rank test in a group-sequential setting with options for the DMC to recommend stop for futility or for compelling and robust efficacy. The group-sequential design can be summarized as follows: • one-sided overall type-I-error probability is fixed to $\alpha = 0.005$ • maximum required information is specified as 331 first MM events confirmed by the CEC • one-sided type-I-error probability at the interim analysis is

	fixed to 0.00005 - one interim analysis is planned with 202 first MM events (an information fraction of $f = 202/331 = 0.61$) confirmed by the CEC (however, if there are a few less or more such events available at the interim analysis, the one-sided type-I-error probability spent at the interim analysis will not be changed). Per Study Protocol Amendment 5, CEC confirmed MM events with onset date (as per CEC) up to 16 August 2011 are considered as censored at time of event onset in the primary statistical analysis. In order to determine sample size and power, the following assumptions have been made in addition to the group-sequential design features described above: - constant hazard rate of 0.2231 per year for placebo - constant hazard rate of 0.145 per year for selexipag (hazard ratio of 0.65) - constant hazard rate of 0.051 per year for drop-out (end of study without a MM event) in both treatment groups. These lead to a total of 331 MM events confirmed by the CEC in order to obtain an overall power of 90% for rejection of the null hypothesis. Under these assumptions, the probability to (correctly) reject the null hypothesis already at the interim stage is approximately 19%. If the true hazard ratio is 1, then the probability of (correctly) accepting the null hypothesis at the interim stage is approximately 50%. Analysis sets The primary endpoint analysis set for this study is the Full Analysis Set. The per-protocol set will be used for supportive/exploratory analyses. Secondary efficacy endpoints Secondary endpoints will be tested in the conditional sequence provided in the secondary efficacy endpoint section: a null-hypothesis can only be rejected for a secondary efficacy endpoint if the null hypotheses for all preceding efficacy endpoints (including the primary efficacy endpoint) have been rejected. For

	each secondary efficacy endpoint, the one-sided significance level will be set to 0.005 and two-sided 99% confidence intervals will be provided.
STUDY COMMITTEES	An independent Data Monitoring Committee (DMC) will review unblinded safety and tolerability data at regular intervals according to the DMC charter. The DMC will review outputs of the interim analysis for efficacy and safety, and may recommend early stopping for efficacy or futility. An independent Critical Event Committee (CEC) will review and confirm all MM events in a blinded fashion. A Steering Committee is involved in the study design and will provide guidance on the study conduct and study publications. An Ophthalmology safety board will review ophthalmology data and be consulted for their opinion and recommendation in case of specific ophthalmological findings. Two PAH experts blinded to treatment allocation will review the Baseline PAH characteristics of all patients included into the study.

Table 1 Visit and assessment schedule

	Screening	Visit 1	Tel. ^a W1	Tel. ^a W2	Tel. ^a W3	Visit 2	Tel. ^a W5	Tel. ^a W6	Tel. ^a W7	Visit 3	Tel. ^a W12	Visit 4	Visit 5 & onwards	Tel. ^a	Morbidity Mortality Event ^b	EOS Visit ^k	Safety Follow-up ^a 30 days after drug discontinuation ^o	EOTE visit ^m
	≤ 28 days before Day 1	BL D1 Randomization	Day 8 ± 3 d	Day 15 ± 3 d	Day 22 ± 3 d	Week 4 ± 3 d	Week 5 ± 3 d	Week 6 ± 3 d	Week 7 ± 3 d	Week 8 ± 3 d	Week 12 ± 3 d	Week 16 ± 3 d	W26 (M6) & every 6M ± 7 days	M9 & every 6 M ± 7d				
Written informed consent	X ^t																	
Inclusion/exclusion crit. (incl. hemodynamics)	X	Re-confirm																
Med. history incl. PAH	X	X																
Concomitant medications	X	X				X				X		X	X	X	X	X		X
Mod. NYHA/WHO FC	X	X				X				X		X	X		X	X		
Physical examination	X	X				X				X		X	X		X	X		
Weight and height ^h	X	X				X				X		X	X		X	X		
Vital signs	X	X				X				X		X	X		X	X		
12-lead ECG		X				X				X		X	X ^p		X	X		
6-minute walk test	X ^c	X								X		X	X		X	X		
Borg dyspnea score	X ^c	X								X		X	X		X	X		
CAMPBOR (subset)		X										X	X ^f			X		
Pregnancy test (if appl.) ⁱ	X	X				X				X	X	X	X			X		X
Laboratory test ^d	X	X				X				X		X	X		X	X		
Plasma NT pro-BNP		X				X				X		X	X			X		
PK sampling		X				X				X		X ⁿ	X ^e			X		
Ophthalmology (subset)		X ^q											X ^r			X ^s		
Study drug dispensing		X				X				X		X	X					
First dose of study drug		X p.m																
Dose titration			X	X	X	X	X	X	X		X ^g							
Drug accountability						X				X		X	X			X		X
(Serious) adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital status																X ^l		
Addendum to written ICF																X ^u		

a: Tel. = Scheduled telephone call. **b:** In case of suspected clinical worsening. **c:** Conducted ≤ 14 days before Day 1. **d:** Laboratory test (hematology and blood chemistry). **e:** On Visit 5 (Week 26, Month 6) & Visit 6 (Month 12) only. **f:** On Visit 5 (Week 26, Month 6), Visit 6 (Month 12) and Visit 8 (Month 24) only. **g:** Confirmation of MTD. **h:** Height measured only at screening. **i:** Serum pregnancy test to be performed at screening and urine pregnancy tests monthly until 1 month after study drug discontinuation. **k:** In case of premature discontinuation of study drug and for all patients on study drug at Study Closure. **l:** Survival follow-up phone call at Study Closure for patients with premature EOS not entering the post-treatment observation period. **m:** The End of Treatment Extension visit must be performed only for patients still on study drug at Study Closure and who wish to enter study AC-065A303/GRIPHON OL (if approved by the national Health Authority in the country). **n:** Two PK samplings will be taken at this visit, one pre-dose and one post-dose. **o:** For patients who will enter the OL study, SAEs must be followed-up until the first dose of ACT-293987 in the OL study. **p:** At Visit 6 (Month 12), two additional ECGs will be performed 2 and 4 hours after study drug intake. **q:** Performed at Baseline/Randomization Visit (Visit 1) (or within the screening period [28 days before Day 1]) **r:** Only at Visit 6 (Month 12). **s:** Performed at EOS Visit or within 2 weeks before or after the scheduled EOS Visit. (* 6 months corresponds to 26 weeks). **t:** Confirm that treatment-naïve patients cannot tolerate or have no access to PAH-specific therapy and that NYHA FC IV patients cannot be treated with i.v. prostanoïd. Throughout the course of the study, it is recommended to regularly discuss with the patient whether new PAH therapy is becoming available. **u:** applies to patients who will enter the post-treatment observation period after approval of amendment 6 while under study drug.

Table 1 (Con't) Visit and assessment schedule in the post-treatment observation period

	Site visits for patients in the post-treatment observation period	Phone calls for patients in the post-treatment observation period	Unscheduled visit in case of PAH worsening	Post-Treatment Observation Closure Visit (within 4 weeks after Study Closure announcement)
	Site visit ² : 6 months after EOS visit and every 6 months thereafter	Phone call: 3 months after EOS visit/first site visit ³ and every 6 months thereafter		
Addendum to Written Informed Consent Form	X if not already signed at EOS			
Concomitant medications for PAH ¹ (incl. O ₂ therapy)	X	X	X	X
Mod. NYHA/WHO functional class	X		X	X
Hospitalization for PAH worsening since last visit		X		
MM event details (excluding disease progression) ⁴	X		X	X
Vital status	X	X		X

¹ Concomitant medications for PAH include ERA, PDE5-I, Prostanoids and chronic O₂ therapy (change in dose will not be collected)

² For patients who had their EOS visit prior to approval of amendment 6, the first site visit of the post-treatment observation period may be scheduled more than 6 months after EOS visit. In such case, a retrospective data collection covering the entire period since EOS visit will be done.

³ For patients who had their EOS visit prior to approval of amendment 6, the first phone call will be three months after the first site visit

⁴ MM event form records clinical information needed for the adjudication of the event (e.g. hospitalization for PAH worsening, PAH worsening resulting in need of lung transplantation/atrial septostomy, symptoms of PAH worsening, ...).

1 BACKGROUND AND RATIONALE

1.1 Pulmonary arterial hypertension

The most serious chronic disorder of the pulmonary circulation is pulmonary arterial hypertension (PAH). PAH is characterized by pulmonary arterial vasoconstriction and vascular remodeling resulting in a progressive increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), ultimately leading to right ventricular failure and death. PAH is defined as a sustained elevation of mean pulmonary arterial pressure (mPAP) > 25 mmHg at rest (or > 30 mmHg with exercise), with a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg and PVR > 3 Wood units ($> 240 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$) [Rubin 2004].

The Updated Clinical Classification of Pulmonary Hypertension (Dana Point 2008) [Simonneau 2009] classifies the numerous conditions that are known to lead to, or to be associated with, the development of PAH into five groups, based on their similar clinical presentation, pathology, pathophysiology, prognosis, and, most of all, similar therapeutic approach. PAH may occur in the absence of a demonstrable cause (idiopathic or heritable), as the result of the use of drugs and toxins, or as a complication of congenital heart disease, systemic conditions such as connective tissue disease, particularly scleroderma, HIV infection, portal hypertension, schistosomiasis, or chronic hemolytic anemia.

The pathophysiology of PAH involves multiple pathways, which are influenced by many overlapping secondary messenger systems. Vasoconstriction, obstructive remodeling of the pulmonary vessel wall caused by extensive cell proliferation and reduced rates of apoptosis, inflammation, and thrombosis within the pulmonary arteries are promoted by activation of these pathways, and lead to elevated PAP and PVR, and eventually right ventricular failure.

Currently, there is no cure for PAH. However, improved understanding of the pathogenic factors of the disease has led to the development of new therapies targeting specific pathways (the prostacyclin pathway; the endothelin pathway and the nitric oxide pathway) [Humbert 2004, Farber 2004] that are believed to play an important role in the pathogenesis of PAH.

Today, a total of seven agents are currently approved for the treatment of PAH in the United States and/or in Europe: intravenous prostacyclin (epoprostenol), other prostanoid analogs, i.e., treprostinil (intravenous, subcutaneous and inhaled), and iloprost (inhaled), endothelin receptor antagonists (bosentan, ambrisentan) and phosphodiesterase type-5 (PDE-5) inhibitors (sildenafil, tadalafil). All of these agents have been shown to improve exercise capacity as assessed by 6-minute walk test (6MWT) in short-term randomized placebo-controlled trials.

Pure vasodilators, such as calcium channel blockers, are effective only in a minority of patients who have an acute response to vasodilator testing [Rich 1992, Sitbon 2005].

The available therapies have positive effects in PAH, but in many patients the disease will progress and PAH remains a serious life-threatening condition.

Early recognition and an understanding of the selection and timing of therapeutic options remain critical elements in the optimal management of patients with this disorder.

Before the development of recent therapeutic options, idiopathic PAH was rapidly progressive and led to right heart failure and death. In the early 1990s, it was reported that the median survival of patients was 2.8 years after diagnosis [D'Alonzo 1991]. The first large prospective studies showed an actuarial survival rate of 68 to 77%, 40 to 56%, and 22 to 38% at 1, 3, and 5 years respectively [D'Alonzo 1991, Galie 2009].

1.2 Prostacyclin (PGI₂) and pulmonary hypertension

Prostacyclin (Prostaglandin I₂, PGI₂), a metabolite of arachidonic acid, is formed via the cyclooxygenase pathway. Endothelial cells are the main source of prostacyclin and its action is directed to both the local vascular wall and to blood cells, particularly those that adhere to the endothelium. It is a potent endogenous vasodilator, inhibitor of platelet aggregation and smooth muscle cell proliferation through its activity at the prostacyclin (IP) receptor [O'Grady 1980].

The IP receptor is a G protein-coupled receptor (GPCR) that activates adenylate cyclase, leading to increased cyclic adenosine monophosphate (cAMP) levels in the target cells. cAMP has been widely implicated in the control of pulmonary vascular tone and inhibition of mitogenic pathways in vascular smooth muscle cells.

Patients with PAH have been shown to have a deficiency of prostacyclin [Christman 1998] and of PGI₂ synthase [Tuder 1999] causing an imbalance in prostacyclin (PGI₂) and thromboxane A₂ (TXA₂), its physiological antagonist. These findings led to the rationale that targeting the PGI₂ pathway with IP receptor agonists could be beneficial.

The first, epoprostenol, the chemical analog of prostacyclin, was approved in 1996 for NYHA/WHO functional class III–IV idiopathic PAH (IPAH) and PAH associated with scleroderma, and showed to improve exercise tolerance and survival in patients with IPAH [Barst 1996]. Since continuous intravenous epoprostenol became available, the prognosis for patients suffering from PAH has significantly improved. However, due to its short half-life and chemical instability, long-term epoprostenol therapy requires a permanently implanted central venous catheter and a portable infusion pump, exposing patients to a series of complications including catheter-related embolism or thrombosis,

infection, and delivery system malfunctions resulting in poorly tolerated overdosing or underdosing.

The complexity of epoprostenol therapy has led to attempts to develop other prostanoids with simpler modes of delivery. Treprostinil, a stable prostacyclin analog with a half-life of 3 h, has been developed for intravenous, subcutaneous delivery, and inhalation. It has beneficial effects on exercise and hemodynamics, which depend on the dose achieved. This, in turn, is determined by the patient's ability to tolerate the drug's side effects. Iloprost, another prostacyclin analog, has been approved for intravenous delivery and inhalation. Inhaled iloprost shows some selectivity of the hemodynamic effects to the lung vasculature, thus reducing systemic side effects, but has to be inhaled between 6 to 9 times per day, which may limit compliance.

The inconveniences of the administration routes of the above-mentioned drugs, such as injection site pain and reaction (redness and swelling) for subcutaneous administrations, or line infections, sepsis, hematoma, and local pain for intravenous infusions, are another factor influencing the patient's benefit from these treatments.

1.3 ACT-293987 – a non-prostanoid IP receptor agonist

ACT-293987 is an orally available drug that is readily hydrolyzed to the active metabolite ACT-333679. Both ACT-293987 and ACT-333679 are potent and selective agonists at the human IP receptor.

ACT-333679 has a 13-fold higher affinity for the human IP receptor [ACT-293987 IB] and is 15-fold more potent than ACT-293987 in activating the human IP receptor. *In vitro* studies showed that ACT-333679 has at least 130-fold lower affinity for other human prostanoid receptors such as the prostaglandin E₁₋₄, D₂, and F₂ receptors, as well as the thromboxane A₂.

ACT-293987 has been selected for further clinical development based on its pharmacokinetic (PK) profile observed in Phase 1 studies and the results from the Phase 2 study [Section 1.3.2].

1.3.1 Preclinical information

In vivo pharmacology studies demonstrated that orally administered ACT-293987 significantly reduced right ventricular systolic pressure (RVSP) and right ventricular hypertrophy (RVH) in a rat model of PAH. ACT-293987 also ameliorated the impaired relaxant response of the pulmonary artery from these animals.

Furthermore, ACT-293987 significantly increased survival of rats with monocrotaline-induced PAH [Kuwano 2008].

In normotensive rats prolonged administration of ACT-293987 did not attenuate the acute increase in femoral skin blood flow induced by the compound, suggesting lack of desensitization of the IP receptor [Kuwano 2007].

In a long-term toxicity study in rats, tortuosity and dilatation of retinal vessels were observed in Week 104 of treatment. Toxicity studies in rats (up to 26 weeks), mice (up to 13 weeks), and dogs (up to 39 weeks) did not show these findings, suggesting species specificity and a relatively late onset of toxicity. These findings were not accompanied by histopathological findings. Indeed, neither retinal edema nor retinal hemorrhage was reported.

In a 2 year carcinogenicity study in mice, nonmalignant neoplastic changes in the thyroid were observed.

1.3.2 Clinical information

1.3.2.1 Phase 1 studies in healthy subjects

A total of five Phase 1 studies have been performed to date (studies PS003, QGUY/2006/NS304/-01, AC-065-101, 186933, and NS304/P1/01).

During the Phase 1 program, a total of 187 healthy male subjects have been exposed to ACT-293987 (n = 150) or placebo (n = 37). In these studies ACT-293987 was well tolerated after single and multiple daily oral doses of up to and including 1,600 µg b.i.d. No serious adverse events (SAEs) were reported in any of the Phase 1 studies and the majority of the AEs were of mild intensity. The most frequently reported adverse events (AEs) were headache, myalgia, jaw pain, dizziness, nausea, vomiting, arthralgia, diarrhea, and abdominal pain. No clear dose relationship could be established for the above- mentioned AEs.

Multiple doses of ACT-293987 up to 1,600 µg b.i.d (study AC-065-101), starting with 400 µg b.i.d. and up-titrated in increments of 200 µg every 3rd day, were well tolerated. Most AEs were mild or moderate in intensity. The incidence of AEs was similar for all treatment groups, which suggests improved tolerability after repeated dosing. Tolerability decreased at a dose of 1,800 µg ACT-293987 b.i.d. and led to an increase in moderate AEs (headache, myalgia, and nausea) that required concomitant medication. The maximum dose tested in Japanese subjects was 600 µg b.i.d. There were no consistent differences in the number and type of AEs with increasing dose of ACT-293987.

Treatment with ACT-293987 up-titrated in increments of 200 µg to 1,800 µg (the highest dose tested in Caucasian subjects) or 600 µg (the highest dose tested in Japanese subjects) (study AC-065-101 and NS304/P1/01), were not associated with clinically relevant changes in systolic and diastolic blood pressures, heart rate, electrocardiogram (ECG) intervals and morphology, vital signs and laboratory tests. In addition, in the AC-065-101 study, no changes were observed in thyroid markers, orthostatic hypotension,

platelet aggregation test, bone formation, bone resorption markers, and coagulation markers.

Plasma concentration-time profiles and PK parameters of ACT-293987 and ACT-333679 were comparable across the studies performed in healthy subjects. The plasma concentration-time profiles of ACT-293987 revealed that, in general, maximum plasma concentrations were achieved in about 1–2 h after single-dose and multiple-dose administration. Thereafter, plasma concentrations of ACT-293987 decreased quickly. The plasma concentration-time profiles of ACT-333679 showed that, in general, maximum plasma concentrations were achieved in about 3–4 h after single- and multiple-dose administration. Thereafter, plasma concentrations of ACT-333679 compared to ACT-293987 decreased more slowly. In the study AC-065-101 the exposure (AUC) to ACT-333679 is approximately four times higher than to ACT-293987.

Following multiple oral administrations of ACT 293987, the apparent elimination half-lives of ACT 293987 and its active metabolite ACT 333679 were between 0.9 and 1.9 hours and between 7.9–14.5 h, respectively, which supports twice daily oral administration. The PK of ACT-293987, after both single- and multiple-dose administration, were approximately dose-proportional over the tested dose range, i.e., up to a single dose of 800 µg and multiple doses of 1,800 µg b.i.d. of ACT-293987. After multiple-dose administration, steady-state conditions of ACT-293987 and ACT-333679 were reached on Day 3. No relevant accumulation in plasma either of ACT-293987 or ACT-333679 occurred after multiple-dose administrations.

Results from study QGUY/2006/NS304/-01 indicate that food intake delayed the exposure to ACT-333679, as the median $t_{\max}$ increased from 2.5 hours during fasting to 4 hours in fed state, and decreased the exposure to ACT-333679 by 27%.

More subjects reported AEs in the fasted period than in the fed period. These results may indicate better tolerability of ACT 293987 when administered with food.

ACT-293987 did not influence the PK or pharmacodynamics (PD) of warfarin. Similarly, co-administration of warfarin with ACT-293987 did not have an impact on the exposure to ACT-293987 or its active metabolite ACT-333679.

The metabolism and excretion of ACT 293987 were studied following a single dose administration of radioactively labeled ACT 293987A (400 µg) (study 186933). 105% of the radioactivity was excreted primarily via feces (93%) and urine (12%). Excretion was complete after 5 days indicating no relevant retention of drug-related material in man.

When comparing the PK of ACT-293987 and ACT-333679 from study QGUY/2006/NS30/-01, which mainly included Caucasian subjects, to those of study NS304/P1/01, which included only Japanese subjects, the concentrations of both ACT-293987 and ACT-333679 were higher in Japanese subjects. The difference in the

PK was mainly due to the difference in body weight. When corrected for body weight a small residual difference was observed, however this difference was within one standard deviation of the mean and not consistent between the different dose levels. The clinical relevance of this observation is currently unknown.

In study AC-065-102 investigating the photosensitizing potential of ACT-293987, doses of 800 and 1,200 µg ACT-293987 did not show any difference in the phototoxic index compared to placebo and the mild photosensitizing agent ciprofloxacin. The study did not indicate that ACT-293987 has clinically relevant photosensitizing potential in humans.

For more detailed information please refer to the Investigator's Brochure [\[ACT-293987 IB\]](#).

1.3.2.2 *Phase 2 studies in patients with pulmonary arterial hypertension*

A Phase 2a proof-of-concept study in PAH (NS-304/-02) was completed in July 2009.

The study NS-304/-02 was conducted in seven European centers and enrolled 43 patients with PAH, who were randomized in a 3:1 ratio to ACT-293987 (n = 33) or placebo (n = 10). All enrolled patients received double-blind study treatment, which was prematurely discontinued in three patients (two on ACT-293987 and one on placebo). Median exposure to study treatment was 146 days in the placebo group and 149 days in the ACT-293987 group. For most patients, PAH was idiopathic (70% and 73% of patients in the placebo and ACT-293987 groups, respectively). At baseline, all patients were receiving either an ERA (bosentan, 70% and 61% of patients in the placebo and the ACT-293987 group, respectively), or sitaxentan in four patients in the ACT-293987 group only) or a PDE-5 inhibitor (sildenafil 60% and 64% of patients in the placebo and the ACT-293987 group, respectively). Three patients in the placebo group (30%) and 12 patients in the ACT-293987 (36%) were receiving both an ERA and a PDE-5 inhibitor.

After 17 weeks of treatment, mean PVR was decreased from baseline in the ACT-293987 group (-168 ± 45 dyn·sec/cm⁵) and increased in the placebo group (137 ± 35 dyn·sec/cm⁵). Values at Week 17 expressed as a percent of baseline values showed a significant 30.3% reduction in PVR with ACT-293987 compared with placebo (P = 0.0045, Wilcoxon rank sum test). Similar improvements in PVR were observed in the All-randomized analysis set.

After 17 weeks of treatment, the mean 6-minute walk distance (6MWD) increased from baseline in the ACT-293987 group ($+24.7 \pm 12.9$ meters) and was unchanged in the placebo group ($+0.4 \pm 8.9$ meters), which resulted in a mean treatment effect of 24.2 ± 23.7 meters (P = 0.2218, Wilcoxon rank sum test). Three subjects showed aggravation of PAH during the double blind study, two patients in the placebo group (20%) and one (3.3%) patient in the ACT-293987 group. All three patients were in

NYHA/WHO functional class III at baseline. A statistically significant increase of Cardiac Index was observed in the ACT-293987 group when compared to a decrease in the placebo group, which resulted in a mean treatment effect: 0.48 ± 0.17 L/min/m², ($\pm$ standard error) ($P = 0.0137$, Wilcoxon rank sum test). A statistically significant decrease of SVR was observed in the ACT-293987 group when compared to an increase in the placebo group, which resulted in a mean treatment effect: -407.8 ± 164.2 dyn·sec/cm⁵, ($\pm$ standard error) ($P = 0.0071$, Wilcoxon rank sum test).

Ten (100%) patients in the placebo group reported a total of 39 treatment-emergent adverse events, whilst 31 (93.9%) patients in the ACT-293987 group reported a total of 182 adverse events (AE). The most frequently reported AE in the active group was headache, reported in 22 patients (66.7%) in the ACT-293987 group compared with two patients (20%) in the placebo group. In the ACT-293987 group, pain in jaw, pain in extremity, nausea, diarrhea, flushing, dizziness, cough, and myalgia were reported in 12 patients (36.4%), 10 patients (30.3%), nine patients (27.3%), six patients (18.2%), six patients (18.2%), five patients (15.2%), four patients (12.1%), and four patients (12.1%) respectively. Most AEs in both treatment groups were of mild or moderate intensity, but a severe event was experienced by a larger proportion of patients on placebo (40%) than in the ACT-293987 group (18.2%). Seven serious adverse events (SAEs) were reported in four patients (40%) in the placebo group. Fourteen SAEs were reported in six patients (18.2%) in the ACT-293987 group. There were no changes from baseline to the end of treatment in either systolic or diastolic blood pressure, or in heart rate in the placebo group and in the ACT-293987 group. The analysis of marked laboratory abnormalities (MLA) in the ACT-293987 compared to the placebo group did not reveal any relevant increase of the incidence of MLA after ACT-293987 treatment. No clinically relevant ECG changes were observed in either treatment groups.

The open-label extension study (NS-304/-03) with 39 patients enrolled is ongoing and will continue in order to gather long-term safety information.

1.4 Study rationale

1.4.1 Medical and regulatory background

ACT-293987 is a new, selective, orally active non-prostanoid IP-receptor agonist selected for clinical development in PAH.

Prostacyclin (epoprostenol) and analogs like treprostinil (intravenous, subcutaneous, and inhaled) and iloprost (inhaled) have been approved for PAH. However, the administration routes are not always convenient. For subcutaneous administrations, injection site pain and reaction (redness and swelling) occur in the majority of patients. For intravenous infusions, line infections, sepsis, hematoma, and local pain are most common. Inhaled iloprost has to be given between 6 to 9 times per day, which may limit compliance. An orally available medicinal product, such as ACT-293987, which, by targeting the

prostacyclin pathway, could affect the progressive course of PAH would represent an important advancement in the clinical management of PAH patients, and provide a significant contribution in the treatment options for these patients

To date, several medicinal products have been approved for the treatment of pulmonary hypertension (PH), specifically PAH. The majority of controlled trials performed in PAH have been relatively short-term studies in selected populations.

This Phase 3 study will be event-driven and will aim at comparing ACT-293987 (at the maximal tolerated dose of 200–1,600 µg b.i.d.) with placebo in patients with PAH. The main objective in this study will be to demonstrate prolongation of time to the first morbidity and mortality (MM) event.

This Phase 3 study is considered pivotal for the registration of ACT-293987 for the indication pulmonary arterial hypertension.

1.4.2 Patient population

The target population will be patients with PAH (groups 1.1 to 1.4 of the updated Dana Point classification [Simonneau 2009]) occurring in the absence of a demonstrable cause (idiopathic or heritable), or associated with collagen vascular disease, congenital heart disease with simple systemic-to-pulmonary shunts surgically corrected (at least 1 year post-surgical), HIV infection, or drugs and toxins.

Patients will not be eligible for the study if they have PAH associated with portal hypertension, or if their PAH is associated with significant venous or capillary involvement, or has other causes than those mentioned above.

The study will enroll males and females aged from 18 years old to 75 years old with symptomatic PAH, who will receive ACT-293987 or placebo. Background therapy with existing PAH therapies, except for prostacyclin and prostacyclin analogs, will be allowed.

1.4.3 Study design

The study is designed as a multicenter, randomized, double-blind, parallel-group, placebo-controlled Phase 3 study to compare ACT-293987 (at the maximal tolerated dose of 200–1,600 µg b.i.d.) with placebo.

It is planned to randomize up to 1,150 patients (575 patients per group) in approximately 190 centers in 44 countries.

1.4.4 Comparative drug(s) and/or placebo

Patients participating in this study will receive ACT-293987 or matching placebo. Study medication can be given on top of a stable dose of endothelin receptor antagonists (ERAs) and/or phosphodiesterase-5 (PDE-5) inhibitors.

1.4.5 Dose selection

Up-titration to the individual patient's highest tolerated dose appears to be the most adequate treatment regimen for prostacyclin receptor (IP receptor) agonists, including epoprostenol (i.v.), treprostinil (i.v., s.c. and inhaled) and iloprost (inhaled). Starting with high doses of these compounds is associated with poor tolerability due to typical prostanoid-associated pharmacological effects such as headache, myalgia, flushing, nausea, and vomiting. Clinical experience with IP receptor agonists has shown that it is important to start at lower doses and up-titrate in order to improve tolerability.

ACT-293987 and its active metabolite ACT-333679 are potent and selective agonists at the human IP receptor. The pharmacological profile suggests that similar pharmacological and clinical effects as seen with other chronic-use IP receptor agonists can be expected, and therefore, a similar dosing regimen is recommended.

Results from Phase 1 studies with ACT-293987 have shown the occurrence of typical PGI₂-related AEs such as headache, nausea, flushing, leg pain, and jaw pain. The data indicate that an up-titration regimen improves tolerability. The findings from the completed Phase 1 study (AC-065-101), and from study NS-304/-02 support a titration regimen starting with a low dose (200 µg b.i.d.) and up-titration in increments of 200 µg up to a maximum of 1,600 µg b.i.d.

This approach, using gradually up-titration to each individual patient's highest tolerated dose is therefore expected to increase the potential of reaching an efficacious dose for each patient.

1.4.6 Treatment duration

The maximum treatment duration for this study is foreseen to be 4.3 years.

The study will be event-driven and, by definition will be terminated as soon as the targeted overall number of 331 CEC-confirmed MM events (defined in the primary endpoint) has been reached. With the recruitment of up to 1,150 patients randomized 1:1 to active treatment and placebo, over a period of 3.1 years (150 patients/1st year and 520 patients/year afterwards), this number of events is expected within a maximum of 4.3 years.

An interim analysis will be conducted by the independent Data Monitoring Committee (DMC) after observing approximately 202 CEC-confirmed MM events.

1.4.7 Primary endpoints

To date, most clinical studies have assessed exercise capacity in patients with PAH by measuring the 6MWD, used as primary surrogate endpoint.

However, PAH is a serious and progressive life-threatening disease with a life expectancy of 2.8 years from the time of diagnosis, if not treated [D'Alonzo 1991]. The goal of PAH therapy is to prolong survival of patients while improving symptoms and

preventing disease progression [Barst 2009]. Thus, the time to MM is considered to be a hard and more clinically relevant endpoint.

In this study, the primary endpoint will be the time to first CEC-confirmed MM, up to 7 days after last study drug intake, defined as:

- Death (all-cause mortality)
or
- Hospitalization for worsening of PAH based on predefined criteria¹
or
- Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy
or
- Initiation of parenteral² prostanoid therapy or chronic oxygen therapy³ due to PAH worsening
or
- Disease progression (patients in NYHA/WHO functional class II–III at baseline) confirmed by :
 - decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) **and**
 - worsening of NYHA/WHO functional classor
- Disease progression (patients in NYHA/WHO functional class III–IV at baseline) confirmed by :
 - decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) **and**
 - need for additional PAH specific therapy.

MM events will be adjudicated in a blinded fashion by an independent CEC.

1.4.8 Statistical hypotheses and sample size

For the statistical analysis of the primary endpoint, the null hypothesis is that there is no difference between selexipag and placebo for the distribution of time to first CEC-confirmed MM event.

¹ Hospitalization for worsening of PAH based on predefined criteria is defined as any non-elective hospital stay (≥ 24 hours) for worsening of PAH. Worsening of PAH includes signs and symptoms of right heart failure (e.g., syncope or near syncope, cyanosis, increase of breathlessness, clinically relevant deterioration of exercise capacity, decrease of oxygen saturation, increased peripheral edema, hepatomegaly and ascites)

² Subcutaneous or intravenous

³ Chronic oxygen therapy is defined as a continuous use (at least 24 hours, 7 days per week) of oxygen, with the intention of maintaining the therapy long term.

The primary statistical analysis will be performed on the Full Analysis Set by a one-sided unstratified log-rank test in a group-sequential setting with options for the DMC to recommend stop for futility or for compelling and robust efficacy.

The group-sequential design can be summarized as follows:

- one-sided overall type-I-error probability is fixed to $\alpha = 0.005$
- maximum required information is specified as 331 first events confirmed by the CEC
- one-sided type-I-error probability at the interim analysis (planned with 202 events) is fixed to 0.00005.

In order to determine sample size and power, the following assumptions have been made:

- constant hazard rate of 0.2231 per year for placebo
- constant hazard rate of 0.145 per year for selexipag (hazard ratio of 0.65)
- constant hazard rate of 0.051 per year for drop-out (end of study without a MM event) in both treatment groups.

These lead to a total of 331 CEC-confirmed MM events in order to obtain an overall power of 90% for rejection of the null hypothesis.

Under these assumptions, the probability to (correctly) reject the null hypothesis already at the interim stage is approximately 19%.

If the true hazard ratio is 1, then the probability of (correctly) accepting the null hypothesis at the interim stage is approximately 50%.

This study design was introduced for the first time with the global amendment 4 which was submitted on 17 August 2011 to the FDA only. In order to eliminate any concern that the protocol change could be considered informed, all events with onset date up to 16 August 2011 are censored in the primary endpoint analysis.

2 STUDY OBJECTIVES

2.1 Primary objective

To demonstrate the effect of ACT-293987 on time to first morbidity and mortality event in patients with PAH.

2.2 Secondary objectives

To evaluate the effects of ACT-293987 on exercise capacity and other secondary and exploratory efficacy endpoints in patients with PAH.

To evaluate the safety and tolerability of ACT-293987 in patients with PAH.

3 INVESTIGATIONAL PLAN

3.1 Overall study design and plan

The study is designed as a multicenter, randomized, double-blind, parallel-group, placebo-controlled, prospective Phase 3 study to compare the effects (defined as efficacy, safety, tolerability, PK/PD) of ACT-293987 (at the maximal tolerated dose of 200–1,600 µg b.i.d.) versus placebo over a maximum treatment period of up to 4.3 years.

Patients will be up-titrated with weekly increments of 200 µg b.i.d. until reaching the individual maximum tolerated dose (MTD) [Section 3.3.2].

The study consists of the following periods:

- The **Screening period** will be completed within a maximum of 28 days before Baseline
 - The Screening period ends with the Baseline Visit at which randomization (1:1) will take place.
- **Treatment period:** From Baseline Visit to end of study (EOS) visit
 - Due to the fact that patients will take their first dose of study medication on the evening of the Baseline Visit, this day is called Day 1.
 - For an individual patient, the EOS Visit may occur before the Study Closure (in the case of premature study drug discontinuation) or shortly after Study Closure (within 4 weeks). Patients who discontinue study drug must have an EOS Visit and a post-treatment safety follow-up phone call.
 - Study Closure will be announced by the sponsor when the overall target number of 331 CEC-confirmed MM events has been reached or earlier, following the recommendation of the DMC. All patients still on study drug at Study Closure must have an EOS Visit shortly thereafter (within 4 weeks). Patients who have prematurely discontinued study drug should enter the post-treatment observation period. However, patients who do not enter the post-treatment observation period must be called at the time of Study Closure to ascertain vital status.
- **Treatment Extension period:** From the EOS Visit following the Study Closure, until the End-Of-Treatment-Extension (EOTE) visit following unblinding of the database. The unblinding of the database will be announced by the sponsor, and the patients must have the EOTE visit shortly thereafter (within 14 days).

Patients who had an EOS Visit following a MM event confirmed by the CEC, or an EOTE visit, are eligible to enter the Open-label study AC-065A303/GRIPHON OL (if approved by the national Health Authority in the country).

- **Observation period:** From Baseline Visit to EOS/Post-Treatment Observation Closure Visit (PTOCV) within 4 weeks after study closure announcement by the sponsor.
- **Post-treatment observation period:** After the EOS visit until the PTOCV for patients prematurely withdrawn from study drug

After their EOS visit, all patients who prematurely discontinued study drug will enter a post-treatment observation period until the announcement of study closure by the sponsor. Then, the PTOCV must be scheduled shortly thereafter (within 4 weeks). During the post-treatment observation period, site visits and telephone calls alternating every three months will be performed. Unscheduled site visits may also be performed if the patient's PAH condition deteriorates.

- **Post-treatment safety follow-up for SAEs:** SAEs must be reported up to 30 days after last study drug intake or until administration of the first dose of ACT-293987 in the open-label study, whichever comes first.

The length of treatment for subjects, who are on treatment until Study Closure, is 1.2–4.3 years. Based on the planned recruitment rate, up to 1,150 patients will be randomized over a period of 3.1 years.

An independent DMC will review unblinded safety and tolerability data at regular intervals to ensure patient safety. The DMC will perform one interim efficacy/futility analysis which is planned after observing approximately 202 CEC-confirmed MM events, corresponding to approximately 61% of the total target number of events in the primary endpoint analysis.

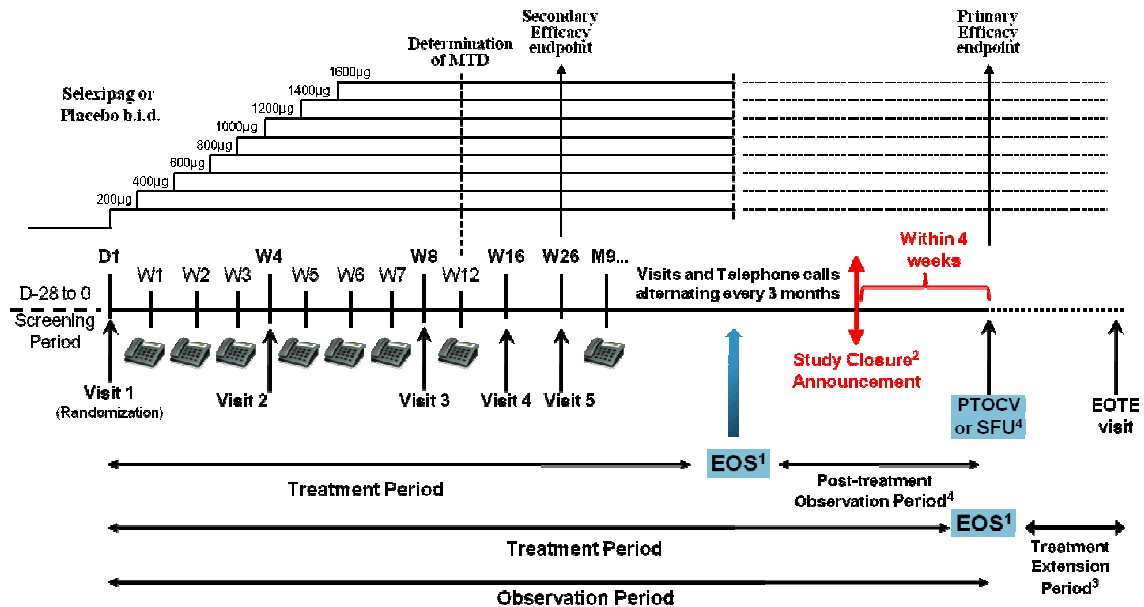
An independent **Critical Event Committee (CEC)** will review and confirm all MM events in a blinded fashion.

A **Steering Committee** is involved in the study design and will provide guidance on the study conduct and study publications.

An **Ophthalmology safety board** will review ophthalmology data and be consulted for their opinion and recommendation in case of specific ophthalmological findings.

Two PAH experts blinded to treatment allocation will review baseline characteristics related to PAH of all patients included into the study.

Figure 1 Study design



1. EOS Visit for an individual patient may occur before Study Closure (in the case of premature study drug discontinuation) or shortly after Study Closure (within 4 weeks). Patients who discontinue study drug before Study Closure must have an EOS Visit and a Post-treatment safety follow-up phone call.
2. Study Closure will be announced either after interim analysis or when the target number of CEC-confirmed MM events has been reached.
3. If the Open Label study AC-065A303 is approved by the national Health Authority, patients who are on study drug at Study Closure and who wish to enter the open-label study AC-065A303/GRIPHON OL must enter the Treatment Extension period.
4. Patients who prematurely discontinued study drug before Study Closure enter the post-treatment observation period, irrespectively of whether they are enrolled in the open-label study. When Study Closure is announced by the sponsor, a PTOCV is scheduled (within 4 weeks). Patients not consenting to participate in the post-treatment observation period will have their survival follow-up (SFU) phone call at Study Closure.

3.2 Study population

3.2.1 Patient population

Patients participating in this study are adult males and females with symptomatic PAH as defined in the inclusion criteria in Section 3.2.2 below.

3.2.2 Inclusion criteria

Eligible patients must meet all of the following inclusion criteria:

1. Signed informed consent prior to initiation of any study-mandated procedure.
2. Male and female^{4,5} patients aged from 18 years to 75 years inclusive with symptomatic PAH.
3. Patients with PAH belonging to one of the following subgroups of the Updated Clinical Classification Group 1 (Dana Point, 2008):
 - Idiopathic (IPAH)⁶, or
 - Heritable (HPAH)⁶, or
 - Drug or toxin induced, or
 - Associated (APAH) with one of the following:
 - Connective tissue disease
 - Congenital heart disease with simple systemic-to-pulmonary shunt at least 1 year after surgical repair
 - HIV infection

⁴ Women of childbearing potential must use a reliable method of contraception (failure rate less than 1% per year) from screening until 1 month after study drug discontinuation.

⁵ A woman is considered to have childbearing potential unless she meets at least one of the following criteria:

- previous bilateral salpingo-oophorectomy or hysterectomy
- premature ovarian failure confirmed by a specialist gynecologist
- pre-pubescence, XY genotype, Turner syndrome, uterine agenesis
- age > 50 years with amenorrhea for at least 24 consecutive months prior to screening.

⁶ Other forms of PH must have been excluded and must be appropriately documented in the patient chart (e.g., results of pulmonary function tests, ventilation/perfusion lung scan, echocardiogram/or cardiac MRI, hospital summary from referred patients).

4. Documented hemodynamic diagnosis of PAH by right heart catheterization – performed at any time prior to Screening showing:
 - Resting mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg
and
 - Resting pulmonary vascular resistance (PVR) $\geq 400 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$
and
 - Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVDEP) ≤ 15 mmHg (if available).
5. 6-minute walk distance between 50 and 450 m (inclusive) at Screening (within 2 weeks prior to the Baseline Visit and on a different day than this visit).

3.2.3 Exclusion criteria

Patients will not be entered into the study if they meet any of the following criteria:

1. Patients with pulmonary hypertension (PH) in the updated Dana Point Clinical Classification Groups 2–5, and PAH Group 1 subgroups that are not covered by the inclusion criteria.
2. Patients who have received prostacyclin (epoprostenol) or prostacyclin analogs⁷ (i.e., treprostinil, iloprost, beraprost) within one month before Baseline Visit, or are scheduled to receive any of these compounds during the trial.
3. Patients with moderate or severe obstructive lung disease: $\text{FEV}_1/\text{FVC} < 70\%$ and $\text{FEV}_1 < 65\%$ of predicted value after bronchodilator administration.
4. Patients with moderate or severe restrictive lung disease: Total Lung Capacity $< 70\%$ of predicted value.
5. Patients with moderate or severe hepatic impairment (Child-Pugh B and C).
6. Patients with documented left ventricular dysfunction (i.e., ejection fraction $< 45\%$)
7. Patients with severe renal insufficiency (estimated creatinine clearance $< 30 \text{ mL/min}$, or serum creatinine $> 2.5 \text{ mg/dL}$).
8. Patients with $\text{BMI} < 18.5 \text{ kg/m}^2$.
9. Patients who are receiving or have been receiving any investigational drugs within 1 month before the Baseline Visit.
10. Acute or chronic impairment (other than dyspnea), limiting the ability to comply with study requirements, in particular with 6MWT (e.g., angina pectoris, claudication, musculoskeletal disorder, need for walking aids).
11. Recently conducted (the program must be completed at least 8 weeks prior to

⁷ Single administration of medications used for acute vasodilator testing during RHC procedure is allowed (e.g. i.v./inhaled prostacyclin analogs or inhaled nitric oxide or oral sildenafil).

- screening) or planned cardio-pulmonary rehabilitation program based on exercise training
12. Psychotic, addictive or other disorder limiting the ability to provide informed consent or to comply with study requirements.
 13. Life expectancy less than 12 months.
 14. Females who are lactating or pregnant (positive pre-randomization serum pregnancy test) or plan to become pregnant during the study.
 15. Known hypersensitivity to any of the excipients of the drug formulations.

3.2.4 Concomitant medications

3.2.4.1 *Allowed concomitant medications*

Approved endothelin receptor antagonists (ERAs) and/or phosphodiesterase type-5 (PDE-5) inhibitors are permitted for the treatment of PAH. The dose must be stable for at least 3 months prior to Baseline/Randomization Visit and until Week 26 (Month 6). For diuretic therapy, the dose must be stable for at least 1 month prior to Baseline/Randomization Visit and until Week 26 (Month 6). Any change of dose must be recorded in the Case Report Form (CRF).

Single administration of medications used for acute vasodilator testing during RHC procedure is allowed (e.g. i.v./inhaled prostacyclin or inhaled nitric oxide or oral sildenafil).

3.2.4.2 *Prohibited concomitant medications*

- Due to the fact that ACT-293987 and its active metabolite, ACT-333679, are IP receptor agonists, prostacyclin (epoprostenol) and prostacyclin analogs⁸ (i.e. treprostinil, iloprost, beraprost) are prohibited from 1 month prior to Baseline until EOS Visit.
- Any investigational drug other than the study drug is prohibited from 1 month prior to Baseline until EOS or EOTE.

Introduction of new treatment for PAH (or increasing the dose) without CEC-confirmed MM event of PAH is strongly discouraged during the study period.

3.3 Study drugs

The study drugs are the investigational drug ACT-293987, and matching placebo.

3.3.1 Investigational drug and matching placebo

Patients who meet all inclusion criteria and none of the exclusion criteria will receive ACT-293987 or matching placebo.

⁸ except for acute vasodilator testing during RHC procedure.

- The study drug will be provided by the sponsor in child-proof bottles containing 120 tablets which must not be stored above 25 °C and must be protected from moisture.
- The study drug is to be administered orally (p.o.) in tablets of 200 µg ACT-293987 or matching placebo.
- The dose regimen is b.i.d. (twice daily) with an interval of approximately 12 hours.
- Depending on the MTD of the patient, a single dose will consist of 1 to 8 tablets (200 to 1,600 µg) of investigational drug or placebo.
- The MTD of an individual patient will be determined after a 12 weeks up-titration phase, and kept stable at least until the Week 26 assessment of the secondary endpoint [as described in Section 3.3.2]. After Week 26, the investigator will be allowed to further increase the dose if needed (only at scheduled visits and up to the maximum of 1,600 µg b.i.d.) by 200 µg b.i.d. increments. Dose reduction may occur at anytime if the investigator identifies a tolerability concern for a patient.
- Due to the fact that this study drug must be up-titrated in order to reach an individual MTD, any interruption of study drug intake of 3 days or more will require a new up-titration [see Section 3.4.1].

3.3.2 Study drug up-titration

The study drug must be up-titrated to each individual patient's MTD in the range of 200 µg to 1,600 µg b.i.d.

Patients will start with one tablet of ACT-293987 (200 µg) in the evening of Day 1 and with 200 µg b.i.d. on Day 2. If this dose is well tolerated, the dose will be up-titrated by the investigator in 200 µg b.i.d. increments at weekly intervals during scheduled telephone calls or visits until reaching the patient's MTD.

The decision to not further up-titrate the dose will be based on the investigator's medical judgment based on the occurrence and severity of typical pharmacological effects of IP-receptor agonists, such as headache, jaw pain, myalgia, flushing and nausea, that cannot be tolerated by the patient.

The dose will then be reduced by 200 µg b.i.d., and this adjusted dose will be defined as the MTD.

At Week 12 (scheduled phone call), the MTD for each patient will be determined: this dose must be kept stable for the next 14 weeks (from Week 12 on) until the Week 26 (Visit 5) assessment of the secondary endpoint, change in 6MWD.

After Week 26, investigators will be allowed to titrate the dose of the patient further if needed (up to the maximum of 1,600 µg b.i.d.) by 200 µg b.i.d., and only at scheduled visits. All titrations must be documented in the CRF.

3.3.3 Study drug dosing scheme

Table 2 Dosing scheme

Period	Duration	Dose regimen	
First dose	Day 1 in the evening (p.m.)	200 µg	1 tablet
Up-titration	Day 2 a.m. to Day 8 a.m.	200 µg b.i.d.	1 tablet b.i.d.
	Day 8 p.m. to Day 15 a.m.	400 µg b.i.d.*	2 tablets b.i.d.
	Day 15 p.m. to Day 22 a.m.	600 µg b.i.d. *	3 tablets b.i.d.
	Day 22 p.m. to Week 4 a.m.	800 µg b.i.d. *	4 tablets b.i.d.
	Week 4 p.m. to Week 5 a.m.	1,000 µg b.i.d. *	5 tablets b.i.d.
	Week 5 p.m. to Week 6 a.m.	1,200 µg b.i.d. *	6 tablets b.i.d.
	Week 6 p.m. to Week 7 a.m.	1,400 µg b.i.d. *	7 tablets b.i.d.
	Week 7 p.m. to Week 12 a.m.	1,600 µg b.i.d. *	8 tablets b.i.d.
Maintenance	From Week 12 throughout the study	Max. tolerated dose: 200–1,600 µg b.i.d.	1–8 tablets b.i.d.

* Or the highest tolerated dose until Week 12.

At the beginning of each up-titration phase, patients will be recommended to take the first dose in the evening in order to reduce the likelihood of the occurrence of headache, jaw pain, flushing, and nausea. The study drug should be taken with food.

Beginning with the morning of Visit 2, and at each visit thereafter, patients must not take the morning dose before completion of the CAMPHOR questionnaire (when applicable), the 6MWT (when applicable), the ECG and the blood samplings. In addition, at Week 16 a post-dose blood sampling will be taken for PK analysis. At Month 12 (Visit 6), two additional ECGs will be done 2 and 4 hours after study drug intake.

3.4 Study drug discontinuation and study withdrawal

3.4.1 Study drug interruption or discontinuation

The investigator must interrupt or permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the patient.

The interruption or premature discontinuation of study drug might be triggered by an AE, a diagnostic or therapeutic procedure, an abnormal assessment (e.g., ECG or laboratory abnormalities), or for administrative reasons (in particular withdrawal of the patient's

consent). The reason for study drug interruption or premature discontinuation must be documented in the CRF.

If the investigator becomes aware that a patient has developed moderate hepatic impairment (Child-Pugh B) at any time during the GRIPHON study, then it is the responsibility of the investigator to evaluate the benefit-risk of keeping the patient on study drug. In case a patient has developed severe hepatic impairment (Child Pugh C), the study drug must be discontinued.

Study drug must be permanently discontinued when a MM event is confirmed by the CEC. The patient must perform the EOS Visit and then enters the post-treatment observation period. For some patients prematurely withdrawn due to a MM event confirmed by the CEC, the entry into the post-treatment observation period will coincide with the participation into the OL study. During this period, regular clinic visit/phone contacts will be done until the PTOCV.

Any study drug interruption of 3 days or more will require new up-titration. Patients will start with one tablet of ACT-293987 (200 µg) b.i.d. If this dose is well tolerated, the dose will be up-titrated by the investigator in 200 µg increments up to the patient's maximum dose achieved before study drug interruption. The frequency of dose increment will be based on the medical judgment of the investigator, considering patient's tolerability to study drug prior to its interruption.

Interruptions of 1 day or more must be recorded on the study drug log in the CRF.

3.4.2 Patient's follow-up after study drug discontinuation

In the event of permanent discontinuation of study drug, patients must have an EOS Visit. Patients will be followed up for SAEs for 30 days after study drug discontinuation or until the first dose of ACT-293987 in the open-label study. In addition, patients will enter the post-treatment observation period and have a PTOCV at the time of Study Closure.

Patients who did not give their consent to the post-treatment observation period will be called at the time of Study Closure (approximately 4.3 years after study initiation) for vital status assessment, as previously agreed.

3.4.3 Study withdrawal

A patient will be considered as withdrawn from the study if, and only if, he/she is lost to follow-up after exhausting all means of contact.

The potential follow-up of patients after their withdrawal of consent will depend upon local regulations or specific agreement with the patients.

3.4.4 Replacement policy

3.4.4.1 Patients

Patients who prematurely discontinue from the study drug for any reason will not be replaced.

3.4.4.2 Centers

To ensure the successful completion of the study, the sponsor may wish to replace centers which have no patient enrollment. Centers not able to recruit any patients within 3 months of study initiation will be considered for closure.

3.5 Treatment exposure and compliance

Records of study drug used, dosages administered, and intervals between visits are to be kept during the study. Study drug accountability is to be performed on an ongoing basis by the study staff and checked by the monitor during site visits and at the completion of the study. Patients are to be asked to return all unused study drug at each visit.

Compliance with study treatment is based on drug accountability.

3.6 Treatment assignment and blinding

3.6.1 Treatment assignment

Both randomization and drug packaging are performed by the independent Contract Research Organizations (CROs) ICON (see contact details on page 2) and Creapharm, respectively.

Patients will be randomized to one of the treatment groups using a centralized randomization system via the Interactive Web/Voice Response System (IWRS/IVRS). A unique randomization number will be assigned to each patient (patient randomization number). The randomization will be stratified by site. Further details are provided in the IWRS/IVRS specification document and study-specific IWRS/IVRS user manual.

The randomization code must be kept strictly confidential, and accessible only to authorized persons who are not involved in the conduct and analysis of the study, until time of unblinding. A sealed randomization code is kept by Actelion Global Quality Management in a safe cabinet. A second set will be provided to the statistician of the independent Statistical Analysis Center (SAC).

The randomization code will be unblinded/broken and made available for data analysis only after Study Closure, i.e., when the study has been completed, the protocol deviations determined and the clinical database declared complete, accurate and locked.

3.6.2 Blinding

This study is performed in a double-blind fashion. The investigator and study staff, the patients, the monitors, and the sponsor staff will remain blinded to the treatment until study closure. The investigational drug and its matching placebo are indistinguishable and all patient kits will be packaged in the same way.

At regular intervals an independent DMC will review unblinded safety and tolerability data to ensure patient safety. In addition, the DMC will review the results of a single efficacy and safety interim analysis after observing approximately 202 CEC-confirmed MM events, corresponding to approximately 61% of the total target number of events in the primary endpoint analysis. The access to randomization information will be limited to the independent Statistical Analysis Center which will prepare all outputs for the DMC.

3.6.3 Emergency procedure for unblinding

The investigator and the study staff must remain blinded to the patient's treatment assignment, even if the patient refuses to participate in any study procedures or experiences an AE, or if the patient dies. The identity of the study drug may be revealed only if the patient experiences a medical emergency whose management would be improved by the knowledge of the blinded treatment assignment. In this case, emergency unblinding will be performed via IWRS/IVRS. A back-up system for code breaking will be put in place to ensure that this procedure remains possible, even if the IWRS fails.

The occurrence of any code break during the study must be clearly justified and explained by the investigator. Before breaking the code via the IWRS, every attempt must be made by the investigator to discuss the intended code break with the sponsor. In all cases, the sponsor must be informed as soon as possible before or after the code break.

Any code break must be documented in a detailed report with the date and time of the code break, and signed by the investigator. This report is to be attached to the CRF.

3.7 Study drug packaging and labeling

3.7.1 Study drug packaging

The sponsor will provide study drug or matching placebo as tablets in child-proof bottles containing 120 tablets.

3.7.2 Study drug labeling

The labeling and packaging of ACT-293987 and matching placebo will be conducted according to Good Manufacturing Practice, Good Clinical Practice, and any local or national regulatory requirements.

3.7.3 Study drug storage and dispensing

The investigator is responsible for safe and proper handling and storage of the study drug at the investigational site, and for ensuring that the study drug is administered only to patients enrolled in the study and in accordance with the protocol.

Study drug must be kept in a locked cabinet or room, which can be accessed only by the pharmacist, the investigator, or another duly designated person. The study drug must not be stored above 25 °C and must be protected from moisture. The study centers will be supplied with study drug according to each center's needs, depending on the rate of patient enrollment. Each center will have an individual stock of study drug, which will be re-supplied continuously as soon as a predefined minimum level of study drug has been reached.

Patients will receive child-proof bottles with 120 tablets each at Visit 1 (Randomization, Day 1), Visit 2 (Week 4), Visit 3 (Week 8), Visit 4 (Week 16), Visit 5 (Week 26, Month 6) and at the 6-monthly visits thereafter up to the EOS Visit. The patient will receive the amount of study medication at each of these visits needed to supply enough medication for the time interval between the visits.

Each bottle will have a label with a tear-off part specifying the study protocol number and the bottle number. When the medication is issued to the patient, the investigator or pharmacist (if applicable) must remove the tear-off part and attach it to the Drug Dispensing Log.

3.8 Study endpoints

3.8.1 Efficacy endpoints

3.8.1.1 *Primary efficacy endpoint*

The primary endpoint in this study is time to first MM event confirmed by the CEC up to 7 days after last study drug intake, defined as time from Baseline to the first of the following events:

- Death (all-cause mortality)
or
- Hospitalization for worsening of PAH based on predefined criteria⁹
or
- Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy

⁹ Hospitalization for worsening of PAH based on predefined criteria is defined as any non-elective hospital stay (≥ 24 hours) for worsening of PAH. Worsening of PAH includes signs and symptoms of right heart failure (e.g., syncope or near syncope, cyanosis, increase of breathlessness, clinically relevant deterioration of exercise capacity, decrease of oxygen saturation, increased peripheral edema, hepatomegaly and ascites).

- or**
- Initiation of parenteral¹⁰ prostanoid therapy or chronic oxygen therapy¹¹ due to worsening of PAH
- or**
- Disease progression (patients in modified NYHA/WHO functional class II-III at baseline) confirmed by :
 - decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) **and**
 - worsening of NYHA/WHO functional class
- or**
- Disease progression (patients in modified NYHA/WHO functional class III-IV at baseline) confirmed by :
 - decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) **and**
 - need for additional PAH specific therapy.

MM events will be adjudicated in a blinded fashion by an independent CEC. Each individual component of the primary endpoint (and its associated date) will be adjudicated by the CEC. The cause of death (related to PAH vs. not related to PAH) will be assessed by the CEC. These new CEC responsibilities have been implemented in Version 3 of the GRIPHON CEC Charter and re-adjudication of all MM events previously submitted to CEC will be done.

If there is a missing assessment (e.g. no confirmatory 6MWT, no modified NYHA/WHO functional class), the CEC will ultimately be responsible for confirming or not confirming the event and the associated date for the analysis of the primary endpoint using all available clinical data.

3.8.1.2 *Secondary efficacy endpoints*

- Change from Baseline to Week 26 in 6MWD measured at trough.
- Absence of worsening from Baseline to week 26 in modified NYHA/WHO functional class
- Borg Dyspnea Index at Week 26
- Time to death up to Study Closure.
- Change from Baseline to Week 26 in the sub-scale ‘Breathlessness’ of the ‘Symptoms’ score in the CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) questionnaire (at selected centers).

¹⁰ subcutaneous or intravenous

¹¹ Chronic oxygen therapy is defined as a continuous use (at least 24 hours, 7 days per week) of oxygen, with the intention of maintaining the therapy long term.

- Change from Baseline to Week 26 in the ‘Symptoms’ score of the CAMPHOR questionnaire (at selected centers).

The endpoints “Change from Baseline to Week 26 in 6MWD”, “Absence of worsening from Baseline to Week 26 in modified NYHA/WHO functional class” and “Borg dyspnea index at Week 26” are derived from the assessments at Baseline and Week 26.

The endpoints “Change from Baseline to Week 26 in the sub-scale ‘Breathlessness’ of the ‘Symptoms score’ in the CAMPHOR questionnaire” and “Change from Baseline to Week 26 in the ‘Symptoms’ score of the CAMPHOR questionnaire” are derived from the assessments of the CAMPHOR questionnaire at Baseline and at Week 26 evaluated at selected centers.

3.8.1.3 *Exploratory efficacy endpoints*

- a. Time from randomization to first CEC-confirmed MM event (excluding disease progression) up to Study Closure
- b. Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the treatment period
- c. Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the treatment period
- d. Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study closure
- e. Time from randomization to first CEC-confirmed MM event up to Study Closure
- f. Time from randomization to CEC-confirmed death due to PAH up to Study Closure
- g. CEC-confirmed (potentially recurrent) hospitalizations due to worsening of PAH up to Study Closure
- h. Time course of CEC-confirmed (potentially recurrent) MM events hospitalization due to worsening of PAH, initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH, and death up to Study Closure
- i. Change from Baseline to Week 16 in 6MWD measured at trough
- j. Change from Baseline to EOS in 6MWD measured at trough

- k. Borg dyspnea index at Week 16
- l. Borg dyspnea index at EOS
- m. Absence of worsening from Baseline to Week 16 in modified NYHA/WHO functional class
- n. Change from Baseline to EOS in modified NYHA/WHO functional class
- o. Change from Baseline to EOS in plasma NT pro-brain natriuretic peptide (NT pro-BNP)
- p. Change from Baseline to Week 16 in the sub-scale 'Breathlessness' of the 'Symptoms' score in the CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) questionnaire (at selected centers)
- q. Change from Baseline to Week 16 in the 'Symptoms' score of the CAMPHOR questionnaire (at selected centers)
- r. Change from Baseline to EOS in the sub-scale 'Breathlessness' of the 'Symptoms' score in the CAMPHOR questionnaire (at selected centers)
- s. Change from Baseline to EOS in the 'Symptoms' score of the CAMPHOR questionnaire (at selected centers)

3.8.1.4 *Imputation methods for efficacy endpoints*

Handling of missing data will be described in the Statistical Analysis Plan which will be finalized before the interim analysis.

3.8.2 **Safety and tolerability endpoints**

Except where otherwise specified, the last valid post-baseline value is carried forward in substitution for the missing values.

- Treatment-emergent AEs up to 7 days after last study drug intake.
- Adverse events leading to premature discontinuation of study drug.
- Treatment-emergent SAEs until 7 days after last study drug intake.
- Treatment-emergent ECG abnormalities up to 7 days after last study drug intake.
- Treatment-emergent marked laboratory abnormalities up to 7 days after last study drug intake. Marked laboratory abnormalities are defined in the sponsor's internal guidelines and will be assessed for the laboratory parameters described in Section 3.9.2.4.
- Change from Baseline to EOS in vital signs.
- Change from Baseline to EOS in bone turnover markers.
- Change from Baseline up to EOS in retinal arterial tortuosity.

The date of the "last study drug intake" refers to the date of the actual last study drug intake reported in the CRF during the treatment period.

For patients who prematurely discontinue due to a CEC-confirmed MM event, and who continue in the open-label study, the treatment-emergent AEs, ECGs and marked laboratory abnormalities will be counted until last study drug intake during the treatment period.

EOS will be derived from the date of EOS Visit as recorded in the CRF.

3.8.3 Pharmacoeconomic endpoints

- Number per year of all-cause and PAH-related hospitalizations from Baseline to EOS.
- Number per year of in-patient hospital days for all causes and PAH-related causes from Baseline to EOS.

3.8.4 Pharmacokinetic and pharmacodynamic endpoints

- Trough plasma concentrations of ACT-293987 and ACT-333679 at Baseline, Week 4, Week 8, Week 16, Week 26 (Month 6), Week 52 (Month 12), and EOS.
- Plasma concentrations of ACT-293987 and ACT-333679 will be evaluated by PK sampling at specific time intervals after drug administration at Week 16.
- The relationship between ACT-293987/ACT-333679 plasma levels and clinical endpoints and the effects of ACT-293987 on plasma NT pro-BNP levels.

3.9 Study assessments

When applicable, the patient must perform the specified assessments in the following order:

1. CAMPHOR questionnaire (at selected sites)
2. 6MWT / Borg dyspnea index

Beginning with the morning of Visit 2, and at each visit thereafter, patients must not take the morning dose before the completion of the CAMPHOR questionnaire (when applicable), the ECGs (except the post-dose ECGs at Visit 6), the 6MWT (when applicable) and the blood samplings. In addition, at Week 16 a post-dose blood sampling will be taken for PK analysis.

3.9.1 Efficacy assessments

3.9.1.1 6MWT and Borg dyspnea index

The 6MWT is recorded at Screening, Baseline, Week 8, Week 16, Week 26 (Month 6), and every 6 months thereafter, at EOS Visit, and also if there is a suspected MM event. It is a non-encouraged test, which measures the distance covered by the patient during a 6-minute walk [Appendix 1]. After Baseline, the 6MWT must be performed at trough (i.e., 12 h post dose).

The Borg dyspnea index is recorded after each 6MWT. The index rates dyspnea severity on a scale from '0' to '10' [[Appendix 2](#)].

3.9.1.2 *MM events*

MM events are recorded for the premature discontinuations, up to 7 days after the day of the last study drug intake during the treatment period, or up to 7 days after the EOS Visit for patients still on study drug at study closure. For patients in the post-treatment observation period, MM events (excluding disease progression) are recorded up to the post-treatment observation closure visit.

3.9.1.3 *Modified NYHA/WHO functional class*

Modified NYHA/WHO functional class [[Appendix 3](#)] is recorded at Screening, Baseline, Week 4, Week 8, Week 16, Week 26 (Month 6), and every 6 months thereafter, at EOS and if there is a suspected MM event. Modified NYHA/WHO functional class up to Study Closure is recorded at each site visit for patients in the post-treatment observation period.

3.9.1.4 *Vital status*

Vital status is recorded at each site visit and phone call during the post-treatment observation period. Vital status is also recorded at Study Closure for patients that did not enter the post-treatment observation period unless they withdrew informed consent.

3.9.1.5 *CAMPBOR questionnaire*

At selected sites, the CAMPBOR questionnaire is completed by the patient at Baseline, Week 16, Week 26 (Month 6), Month 12, Month 24, and EOS [[Appendix 4](#)].

The questionnaire consists of three domains (Symptoms, Activities and Quality of Life) with 25, 15 and 25 negatively weighted items respectively. The 25-item Symptoms score includes the Energy, Breathlessness, and Mood subscales, with 10, 8 and 7 items, respectively [[Mc Kenna 2006](#)].

Details about self-administration of the CAMPBOR questionnaire can be found in the CAMPBOR manual provided to the investigator.

3.9.2 *Safety and tolerability assessments*

The definitions, reporting, and follow-up of AEs, SAEs, and potential pregnancies are described in Section [4](#).

3.9.2.1 *Vital signs*

Vital signs (blood pressure and heart rate) are recorded at Screening, Baseline, Week 4, Week 8, Week 16, Week 26 (Month 6) and every 6 months thereafter, and at EOS. Vital signs are also recorded if there is a suspected MM event.

Blood pressure (systolic and diastolic) and heart rate will be measured non-invasively in a sitting position. The patient should rest for 5 minutes before measurement of blood pressure and heart rate. The right or the left arm may be used. However, the arm used for measurement should be kept constant throughout the study for an individual patient.

3.9.2.2 *Weight and height*

Height is recorded at Screening only and weight is measured and recorded at every visit until EOS, and if there is a suspected MM event.

3.9.2.3 *Physical examination*

Physical examination (i.e., inspection, percussion, palpation and auscultation) is performed at Screening, Baseline Visit, Week 4, Week 8, Week 16, Week 26 (Month 6) and every 6 months thereafter, at EOS, and if there is a suspected MM event. Clinically relevant findings that are present prior to study drug initiation must be recorded on the relevant Medical History CRF page. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be documented in the patient's medical records and recorded on an AE page of the CRF.

3.9.2.4 *Laboratory assessments*

□ **Type of laboratory**

A central laboratory (see contact details on page 2) will be used for blood chemistry and hematology tests at all visits from screening to EOS Visit. A serum pregnancy test will be analyzed centrally at screening and urine pregnancy tests will be performed locally at all visits except at screening. The screening laboratory tests may also be performed locally to assess patient eligibility (e.g., serum pregnancy test, creatinine clearance) before availability of the results from the central laboratory.

Laboratory reports will be available to the investigator. Clinically significant marked laboratory abnormalities must be reported by the investigator as an AE/SAE, as appropriate.

Details about collection and shipment of samples, and the reporting of results and abnormalities, can be found in the laboratory manual provided to the investigator.

□ **Laboratory parameters**

• **Hematology and blood chemistry**

Hematology and blood chemistry tests are performed at Screening, Baseline, Week 4, Week 8, Week 16, Week 26 (Month 6) and every 6 months thereafter, EOS, and if there is a suspected MM event. They include hemoglobin, hematocrit, counts of platelets, leukocytes and erythrocytes, liver aminotransferases (AST/ALT), alkaline phosphatase,

total and direct bilirubin, creatinine, urea, glucose, sodium, potassium and albumin, bone markers (bone alkaline phosphatase and carboxy-terminal telopeptide (CTx). Thyroid hormones (tri-iodothyronine [T3], thyroxine [T4]), and thyroid stimulating hormone (TSH) will be analyzed at all visits except screening.

- **Pregnancy test**

A serum pregnancy test for women of childbearing potential must be performed at Screening. Thereafter, urine pregnancy tests should be performed monthly up to at least 1 month after study drug discontinuation. Urine pregnancy tests are either performed during a scheduled visit or at home with the pregnancy test kit provided to the patient from Visit 3 onwards.

Results of pregnancy tests will not be recorded in the CRF but must be recorded in the patient's records.

3.9.2.5 **ECG**

A standard 12-lead ECG is performed at Baseline, Week 4, Week 8, Week 16, Week 26 (Month 6) and every 6 months thereafter, EOS and if there is a suspected MM event. The patient should rest for at least 5 minutes prior to the recording, and should be in a supine position during the recording. The ECG should be performed before the morning dose of study drug is taken.

At Month 12 (Visit 6) two additional ECGs will be done 2 and 4 hours after study drug intake.

Clinically relevant ECG findings that are present prior to the initiation of study drug must be documented in the Medical History section of the CRF.

Clinically relevant ECG findings found after the study drug initiation that were not present at Screening or that worsened during the study must be reported as an AE [see Section 4.2] as appropriate.

A central ECG service (see contact details on page 2) will be used for ECG evaluation.

Details about collection of ECG data, and the reporting of results and abnormalities, can be found in the ECG manual provided to the investigator.

3.9.2.6 ***Ophthalmological assessments (at selected sites for enrolled patients post global amendment 3)***

Ophthalmological monitoring (i.e., fundoscopy with digital pictures) will be performed at the Baseline/Randomization Visit (Visit 1) (or within the screening period [28 days before Visit 1]), Month 12 (Visit 6) and EOS Visit (or within 2 weeks before or after the scheduled EOS Visit) for patients enrolled at selected sites after approval of the global protocol amendment 3. Pictures will be taken by the ophthalmologist/qualified

ophthalmologist technician according to common guidelines. Pictures will be collected and read by an external central reading center.

At Baseline/Randomization and at follow-up assessments, the central reader will list the abnormal findings that have been observed on the fundoscopy images. In addition, arterial retinal tortuosity will be quantitatively assessed in order to measure the change from Baseline in this parameter at each post-baseline time point. In case of treatment-emergent abnormal findings, the central reader may advise on additional ophthalmological check-up.

In addition, an ophthalmology safety board will review ophthalmology data and be consulted for their opinion and recommendation in case of specific ophthalmological findings.

3.9.3 Pharmacokinetic and pharmacodynamic assessments

3.9.3.1 *Pharmacokinetic assessments*

Pharmacokinetic samples will be collected during this study for all patients, in order to provide information about the concentration of the drug and the active metabolite over time in the target population. Trough plasma concentrations of ACT-293987 and ACT-333679 will be measured at Visit 1 (Baseline) and before the morning dose at Visits 2 to 6, and at EOS. One additional PK sample will be taken from each patient at Visit 4 (Week 16) within a defined time-window. This will allow characterization of the time-course of ACT-293987 and ACT-333679. Further, the relationships between plasma concentrations of ACT-293987 and ACT-333679 and changes in efficacy and safety parameters will be evaluated.

□ Timing for sampling

For each patient, eight blood samples will be drawn: trough plasma concentrations of ACT-293987 and ACT-333679 will be evaluated by PK sampling at Baseline, Weeks 4, 8, and 16, Week 26 (Month 6), Month 12, and EOS, and at specified time intervals after drug administration of either 0.5 to 1h, 1 to 2h, 2 to 4h, 4 to 6h, 6 to 8h, and at 8 to 12h (due to b.i.d. dosing) during the dosing interval at Week 16. If for any reason the blood sample cannot be taken as recommended, the sample should be taken pre-dose in the morning within 1 week after the scheduled visit.

If the 8 to 12h time-window falls too late in the evening, the patient can come 1–2 days later, 8–12 hours after the morning dose; however the blood sample must be taken before the evening dose.

□ Procedures for sampling

For the PK sample at Visit 1 and the PK samples at trough at Visits 2 to 6, about 5 mL of blood will be collected in lithium heparin vacutainers, via either direct venipuncture or an

indwelling cannula. For the additional post-dose PK samples at Visit 4 (Week 16), about 5 mL of blood will be collected in lithium heparin vacutainers, via either direct venipuncture or an indwelling cannula. Detailed instructions for the collection, preparation, labeling, storage, and shipment of the plasma samples can be found in the laboratory manual provided to the investigator. The samples must be stored at -20°C or -80°C , and need to be analyzed before the 210-day expiry period.

Importantly, blood samples should be drawn before the morning dose of study drug is administered.

The actual date and clock times of drug intake and withdrawal of each blood sample are to be entered in the CRF.

Details on the assignment of the patient to a defined time-window are described in the site-guideline provided to the investigator.

□ **Bioanalysis**

The concentrations of ACT-293987 and ACT-333679 will be determined using a validated LC-MS/MS assay. The foreseen limit of quantification (LOQ) for both analytes is 0.01 ng/mL. Concentrations will be calculated by interpolation from a calibration curve. Quality control (QC) samples will be used to determine between-run and overall precision and accuracy of the analysis.

□ **Shipping procedures**

The site staff will be responsible for the shipment of the samples. Samples must be sent to the central laboratory, Quest (see contact details page 2) at time intervals as defined in the laboratory manual. The samples, together with the completed shipment forms, must be packed securely in polystyrene insulated shipping containers containing enough dry ice to last for 48 h. The central laboratory will ensure subsequent shipment of the PK samples to Swiss BioQuant AG.

3.9.3.2 Pharmacodynamic assessment (Plasma NT pro-BNP)

Plasma NT pro-BNP samples will be collected at Baseline, Week 4, Week 8, Week 16, Week 26 (Month 6) and every 6 months thereafter, and at EOS.

□ **Procedures for sampling**

About 6 mL of venous blood will be collected into lithium heparin vacutainers, via either direct venipuncture or an indwelling cannula. Detailed instructions for the preparation, labeling, storage, and shipment of the plasma samples can be found in the laboratory manual provided to the investigator. The samples must be stored at -20°C or -80°C .

The actual date and clock time of withdrawal of each blood sample is to be entered in the CRF.

□ Shipping procedures

The site staff will be responsible for the shipment of the samples. Samples must be sent to the central laboratory, Quest (see contact details page 2) at time intervals as defined in the laboratory manual. The samples, together with the completed shipment forms, must be packed securely in polystyrene insulated shipping containers containing enough dry ice to last for 48 h.

3.9.4 Baseline parameters and concomitant medication

3.9.4.1 *Baseline demographics and disease characteristics*

The following characteristics are to be recorded in the CRF at the Screening Visit:

- Medical history (previous and ongoing clinically significant diseases).
- Etiology of PAH, date of initial diagnosis of PAH by right heart catheterization and hemodynamic results (sPAP, dPAP, mPAP, PVR, cardiac output/cardiac index, right atrial pressure, PCWP, LVEDP, HR, MVSO₂) of the latest right heart catheterization, modified NYHA/WHO functional class, 6MWD and Borg dyspnea index.
- Age, gender, race, height, and weight.
- Vital signs (blood pressure and heart rate).

Before unblinding of the data, two PAH experts blinded to treatment allocation will review for all patients the Baseline parameters related to PAH (e.g. PAH etiology) as well as PAH background therapy and medical history. They will check whether patients fulfilled corresponding inclusion criteria and will classify their PAH into three categories:

Typical PAH: refers to PAH patients with no co morbidity that might introduce a doubt on the etiology of PAH (as per inclusion criterion 3)

Consistent PAH: refers to PAH patients not falling in either typical or atypical categories.

Atypical PAH: refers to PAH patients with traits that could suggest that the patients belong to other etiologies such as non group I or no PH.

3.9.4.2 *Concomitant medications*

PAH therapy (ongoing, initiated, discontinued) and diuretic therapy taken in the period between 3 months prior to Randomization (Baseline Visit) and up to EOTE visit following unblinding of the treatment allocation will be recorded on the Concomitant Medication pages of the CRF. Any dose changes in PAH therapy must be recorded in the CRF.

All other concomitant medications taken in the period between Randomization and EOTE visit following unblinding of the treatment allocation will also be recorded on the Concomitant Medication pages of the CRF.

3.10 Visit and assessment schedule

For a tabulated summary of all visits and assessments described in the following section, see [Table 1](#).

3.10.1 Screening period

3.10.1.1 *Screening visit*

The Screening Visit should be performed no more than 28 days prior to Randomization.

It is the responsibility of the investigator to obtain written informed consent from each patient participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

The informed consent form (ICF) must be signed and dated at the latest during the Screening Visit prior to the execution of any study assessment or procedure.

A confirmation that treatment-naïve patients cannot tolerate or had no access to PAH-specific therapy and that Functional Class IV patients cannot be treated with i.v. prostanoid will be requested. In addition, throughout the course of the study, it is recommended to regularly discuss with patients whether new PAH therapy became available to them.

Re-screening will occasionally be accepted and no more than one re-screening per patient will be allowed. The sponsor will review and document the reason for re-screening and inform the investigator if the re-screening is allowed or not.

The Screening Visit includes:

- Patient information and consent form signature
- Demographics
- Medical history
- Hemodynamic results of the latest right heart catheterization
- Concomitant medications
- Vital signs
- Height and body weight
- Physical examination
- NYHA/WHO functional class
- 6MWT and Borg dyspnea index (within 14 days prior to Visit 1)
- Complete laboratory tests including:
 - Hematology
 - Blood chemistry
 - Serum pregnancy test (for women of childbearing potential)

The investigator must check all the inclusion/exclusion criteria and decide on the patient's eligibility for the study.

3.10.2 Treatment period

From the start of treatment up to 7 days after the last study drug intake during the treatment period, MM events will be reported in the event pages of the CRF and as SAEs, if applicable.

For women of childbearing potential, a urine pregnancy test will be assessed monthly after initiation of study medication.

Beginning with the morning of Visit 2, and at each visit thereafter, patients must not take the morning dose before completion of the CAMPHOR questionnaire (when applicable), the 6MWT (when applicable), the ECG and the blood samplings. In addition, at Week 16 a post-dose blood sampling will be taken for PK analysis. At Month 12 (Visit 6), two additional ECGs will be done 2 and 4 hours after study drug intake.

3.10.2.1 Baseline/Randomization Visit (Visit 1)

Visit 1 is the start of the observation and treatment period for patients who are eligible.

- Medical history (including clinically relevant ophthalmological findings)
- CAMPHOR questionnaire (at selected sites)
- Concomitant medications
- Weight
- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG
- 6MWT and Borg dyspnea index
- Pregnancy test for women of childbearing potential
- Blood sampling for hematology, biochemistry and plasma NT pro-BNP
- Blood sampling for PK
- SAEs, only if related to study-mandated procedures
- Randomization and dispensing of study drug (ACT-293987 or matching placebo tablets) for 4 weeks
- Ophthalmological assessment: funduscopy with digital pictures (at selected sites for enrolled patients after approval of global protocol amendment 3)

3.10.2.2 Week 1 (telephone call)

- Recording of AEs/SAEs
- Titration to next dose (2 tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.3 *Week 2 (telephone call)*

- Recording of AEs/SAEs
- Titration to next dose (3 tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.4 *Week 3 (telephone call)*

- Recording of AEs/SAEs
- Titration to next dose (4 tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.5 *Visit 2 (Week 4)*

- Concomitant medications
- Weight
- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG
- Pregnancy test for women of childbearing potential
- Blood sampling for hematology, biochemistry and plasma NT pro-BNP
- Blood trough sampling for PK
- AEs/SAEs
- Return of unused medications including empty bottles, drug accountability
- Dispensing of study drug (ACT-293987 or matching placebo tablets) for 4 weeks
- Titration to next dose (five tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.6 *Week 5 (telephone call)*

- Recording of AEs/SAEs
- Titration to next dose (six tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.7 *Week 6 (telephone call)*

- Recording of AEs/SAEs
- Titration to next dose (seven tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.8 *Week 7 (telephone call)*

- Recording of AEs/SAEs
- Titration to next dose (eight tablets ACT-293987 b.i.d. or matching placebo)

3.10.2.9 *Visit 3 (Week 8)*

- Concomitant medications
- Weight
- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG

- 6MWT measured at trough (i.e., 12 hours post dose) and Borg dyspnea index
- Pregnancy test for women of childbearing potential
- Blood sampling for hematology, biochemistry and plasma NT-pro-BNP
- Blood trough sampling for PK
- AEs/SAEs
- Return of unused medications including empty bottles, drug accountability
- Dispensing of study drug (ACT-293987 or matching placebo tablets) for 8 weeks

3.10.2.10 ***Week 12 (telephone call)***

- Recording of AEs/SAEs
- Confirmation of MTD
- Pregnancy test result for women of childbearing potential (patient to perform pregnancy test at home with validated kit provided by the site)

3.10.2.11 ***Visit 4 (Week 16)***

- CAMPHOR questionnaire (at selected sites)
- Concomitant medications
- Weight
- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG
- 6MWT measured at trough (i.e., 12 hours post dose) and Borg dyspnea index
- Pregnancy test for women of childbearing potential
- Blood sampling for hematology, biochemistry and plasma NT pro-BNP
- Blood trough sampling for PK
- Recording of AEs/SAEs
- Blood post-dose sampling for PK within a defined time-window
- Return of unused medications including empty bottles, drug accountability
- Dispensing of study drug (ACT-293987 or matching placebo tablets) for 10 weeks

3.10.2.12 ***Visit 5 (Week 26, Month 6)***

- CAMPHOR questionnaire (at selected sites)
- Concomitant medications
- Weight
- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG
- 6MWT measured at trough (i.e., 12 hours post dose) and Borg dyspnea index

- Pregnancy test for women of childbearing potential (patient to perform pregnancy test at home with validated kit provided by the site)
- Blood sampling for hematology, biochemistry and plasma NT pro-BNP
- Blood trough sampling for PK
- Recording of AEs/SAEs
- Return of unused medications including empty bottles, drug accountability
- Dispensing of study drug for 6 months

3.10.2.13 ***Visit 6 (and every 6 months thereafter)***

- CAMPHOR questionnaire (at selected sites), only at Visit 6 (Month 12) and Visit 8 (Month 24)
- Concomitant medications
- Weight
- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG before study drug intake, and at Visit 6 (Month 12) 2 and 4 hours after study drug intake.
- 6MWT measured at trough (i.e., 12 hours post dose) and Borg dyspnea index
- Pregnancy test for women of childbearing potential (patient to perform pregnancy test at home with validated kit provided by the site)
- Blood sampling for hematology, biochemistry and plasma NT pro-BNP
- Blood trough sampling for PK, at Visit 6 (Month 12) only
- Recording of AEs/SAEs
- Return of unused medications including empty bottles, drug accountability
- Dispensing of study drug (ACT-293987 or matching placebo tablets) for 6 months
- Ophthalmological assessment: fundoscopy with digital pictures (at selected sites for enrolled patients after approval of global protocol amendment 3) only at Visit 6 (Month 12)

3.10.2.14 ***Telephone call Month 9 (and every 6 months thereafter)***

- Concomitant medications
- Recording of AEs/SAEs
- Patient to perform pregnancy test at home with validated kit provided by the site.

3.10.2.15 ***MM event (in case of suspected MM)***

In the case of a suspected MM event, the MM event's assessments and corresponding AE page must be completed.

For a suspected MM event, the assessments include:

- Concomitant medications

- Vital signs (blood pressure and heart rate)
- NYHA/WHO functional class
- Physical examination
- Weight
- 12-lead ECG
- 6MWT, Borg dyspnea index
- Blood sampling for hematology and biochemistry
- Recording of AEs/SAEs

When a MM event is confirmed by the CEC (as defined in the primary endpoint of the study), the patient must have the EOS Visit. The study medication should be permanently discontinued at EOS Visit. These patients will be offered entry into the open-label study AC-065A303/GRIPHON OL (if approved by the national Health Authority in the country).

3.10.2.16 ***EOS Visit***

The EOS Visit is performed in the case of a permanent discontinuation of study drug due to an AE, withdrawal of consent, or a CEC-confirmed MM event, and for all patients still on study drug at the Study Closure [see Section [3.10.4](#)].

The EOS Visit assessments include:

- CAMPHOR questionnaire (at selected sites)
- Concomitant medications
- Blood trough sampling for PK
- Vital signs (blood pressure and heart rate)
- Weight
- NYHA/WHO functional class
- Physical examination
- 12-lead ECG
- 6MWT measured at trough (i.e., 12 hours post dose) and Borg dyspnea index
- Pregnancy test for women of childbearing potential
- Blood sampling for hematology, biochemistry and plasma NT pro-BNP
- Recording of AEs/SAEs
- Return of unused medications including empty bottles, drug accountability. When applicable, dispensing of study drug for the Treatment Extension Period.
- Ophthalmological assessment: funduscopy with digital pictures (at selected sites for enrolled patients after approval of global protocol amendment 3) at EOS visit or within 2 weeks before or after the scheduled EOS Visit.

3.10.3 Follow-up period

3.10.3.1 30-day follow-up

Patients will be contacted by telephone 30 days after study drug discontinuation (Safety follow-up call). The Safety follow-up call is only applicable for patients who have not entered the open-label study within 30 days after study drug discontinuation.

The Safety follow-up phone call must be documented in the patient chart.

3.10.3.2 *Post-treatment Observation Period*

The post-treatment observation period starts immediately after the EOS visit and terminates with the post-treatment observation closure visit (PTOCV).

- For patients prematurely discontinuing study drug after approval of amendment 6, the addendum to written informed consent form will be signed at the time of the EOS visit. Then, patients will attend regular site visits and phone calls alternating every three months. In addition, unscheduled visits in case of PAH worsening may occur to collect potential morbidity events.
- Patients who did not withdraw their consent and had their EOS visit performed prior to approval of amendment 6 will be contacted to establish their vital status. Patients will be offered to come back to the clinic to participate, upon signature of a new informed consent, in the post-treatment observation period including data collection of potential morbidity events (excluding disease progression) that may have occurred from their EOS visit until their first clinic visit following amendment 6 approval. Afterwards patients will attend regular site visits and phone calls alternating every three months. In addition, unscheduled visits in case of PAH worsening may occur to collect potential morbidity events. For patients who died after their EOS visit, a family member will be proposed to come back once to the clinic to collect, after signature of a separate informed consent, data on hospitalization(s) for PAH worsening that may have occurred between EOS visit and patient's death.
- Patients not consenting to participate in the post-treatment observation period will still have their SFU phone call at study closure as previously agreed.

Site Visit 6 months after EOS visit and every 6 months thereafter until Post-Treatment Observation Closure Visit (within 4 weeks after announcement of Study Closure by the sponsor):

- Concomitant medications for PAH (ERA, PDE5-I, Prostanoids and chronic O₂ therapy)
- Modified NYHA/WHO functional class

- MM event details (excluding disease progression)
- Vital status

Telephone calls 3 months after informed consent signed at EOS visit and every 6 months thereafter:

- Concomitant medications for PAH (ERA, PDE5-I, Prostanoids and chronic O₂ therapy)
- Hospitalization for worsening of PAH since last visit
- Vital status

Unscheduled visit in case of PAH worsening:

- Concomitant medications for PAH (ERA, PDE5-I, Prostanoids and chronic O₂ therapy)
- Modified NYHA/WHO functional class
- MM event details (excluding disease progression)

3.10.4 Study closure

The Study Closure will be communicated by the Sponsor once the overall target number of 331 CEC-confirmed MM events is achieved (regardless whether recruitment was completed) or earlier, following the recommendation of the DMC.

All patients on study drug should perform their EOS Visit assessments for this study within 4 weeks after Study Closure is communicated by the sponsor.

Patients who are on study drug at Study Closure and have performed their EOTE Visit [see Section 3.10.4.1] will be offered entry into the open-label study AC-065A303/GRIPHON OL if the study is approved at the specific site and/or country.

For these patients, the treatment period will be extended from the EOS Visit until the sponsor is able to analyze the study results (database lock and unblinding). Then the End of Treatment Extension Visit will be performed and the patient transferred into the open-label study.

All patients who prematurely discontinue from the study and have their EOS Visit before Study Closure should enter the post-treatment observation period. However, patients who do not enter the post-treatment observation period will be contacted by phone within 4 weeks of the Study Closure to assess their vital status. The potential follow-up of patients after their withdrawal of consent will depend on local regulations or specific agreement with the patients.

3.10.4.1 *End of Treatment Extension Visit*

Patients who are on study drug at Study Closure and are eligible to enter the open-label extension study AC-065A303/GRIPHON OL will be allowed to extend their double-blind treatment period after the EOS Visit until the study is unblinded. After unblinding, patients will perform the End of Treatment Extension (EOTE) Visit and then be transferred into the open-label study and can either continue taking active treatment on their individual MTD or start up-titration of active treatment if the assigned treatment in this study was placebo.

The End of Treatment Extension Visit assessments include:

- Recording of concomitant medications
- Recording of new AEs/SAEs experienced since last visit (if applicable).
- Recording of the outcome and the resolution date of ongoing AEs at EOS Visit, on specific CRF pages.
- Return of unused medications including empty bottles, drug accountability.
- Pregnancy test for women of childbearing potential

4 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

4.1 Summary table

Periods	Screening	Treatment	Follow-up	After follow-up
Time frame	From signature of informed consent to study drug initiation	During study drug administration and until 7 days after last study drug administration ¹	From 7 days to 30 days after study drug discontinuation	After 30 days
AE/SAE reporting on CRF AE page	None	All AEs/SAEs (treatment-emergent ²)	None	None
SAE reporting on SAE form	Only if related to study-mandated procedures	All SAEs (treatment emergent ²)	All SAEs	If considered related to the previous exposure to study drug
Clinical study report	Not applicable	Analyzed	Described	Might be described

¹ or until the first dose of ACT-293987 in the open-label study (whichever occurs first)

² A treatment-emergent AE is any AE temporally associated with the use of study drug (from study drug initiation up to 7 days after study drug discontinuation or until the first dose of ACT 293987 in the open-label study [whichever occurs first]), whether or not considered related to the study drug.

The resolution date and outcome of all AEs that occurred during the double-blind study and are ongoing when the patient is entering the Treatment Extension period must be recorded on specific CRF pages. If the AE is worsening, a new AE must be recorded on specific CRF pages of the Treatment Extension with the onset date equal to the date of worsening.

4.2 Adverse events

4.2.1 Definitions of adverse events

An AE is any adverse change from the patient's baseline condition, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease, that occurs during the course of the study, whether or not considered related to the study drug.

A treatment-emergent AE is any AE temporally associated with the use of a study drug (from study drug initiation up to 7 days after study drug discontinuation or until the first dose of ACT-293987 in the open-label study [whichever occurs first]), whether or not considered related to the study drug.

Adverse events include:

- Exacerbation of a pre-existing disease
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study
- Lack of efficacy in the acute treatment of a life-threatening disease
- Events considered by the investigator to be related to study-mandated procedures
- Abnormal assessments, e.g., incident physical examination abnormalities, ECG findings, if they represent a clinically significant finding that was not present at baseline or worsened during the course of the study
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug

Adverse events do not include:

- Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
- Overdose of either study drug or concomitant medication without any signs or symptoms. However, overdose of study medication must be mentioned in the Study Drug Log.

4.2.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is reported on specific AE pages of the CRF.

If the intensity of an AE worsens during study drug administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

The three categories of intensity are defined as follows:

☐ **Mild**

The event may be noticeable to the patient. It does not influence daily activities, and usually does not require intervention.

☐ **Moderate**

The event may make the patient uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

☐ **Severe**

The event may cause noticeable discomfort, and usually interferes with daily activities. The patient may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious [see Section 4.3.1]. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event (such as severe headache) may be of relatively minor medical significance and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39 °C that is not considered severe may become serious if it prolongs hospital discharge by a day [see Section 4.3.1.2]. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

These definitions do not apply to clinically significant and asymptomatic laboratory test abnormalities or abnormal assessments (e.g., ECG findings) considered as AEs. The investigator should tick “non-applicable” on the AE page of the CRF to qualify the intensity of the AE.

4.2.3 Relationship to study drug

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study drug, and reported as either related or unrelated.

☐ **Related to study drug**

This category applies to any AE (whether serious or not) that appears to have a reasonable possibility of causal relationship to the use of the study drug (i.e., a relationship cannot be ruled out).

Guidelines to determine whether an event might be considered related include (but are not limited to) the following:

- The event occurred in close temporal relationship to study drug administration.

- The event abated (diminished) or disappeared when treatment with the study drug was down-titrated, interrupted, or discontinued.
- The event reoccurred when treatment was reintroduced.
- Environmental factors such as clinical state and other treatments could equally have caused the event.

□ Unrelated to study drug

This category applies to any AE (whether serious or not) that does not appear to have a reasonable relationship to the use of study drug (see above guidelines).

4.2.4 Reporting of adverse events

For patients who do not enter the open-label study AC-065A303:

All AEs occurring after study drug initiation and up to 7 days after study drug discontinuation must be recorded on specific AE pages of the CRF.

For patients who enter the open-label study AC-065A303:

All AEs occurring after study drug initiation and up to 7 days after study drug discontinuation or until the first dose of ACT-293987 in the open-label study (whichever occurs first) must be recorded on specific AE pages of the CRF.

4.2.5 Follow-up of adverse events

For patients who do not enter the open-label study AC-065A303:

Adverse events still ongoing 7 days after study drug discontinuation for a given patient must be followed up for 30 days after study drug discontinuation or until resolution or stabilization or until the event is otherwise explained. The follow-up information must be reported in the patient chart.

For patients who enter the open-label study AC-065A303:

Adverse events still ongoing at the time of entry in the open-label study will be followed and data will be collected as part of the open-label study.

4.3 Serious adverse events

4.3.1 Definitions

4.3.1.1 *Serious adverse events*

An SAE is defined by the International Conference on Harmonisation (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Fatal
- Life-threatening
- Requiring patient's hospitalization, or prolongation of existing hospitalization
- Resulting in persistent or significant disability or incapacity

- Congenital anomaly or birth defect
- Medically significant, or requires intervention to prevent at least one of the outcomes listed above

Life-threatening refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.

Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the patient, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The reference safety document to assess whether or not an SAE should be reported by the sponsor to Health Authorities, ECs/IRBs and investigators in an expedited fashion is the Investigator's Brochure [ACT-293987 IB, see also Section 4.3.2.4].

4.3.1.2 *Hospitalization – prolongation of existing hospitalization*

The following reasons for hospitalizations are not considered AEs, and are therefore also not SAEs:

- Hospitalizations for cosmetic elective surgery, or social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., elective hip replacement for arthritis. Complications that occur during hospitalization are AEs or SAEs (for example if a complication prolongs hospitalization).

4.3.1.3 *Serious adverse events related to study-mandated procedures*

A SAE is defined as related to study-mandated procedures if it appears to have a reasonable possibility of a causal relationship (i.e., a relationship cannot be ruled out) to such a procedure (other than administration of study drug). Examples of study-mandated procedures include discontinuation of a patient's previous treatment during a washout period, complication of a mandated invasive procedure such as blood sampling, car accident on the way to the hospital for a study visit, etc.

4.3.2 **Reporting of serious adverse events**

4.3.2.1 *Screening period*

Serious adverse events occurring between signing the Informed Consent Form and study drug initiation are only required to be reported if they are considered by the investigator to be related to study-mandated procedures.

As these SAEs are not reported as AEs in the CRF, they are collected only on an SAE form, and entered only into the drug safety database.

4.3.2.2 *Treatment period*

All SAEs, regardless of causal relationship, must be reported, including those related to study-mandated procedures.

For patients who do not enter the open-label study AC-065A303:

Those SAEs occurring after study drug initiation and up to 7 days after study drug discontinuation are defined as treatment-emergent SAEs.

For patients who enter the open-label study AC-065A303:

Those SAEs occurring after study drug initiation and up to 7 days after study drug discontinuation or until the first dose of ACT-293987 in the open-label study (whichever occurs first) are defined as treatment-emergent SAEs.

These SAEs are reported on SAE forms and also on AE pages in the CRF. They are therefore entered into both the drug safety and clinical databases, and must be reconciled before study closure.

4.3.2.3 *Follow-up period*

For patients who do not enter the open-label study AC-065A303:

All SAEs regardless of causal relationship occurring from 7 days after study drug discontinuation up to 30 days after study drug discontinuation must be reported on an SAE form.

For patients who enter the open-label study AC-065A303:

All SAEs regardless of causal relationship occurring from 7 days after study drug discontinuation up to the first dose of ACT-293987 in the open-label study must be reported on a SAE form for the study AC-065A302.

These SAEs are therefore entered only into the drug safety database.

4.3.2.4 *Reporting procedures*

All SAEs must be reported by the investigator to the Actelion drug safety department within 24 hours of the investigator's first knowledge of the event.

All SAEs must be recorded on SAE forms, irrespective of the study drug received by the patient, and whether or not this event is considered by the investigator to be related to study drug. These SAE forms must be faxed to the Actelion drug safety department (contact details for which are provided at the beginning of this protocol). The investigator must complete the SAE form in English (unless otherwise specified), and must assess the relationship of the event to study drug.

Such preliminary reports will be followed by detailed descriptions that may include copies of hospital case reports, autopsy reports, hospital discharge summaries and other documents when requested and applicable. Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Actelion drug safety department may contact the investigator to obtain further information.

When a SUSAR occurs for a patient participating in the study, Actelion Drug Safety will request the unblinding of the treatment code. This code will not be communicated to the site staff or to the Actelion study team; unblinded SUSAR information is only provided to Actelion Global Drug Safety, respective health authorities and IRBs/IECs. SUSARs will be anonymized.

The SAEs due to the underlying PAH disease and therefore expected to occur in this patient population, are listed in the Investigator's Brochure (section 6. Reference Safety Information). For expedited reporting, these SAEs will be treated as "disease-related" and expected. They therefore do not require systematic unblinding and do not require expedited reporting to Health Authorities, ECs/IRBs, and investigators. However, these events, as with all safety data, will be monitored during the study by the DMC.

4.3.3 Follow-up of serious adverse events

Serious adverse events still ongoing at the EOS Visit must be followed up until resolution or stabilization, or until the event is otherwise explained. The follow-up information must be reported on a SAE form and will therefore only be entered into the drug safety database.

4.3.4 Reporting of serious adverse events after the 30-day follow-up period

New SAEs occurring at any time after the 30-day follow-up period following study drug discontinuation may be reported on a SAE form to the sponsor's drug safety department within 24 hours of the investigator's knowledge of the event, if considered related to the previous exposure to study drug by the investigator. These SAEs are only entered in the drug safety database.

4.4 Pregnancy

4.4.1 Teratogenicity

In the reproduction toxicity studies performed so far, no changes were observed in fertility and teratogenicity. (A pre- and postnatal development study in the rat is ongoing).

However, appropriate precautions must be taken by women of childbearing potential. Women must not become pregnant during the study and for up to 1 month after study drug discontinuation.

If a woman becomes pregnant while on study drug, permanent discontinuation of study drug must be considered. The investigator must counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

4.4.2 Reporting of pregnancy

Irrespective of the treatment received by the patient, any pregnancy occurring during study drug administration or during the first month following study drug discontinuation must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the sponsor's Pregnancy form, which is to be faxed to the sponsor's drug safety department (see contact details provided on the Pregnancy form), and on an AE page of the CRF, as applicable.

4.4.3 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion and its outcome must be reported to the sponsor's drug safety department.

Such follow-up information will only be entered in the drug safety database, and hence will not affect study closure.

5 STATISTICAL METHODOLOGY AND ANALYSES

5.1 Analysis strategy

Study AC-065A302 is designed to be analyzed for the time to first MM endpoint up to 7 days after last study drug intake as defined in Section 3.8.1. It is assumed that the study can adequately support a New Drug Application (NDA) submission if the null hypothesis of no difference from placebo for time to event is rejected.

5.2 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be written and finalized before the interim analysis. The SAP will provide full details of the analyses and the algorithms to be used for data derivations.

5.3 Analysis sets

Four analysis sets are defined.

1. Full analysis set

The Full Analysis Set (FAS) includes all randomized patients.

All primary statistical analyses of efficacy endpoints are based on the FAS. In order to adhere to the intention-to-treat principle as much as possible, patients are evaluated according to the study treatment they have been randomized to (which may be different from the study treatment they have received).

2. Safety analysis set

The safety analysis set includes all randomized patients who received at least one dose of the study drug.

All statistical safety analyses are based on the safety analysis set. Patients are evaluated according to the study treatment they have received (which may be different from the study treatment they have been randomized to), defined as:

- if a patient has taken at least one dose of selexipag, she/he is assigned to the selexipag treatment group
- if a patient has taken only placebo, she/he is assigned to the placebo treatment group.

3. Per-protocol set

The Per-Protocol Set (PPS) comprises all patients included in the FAS up to the first occurrence of any of the following events:

- relevant violation of the inclusion/exclusion criteria
- missing or invalid assessments that could have a relevant impact on the interpretation of the primary endpoint
- start of any forbidden treatment for PAH

- start of study drug they were not randomized to
- individual (intentional or unintentional) unblinding of study treatment to the investigator.

Patients are evaluated according to the study treatment they have been randomized to (which may be different from the study treatment they have received).

Results for the primary and secondary efficacy endpoints based on the PPS supplement those based on the FAS and assess the robustness of treatment effects.

4. PK analysis set

The PK analysis set includes all patients in the FAS who received at least one dose of the study drug and had at least one PK sample collected after initiation of study drug.

5.4 Statistical analysis

5.4.1 Analysis of the primary efficacy endpoint

For the primary efficacy endpoint, the following MM events are considered up to 7 days after last study drug intake in the treatment period:

- Death (all-cause mortality)
- Hospitalization for worsening of PAH based on predefined criteria
- Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy
- Initiation of parenteral (subcutaneous or intravenous) prostanoid therapy or chronic oxygen therapy due to worsening of PAH
- Disease progression (patients in modified NYHA/WHO functional class II-III at baseline) confirmed by a decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) and worsening of NYHA/WHO functional class
- Disease progression (patients in modified NYHA/WHO functional class III-IV at baseline) confirmed by a decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) and need for additional PAH specific therapy.

Date of the first CEC-confirmed MM event (up to 7 days after last study drug intake in the treatment period) is defined as the onset date as provided by the CEC.

Time to first CEC-confirmed MM event up to 7 days after last study drug intake is defined as the date of the first CEC-confirmed MM event (up to 7 days after last study drug intake in the treatment period) minus randomization date plus 1.

Censoring rules

For patients without a CEC-confirmed MM event up to 7 days after last study drug intake in the treatment period, time to first CEC-confirmed MM event (up to 7 days after last study drug intake in the treatment period) is defined as

- minimum(date of last study drug intake in the treatment period plus 7, EOS visit date, date of last contact, analysis cut-off date) minus randomization date plus 1 for randomized patients with at least one administration of study treatment who did not consent for the post treatment observation period
- minimum(date of last study drug intake in the treatment period plus 7, date of last contact, analysis cut-off date) minus randomization date plus 1 for all other randomized patients with at least one administration of study treatment
- minimum(maximum[EOS visit date, randomization date], date of last contact, analysis cut-off date) minus randomization date plus 1 for all randomized patients without any administration of study treatment.

Per Study Protocol Amendment 5, CEC-confirmed MM events with onset date (as per CEC) up to 16 August 2011 are considered as censored at time of event onset in the primary statistical analysis. However, sensitivity analyses will explore other ways of handling the data up to 16 August 2011 (see Section 5.4.1.3).

5.4.1.1 Hypotheses

Hypotheses are formulated in terms of “survival” functions $S(t)$, i.e., the probability that time to first MM event confirmed by the CEC is $\geq t$ for a day t (relative to the date of randomization).

One-sided hypotheses are expressed in terms of the survival functions $S_{m/m,selexipag}(t)$ and $S_{m/m,placebo}(t)$.

$H_{0,m/m}$: $S_{m/m,selexipag}(t) \leq S_{m/m,placebo}(t)$ for all $t \geq 0$ versus

$H_{A,m/m}$: $S_{m/m,selexipag}(t) \geq S_{m/m,placebo}(t)$ for all $t \geq 0$ and $S_{m/m,selexipag}(t) > S_{m/m,placebo}(t)$ for some $t > 0$.

5.4.1.2 Primary statistical analysis

The primary statistical analysis will be performed on the FAS by a one-sided unstratified log-rank test in a group-sequential setting with options for the DMC to recommend stop for futility or for compelling and robust efficacy.

The group-sequential design can be summarized as follows:

- one-sided overall type-I-error probability is fixed to $\alpha = 0.005$
- maximum information is specified as 331 first MM events confirmed by the CEC
- one-sided type-I-error probability at the interim analysis is fixed to 0.00005

- one interim analysis is planned with 202 first MM events (an information fraction of $f = 202/331 = 0.61$) confirmed by the CEC (however, irrespective of the number of events available at the interim analysis, the one-sided type-I-error probability spent at the interim analysis will not be changed).
- in case the study will be continued to the planned end, one-sided type-I-error probability and its related critical value for the log-rank statistic at the final analysis will be calculated once the number of MM events confirmed by the CEC at the interim analysis is known.

The one-sided log-rank statistic Z is used to test the null hypothesis for time to first CEC-confirmed MM event described in Section 5.4.1. In addition, a non-binding interim futility stopping guidance is foreseen as outlined in Table 3 below.

Table 3 Summary of group-sequential design

Analysis stage (anticipated cumulative number of events ¹)	Efficacy			Futility		
	Cumulative alpha ² spent	Guidance ³ to reject H_0		Cumulative beta spent	Guidance ³ to accept H_0	
		p -value	Z-score		p -value	Z-score
Interim (202 events)	0.00005	≤ 0.00005	≥ 3.8906	0.0013	≥ 0.5	≤ 0
Final (331 events)	0.005	≤ 0.04991	≥ 2.5764	0.1	> 0.04991	< 2.5764

¹ If number of events observed at the interim analysis differs from 202, the interim boundaries are not to be changed.

² All significance levels (alpha) are one-sided.

³ The boundaries for the final analysis are definite whereas they are only guidelines for the DMC at the interim stage.

Efficacy boundaries will not be modified because of the presence of any futility rules. However, the DMC may apply the futility stopping rule as given in Table 3.

At the interim and, if applicable, final analysis stage, the following statistics are calculated:

- log-rank Z score (will be compared to the boundaries given in Table 3 but the DMC may recommend to continue the trial to its planned end even if an interim stopping criterion will have been met;
- point estimates and two-sided repeated 99% confidence interval for the hazard ratio from an unstratified proportional hazard model with treatment as the only covariate.

Supplementary statistical analysis after study termination:

Following termination of the study (after the interim or final analysis), a supplementary statistical analysis will be performed by applying the stage-wise ordering [Tsiatis 1984] of the sample space. Overall p -value as well as point estimate and two-sided 99%

confidence interval for the hazard ratio (all adjusted for the group-sequential design) will be provided.

In case the study is stopped based on the interim results, there will be additional data (in particular events confirmed for the primary efficacy endpoint) prior to the date of Study Closure. An additional analysis including all data up to Study Closure will be performed for an exploratory interpretation.

5.4.1.3 *Supportive statistical analyses*

The following supportive statistical analyses (based on the FAS if not otherwise stated) are planned:

- unstratified proportional hazards model
- log-rank test and proportional hazards model stratified by geographical region
- log-rank test and proportional hazards model stratified by modified NYHA / WHO functional class at Baseline (classes I/II and classes III/IV)
- log-rank test and proportional hazards model stratified by modified NYHA / WHO functional class at Baseline (classes I/II and classes III/IV) and concomitant PAH medication at Baseline (no/yes)
- competing risk analysis for a multi-state model containing the individual components of the primary endpoints as separate states
- attempts to address potential informative censoring, with the following circumstances identified as potentially informative censoring for the MM event:
 - MM events confirmed by the CEC with event onset date up to 16 August 2011
 - MM events not confirmed by the CEC but study treatment prematurely discontinued.
 - patient lost-to follow-up
- one-sided (unstratified and stratified as described above) log-rank tests and proportional hazards models ignoring all data up to 16 August 2011
- one-sided (unstratified and stratified as described above) log-rank tests and proportional hazards models handling MM events confirmed by the CEC with onset data up to 16 August 2011 as events instead of censored observations
- one-sided (unstratified and stratified as described above) log-rank tests and proportional hazards models excluding all data up to 16 August 2011
- subgroup analyses (Kaplan-Meier, log-rank tests, proportional hazards models) defined by the following baseline characteristics:
 - PAH therapy(ies) at baseline
 - gender
 - race: Caucasian/White vs Asian vs Black vs (Hispanic, other)

- PAH etiology: (idiopathic, heritable, drug or toxin induced, HIV infection) vs associated with connective tissue disease vs associated with congenital heart disease with systemic-to-pulmonary shunts
- geographic regions (will be defined in the SAP)
- one-sided unstratified log-rank test and proportional hazards model based on the PPS.

Supportive analyses of the selexipag dose effect on time to first CEC-confirmed MM relative to placebo will be performed:

- unstratified proportional hazards model with individual selexipag MTD as continuous single covariate
- unstratified proportional hazards model with individual selexipag MTD as categorical single covariate
- unstratified proportional hazards model with individual selexipag MTD as continuous covariate separately for patients with / without selexipag dose reductions because of AEs typical for selexipag (both subgroups compared to all patients randomized to placebo)
- unstratified proportional hazards model with individual selexipag MTD as categorical covariate (same categories as above) separately for patients with / without selexipag dose reductions because of AEs typical for selexipag (both subgroups compared to all patients randomized to placebo).

However, interpretation of these analyses is limited as individual selexipag dose has not been randomly assigned but is itself a post-baseline outcome (MTD).

All supportive statistical analyses carried out on the primary endpoint will be conducted with the same significance level as the primary analysis.

5.4.1.4 *Required number of events and power*

In order to determine sample size and power, the following assumptions have been made in addition to the group-sequential design features described in Section 5.4.1.2:

- constant hazard rate of 0.2231 per year for placebo
- constant hazard rate of 0.145 per year for selexipag (hazard ratio of 0.65)
- constant hazard rate of 0.051 per year for drop-out (end of study without a MM event) in both treatment groups.

These lead to a total of 331 MM events confirmed by the CEC in order to obtain an overall power of 90% for rejection of the null hypothesis (using the variance under the alternative hypothesis, an option of software East 5.3).

Under these assumptions, the probability to (correctly) reject the null hypothesis already at the interim stage is approximately 19%, and to (falsely) accept the null hypothesis at the interim stage is less than 0.2%.

If the true hazard ratio is 1, then the probability of (correctly) accepting the null hypothesis at the interim stage is approximately 50%.

5.4.2 Analysis of secondary efficacy endpoints

Secondary endpoints will be tested in the conditional sequence provided below: a null-hypothesis can only be rejected for a secondary efficacy endpoint if the null hypotheses for all preceding efficacy endpoints (including the primary efficacy endpoint) have been rejected. For each secondary efficacy endpoint, the one-sided significance level will be set to 0.005 and two-sided 99% confidence intervals will be provided.

- Absolute change from Baseline to Week 26 in 6MWD measured at trough level of study drug

The absolute change from baseline to Week 26 in 6MWD is defined as the difference between Week 26 value and Baseline value.

The null hypothesis of same distributions in the selexipag and placebo groups will be tested by a rank analysis of covariance (with Baseline 6MWD as covariate) as described in [\[Stokes 2000\]](#).

For patients randomized to selexipag for whom the 6MWT was not done at trough, the result of the 6MWT will be set to “invalid” and considered as missing data in the analysis. In a supportive analysis, all available 6MWT data at Week 26 will be included (irrespective whether the test was performed at trough or not).

- Absence of worsening from Baseline to Week 26 in modified NYHA/WHO functional class

Worsening is defined as any increase in functional class level as compared to modified NYHA/WHO functional class at Baseline. Patient in functional class IV at Baseline are excluded from the analysis because, by definition, they cannot worsen.

The null hypothesis of same probabilities for worsening for selexipag and placebo will be tested by a Cochran-Mantel-Haenszel test stratified by modified NYHA/WHO functional class at baseline. The common odds ratio and confidence interval will be estimated, provided there is no clear evidence against a common odds ratio across the strata (evaluated by the Breslow-Day test).

- Borg dyspnea index at Week 26

The null hypothesis of same distributions of Borg dyspnea index at Week 26 for selexipag and placebo will be tested by a rank analysis of covariance with Baseline Borg dyspnea index as covariate.

- Time from randomization to death up to Study Closure

Time to from randomization to death up to Study Closure is defined as date of death minus randomization date plus 1.

Censoring rules

For patients not known to be deceased, time to death is defined as

- ❑ minimum(EOS visit date, date of last contact, analysis cut-off date) minus randomization date plus 1 for patients who did not consent for the post treatment observation period
- ❑ minimum(maximum[PTOCV date, EOS visit date], date of last contact, analysis cut-off date) minus randomization date plus 1 for all other patients.

Deaths up to 16 August 2011 are considered as censored at date of death.

Hypotheses and statistical analysis will be in analogy to the one for the primary endpoint except of the group-sequential method.

- Absolute change from Baseline to Week 26 in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms'

CAMPHOR questionnaires are administered only in selected centers by availability of validated questionnaire in local language.

The absolute change from Baseline to Week 26 in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' is defined as the difference between Week 26 value and Baseline value. The null hypothesis of same distribution for selexipag and placebo will be tested by a rank analysis of covariance with Baseline sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' as covariate.

- Absolute change from Baseline to Week 26 in CAMPHOR 'Symptoms' score

The absolute change from Baseline to Week 26 in CAMPHOR 'Symptoms' score is defined as the difference between Week 26 value and Baseline value. The null hypothesis of same distribution for selexipag and placebo will be tested by a rank analysis of covariance with Baseline CAMPHOR 'Symptoms' score as covariate.

5.4.3 Analysis of exploratory efficacy endpoints

Significance levels will be set to 0.005 1-sided (equivalent to 0.01 2-sided), two-sided 99% confidence intervals will be provided.

- a. Time from randomization to first CEC-confirmed MM event (excluding disease progression) up to Study Closure

The following MM events are considered:

- Death (all-cause mortality)
- Hospitalization for worsening of PAH based on predefined criteria
- Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy
- Initiation of parenteral (subcutaneous or intravenous) prostanoid therapy or chronic oxygen therapy due to worsening of PAH

Date of the first CEC-confirmed MM event (excluding disease progression) up to Study Closure is defined as the onset date as provided by the CEC.

Time to first CEC-confirmed MM event (excluding disease progression) up to Study Closure is defined as the date of the first CEC-confirmed MM event (excluding disease progression) minus randomization date plus 1.

Censoring rules

For patients without a CEC-confirmed MM event (other than disease progression), time to first CEC-confirmed MM event (excluding disease progression) is defined as

- ❑ minimum(EOS visit date, date of last contact, analysis cut-off date) minus randomization date plus 1 for patients who did not consent for the post treatment observation period
- ❑ minimum(maximum[PTOCV date, EOS visit date], date of last contact, analysis cut-off date) minus randomization date plus 1 for all other patients.

CEC-confirmed MM events with onset date (as per CEC) up to 16 August 2011 are considered as censored at time of event onset.

Hypotheses and statistical analysis will be in analogy to the one for the primary endpoint except for the group-sequential method.

- b. Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the Treatment Period

Definition, censoring, hypotheses and statistical analysis will be in analogy to the one for the primary endpoint except of the group-sequential method.

- c. Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the Treatment Period

Definition, censoring, hypotheses and statistical analysis will be in analogy to the one for the primary endpoint except of the group-sequential method.

- d. Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study closure

Definition, censoring, hypotheses and statistical analysis will be in analogy to the one for the first exploratory efficacy endpoint described above.

- e. Time from randomization to first CEC-confirmed MM event up to Study Closure

Definition, censoring, hypotheses and statistical analysis will be in analogy to the one for the first exploratory efficacy endpoint described above.

- f. Time from randomization to CEC-confirmed death due to PAH up to Study Closure

Definition, censoring, hypotheses and statistical analysis will be in analogy to the one for the secondary endpoint "Time to death up to Study Closure".

- g. CEC-confirmed (potentially recurrent) hospitalizations due to worsening of PAH up to Study Closure

Statistical analysis will be based on the Andersen-Gill model [[Andersen 1982](#)] (with a robust sandwich-type variance estimate) which is an extension of the proportional hazards model for recurrent events. Data for CEC confirmed hospitalizations due to worsening of PAH will be arranged in the counting process structure and patients will be considered "at risk" for hospitalization only at days up to the day of hospital admission or at days after the day of hospital discharge. The treatment effect of selexipag compared to placebo will be estimated by the hazard ratio and confidence interval.

- h. Time course of CEC-confirmed (potentially recurrent) MM events hospitalization due to worsening of PAH, initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH, and death up to Study Closure

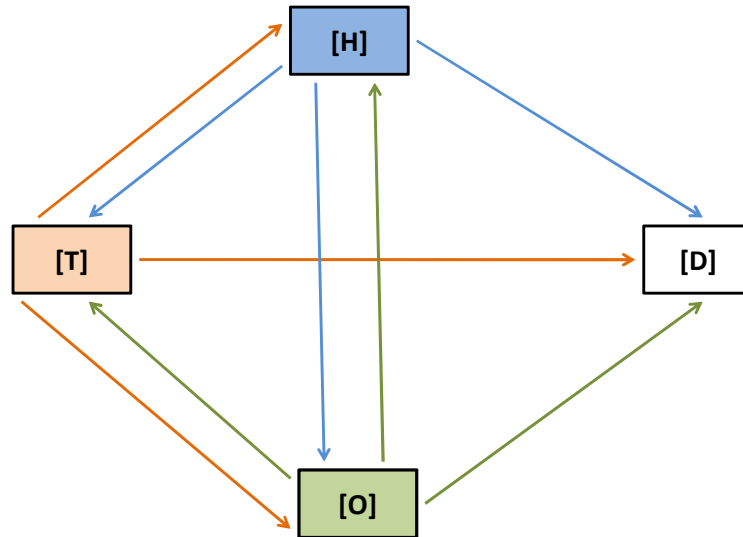
Multistate processes $(X_t)_{t \geq 0}$ are considered where X_t denotes the state a patient is at time t . Four states are defined as follows:

- [T] parenteral (subcutaneous or intravenous) prostanoid treatment or chronic oxygen therapy
[H] hospitalization for worsening of PAH based on predefined criteria
[D] death (all-cause mortality)
[O] other (none of [T], [H], [D])

In case of parenteral prostanoid treatment or chronic oxygen therapy during hospitalization, the state [H] will be used. [D] is an absorbing state (a state out of which transitions are not possible) whereas all other 3 states are transient states (states out of which transitions are modeled). According to the study protocol patients are expected to

be in state [O] at time of randomization ($t=0$). States and possible transitions between states are illustrated in Figure 2.

Figure 2 Multi-state model with possible transitions



It is assumed that $(X_t)_{t \geq 0}$ fulfills the Markov property, i.e., transition probabilities depend only on the current time s and the currently occupied state (time-inhomogeneous Markov process).

For states $[k] \neq [m]$ cumulative transition hazards up to time t will be estimated by the Nelson-Aalen estimator. From these, the Aalen-Johansen estimator of the matrix of transition probabilities will be derived. Two-sided pointwise 95% confidence intervals for the components of the transition probability matrix (for selected times s and t) will be calculated; baseline covariates will be included in the model.

The Borg dyspnea index and changes from Baseline in 6MWD (performed at trough / all) and the two CAMPHOR scores to scheduled visits other than Week 26 will be displayed similarly to the corresponding secondary endpoints. In addition, repeated measures mixed models (respective baseline value as covariate) may be used to analyze the effect of selexipag relative to placebo over time.

The absence of worsening from Baseline at scheduled visits other than Week 26 in NYHA/WHO functional class will be displayed similarly to the corresponding secondary endpoint.

For the changes from Baseline in modified NYHA/WHO functional class at each post-baseline scheduled visit, a transition table will be displayed. Proportions of patients in each functional class at Baseline and at each post-baseline scheduled visit will be displayed, as well as the proportion of patients having an improvement/no change/worsening from baseline at each post-baseline scheduled visit together with confidence limits.

Plasma NT pro-brain natriuretic peptide (NT pro-BNP) levels over time (as well as absolute changes to baseline) will be displayed using descriptive statistics by treatment group. A repeated measures mixed model (baseline value as covariate) may be used to analyze the effect of selexipag relative to placebo over time.

5.4.4 Safety and tolerability endpoints

The Safety analysis set is used to perform all safety analyses.

For patients who prematurely discontinue due to a MM event as adjudicated by the CEC, and who continue in the open-label study, the treatment-emergent AEs, ECGs and marked laboratory abnormalities will be counted until last study drug intake. The date of the “last study drug intake” refers to the date of the actual last study drug intake reported in the CRF during the treatment period.

5.4.4.1 *Adverse events, serious adverse events, deaths and premature discontinuation of study treatment*

All AEs and SAEs are coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA dictionary).

Individual patient listings of all collected AEs will be provided by treatment group.

The frequency and the crude incidence of patients who experienced treatment-emergent AEs until 7 days after last study drug intake will be tabulated by system organ class (SOC), individual preferred terms within each SOC, and by treatment group (in descending order according to the incidence in the investigational study drug group, i.e., ACT-293987).

The frequency and the crude incidence of patients who experienced treatment-emergent AEs until 7 days after last study drug intake coded with the same preferred term will be tabulated by treatment group (in descending order according to the incidence in the investigational study drug group, i.e., ACT-293987).

Treatment-emergent AEs until 7 days after last study drug intake will also be tabulated by severity and by relationship to study drug and for selected subgroups, for example gender and age (18 to 65 years, older than 65 years).

Adverse events leading to permanent discontinuation of study drug will be listed and summarized similarly to AEs.

Treatment-emergent SAEs until 7 days after last study drug intake will be listed and summarized similarly to AEs, separately for treatment-emergent SAEs and SAEs occurring before study drug initiation (only those related to study-mandated procedures) and after 7 days from the study drug discontinuation.

Reasons for treatment-emergent deaths until 7 days after last study drug intake will be listed and summarized similarly to AEs. Deaths occurring before study drug initiation (only those related to study mandated procedures) and after 7 days since last study drug intake will be listed separately by treatment group.

Reasons for premature discontinuation of study drug will be listed and summarized by frequency tables. Individual patient listing will be provided by treatment group.

5.4.4.2 12-lead ECG

Treatment-emergent ECG abnormalities until 7 days after last study drug intake coded with the same preferred term will be summarized by treatment group and presented similarly to the AEs.

Absolute values and changes from baseline of ECG numeric parameters will be summarized by tabulating mean, median, standard deviation, first and third quartiles, minimum and maximum by treatment group.

Individual patient listing of ECG data will be provided by treatment group.

5.4.4.3 Laboratory and bone turnover markers

The frequency and the crude incidence of patients who experienced treatment-emergent marked laboratory abnormalities until 7 days after last study drug intake will be tabulated for each laboratory parameter by treatment group.

Numeric laboratory parameter values in standard international units will be summarized by tabulating mean, median, standard deviation, first and third quartiles, minimum and maximum by treatment group for both the absolute values and the absolute changes from baseline.

Individual patient listings will be provided by treatment group.

The sponsor's internal guidelines will be used for definition of marked laboratory abnormalities.

5.4.4.4 *Vital signs and body weight*

Vital signs (blood pressures and heart rate) and body weight will be summarized by tabulating mean, median, standard deviation, first and third quartiles, minimum and maximum by treatment group for the absolute values and for the changes from baseline.

Individual patient listings will be provided by treatment group.

5.4.4.5 *Retinal arterial tortuosity*

All variables of the ophthalmology sub-study will be summarized descriptively.

For the absolute change from baseline up to EOS in retinal arterial tortuosity, a two-sided 95% confidence interval for the difference of selexipag and placebo means (assuming normal distribution) will be calculated.

5.4.5 Pharmacokinetic and pharmacodynamic endpoints

- Trough plasma concentrations of ACT-293987, ACT-333679 at Baseline, Week 4, Week 8, Week 16, Week 26 (Month 6), Week 52 (Month 12), and EOS.
- Plasma concentrations of ACT-293987, ACT-333679 will be evaluated by PK sampling at specific time intervals after drug administration at Week 16
- The relationship between ACT-293987/ACT-333679 plasma levels and clinical endpoints and on plasma NT pro-BNP levels.

A supplemental PK/PD analysis plan will be written and finalized before the study closure, i.e., database closure and unblinding of the randomization code, to provide full details of the analyses, the data displays and the algorithms to be used for data derivations. All analyses will be exploratory in nature.

5.4.6 PK and PK/PD analyses

The PK and PD analyses will use mixed-effects population PK modeling with the software NONMEM, Version 6 or later. Details will be defined in a separate SAP.

5.4.7 Analysis of pharmaco-economic endpoints

Pharmaco-economic endpoints will be analyzed on the Full Analysis Set.

5.4.7.1 *All-cause and PAH-related hospitalizations up to EOS visit*

For statistical analysis of the annualized hospitalization rate (separately for all-cause and PAH-related hospitalizations), the following data will be used:

- the patient's number of hospitalizations up to the EOS visit
- his/her length of observation expressed in years, defined as: [EOS visit date minus randomization date +1] divided by 365.25.

A generalized linear model with negative-binomial distribution for the number of hospitalizations up to the EOS visit will be assumed.

t_j denotes the length of observation (see above) for patient j
 Y_j denotes the number of hospitalizations for patient j during t_j
 μ_j denotes the mean of the negative binomial distribution of Y_j .

The mean for the distribution of the annualized hospitalization rate for patient j , denoted by μ_j/t_j , will be modeled by the following equation:

$$\log(\mu_j/t_j) = \mathbf{x}'_j \boldsymbol{\theta}, \quad \text{i.e., } \log(\mu_j) = \mathbf{x}'_j \boldsymbol{\theta} + \log(t_j), \quad \text{where}$$

$\mathbf{x}_j$ is the vector denoting study treatments and covariates for patient j
 $\boldsymbol{\theta}$ is the vector of unknown fixed model parameters (randomized study treatment and baseline covariates).

Within the negative binomial regression model, the null hypothesis of no treatment effect ($\theta_{\text{treatment}} = 0$) will be tested by a two-sided Wald-type test at a two-sided significance level of 0.01. A two-sided 99% Wald confidence interval will be calculated for the relative reduction in mean annualized hospitalization rate for selexipag compared to placebo.

An additional analysis will be based on the Andersen-Gill model (with a robust sandwich-type variance estimate) as described in Section 5.4.3.

5.4.7.2 *In-patient hospital days for all causes and PAH-related causes up to the EOS visit*

For statistical analysis of the annualized number of in-patient hospital days (separately for all-cause and PAH-related hospitalizations) up to the EOS visit, the following data will be used:

- the patient's number of in-patient hospital days up to the EOS visit
- his/her length of observation expressed in years, defined as: [EOS visit date minus randomization date +1] divided by 365.25.

A generalized linear model with negative-binomial distribution for the number of in-patient hospital days will be assumed. Model equation, hypotheses and analysis will be in analogy to the negative-binomial model described in Section 5.4.7.1.

5.4.8 Exposure to study drug(s)

Exposure to study drug will be described in terms of duration, dose, and maximum tolerated dose. The duration of exposure is defined as the time elapsing between the study drug initiation and discontinuation, inclusive. The exposure time will be tabulated by treatment group using mean, median, standard deviation, first and third quartiles, minimum and maximum. The cumulative distribution of exposure time by different class intervals (i.e., at least 4 weeks, at least 8 weeks, at least 16 weeks, and at every interval of 26 weeks thereafter) will be tabulated to show the number and percentage of patients in each class interval. Count and percentages of patients within each maximum tolerated dose class will be tabulated by treatment group.

5.4.9 Baseline parameters and concomitant medications

Continuous baseline parameters and disease characteristics (i.e., age, height, weight, BMI, blood pressure, heart rate, 6MWT, and Borg Dyspnea index and time from PAH diagnosis) will be summarized by treatment group using mean, median, standard deviation, first and third quartiles, minimum and maximum.

Qualitative baseline parameters and disease characteristics (i.e., gender and race, etiology of PAH, modified NYHA/WHO functional class, previous and concomitant medications) will be summarized by treatment group using counts and percentages.

Individual patient listings will be provided by treatment group.

Other baseline characteristics (e.g., medical history) will only be listed by treatment group.

Distributions of these parameters will only be compared between the treatment groups descriptively. No statistical inference will be performed.

Previous and concomitant medications will be coded according to the latest available version of the World Health Organization (WHO) drug code and the anatomic therapeutic chemical (ATC) class code. They will be summarized by type (i.e., previous and concomitant) and treatment group by tabulating the number and percentages of patients having received each treatment.

5.5 Exploratory analyses

Exploratory data-driven analyses can be performed, with the caveat that any statistical inference will not have any confirmatory value.

5.6 Interim analyses

An independent DMC will review unblinded efficacy, safety and tolerability data at regular intervals.

The DMC is empowered to recommend modifications of the protocol (to enhance patient safety) or to recommend early termination of the study if major concerns arise about patient safety at any time during the course of this study or during any other study with the same investigational drug. There is no limit to the number and timing of interim analyses aimed at guaranteeing the safety of the patients.

In addition, the DMC will review the results of a single efficacy and safety interim analysis after observing approximately 202 events, corresponding to approximately 61% of the total target number of events in the primary endpoint analysis. The access to randomization information will be limited to the independent Statistical Analysis Center (SAC) which will prepare all outputs for the DMC.

The SAC will be represented by an independent statistician affiliated to Frontier Science, Technology and Research Foundation.

6 PROCEDURES AND GOOD CLINICAL PRACTICE

6.1 Procedures

6.1.1 Protocol amendments

Any change to a protocol must be considered to be an amendment if the documents have already been submitted to ECs/IRBs or Health Authorities. An amendment could therefore occur before or after the approval of these documents by ECs/IRBs or Health Authorities. Each amendment must be documented in writing and approved by the sponsor, and must be reviewed by the Coordinating/Principal Investigator(s) or Steering Committee, as appropriate.

Changes to the Core Patient Information and Informed Consent requested by ECs/IRBs are not considered to be formal amendments, as long as they do not significantly change the core document or affect the protocol.

6.1.1.1 Non-substantial amendment

Purely administrative or minor logistical changes require only a non-substantial amendment. Such changes include but are not limited to changes in study staff or contact details (e.g., the sponsor instead of CRO monitors), or minor changes in the packaging or labeling of study drug.

The implementation of a non-substantial amendment may be undertaken with or without notification to the appropriate ECs/IRBs and Health Authorities (subject to national regulations).

6.1.1.2 Substantial amendment

A substantial amendment is required for significant changes. These include, but are not limited to, new data affecting the safety of patients, and changes to the objectives/ or endpoints of the study, eligibility criteria, dose regimen, study assessments/procedures, or treatment or study duration, with or without the need to modify the Core Patient Information and Informed Consent.

Substantial amendments must be approved by the appropriate ECs/IRBs, and in some jurisdictions by the Health Authorities. The implementation of a substantial amendment may only occur after formal approval by the appropriate ECs/IRBs and/or Health Authorities, and must be signed by the investigators.

6.1.1.3 Urgent amendment

An urgent amendment might become necessary to preserve the safety of the patients included in the study. The requirements for approval must not prevent any immediate action being taken by the investigators or the sponsor in the best interests of the patients.

If deemed necessary, an investigator may therefore implement an immediate change to the protocol for safety reasons, and in such exceptional cases the implementation of urgent amendments will occur before submission to, or approval by, ECs/IRBs and Health Authorities.

In such cases, the investigator must notify the sponsor within 24 hours. A related substantial amendment will be prepared and submitted by the sponsor to the appropriate ECs/IRBs and Health Authorities within 10 working days of receiving the notification.

6.1.2 Monitoring

The monitor will contact and visit the investigator regularly, and must be permitted to have access to all source documents needed to verify the entries on the CRF and other protocol-related documents on request, provided that patient confidentiality is maintained in accordance with local regulations. It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on the CRFs. The sponsor's monitoring standards require full verification that informed consent has been provided, and verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety and tolerability endpoints. Additional checks of the consistency of the source data with the CRFs will be performed according to the study-specific monitoring plan.

The rules regarding identification of any data recorded directly on the CRFs and considered to be source data are specified in the following document: "Site Guidelines". The investigator must ensure that patient anonymity is maintained. On CRFs or other documents submitted to the sponsor, patients must be identified only by number, and never by name. The investigator must keep a patient identification code list showing the randomization number, the patient's name, date of birth and address or any other locally accepted identifiers. Documents identifying the patients (e.g., signed informed consent forms) should not be sent to the sponsor, and must be kept in strict confidence by the investigator.

The investigator and co-investigators agree to cooperate with the monitor(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the patient is hospitalized or dies in a hospital other than the study center, the investigator is responsible for contacting that hospital in order to document the SAE.

The investigator must on request supply the sponsor with any required background data from the study documentation or clinical records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In the case of special problems and/or governmental queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

An initiation visit will be performed before the first patient is included in the study. Monitoring visits and contacts will occur at regular intervals thereafter, according to a

frequency defined in the study-specific monitoring plan. A close-out visit will be performed after study closure.

6.1.3 Data management

6.1.3.1 Data collection

A Patient Screening and Enrollment Log will be completed for all patients, both eligible and non-eligible, with the reasons for exclusion where applicable.

For each patient enrolled, regardless of study drug initiation, a CRF must be completed and signed by the principal investigator or co-investigator. This also applies to those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the CRF. Case report forms are to be completed on an ongoing basis, and will be collected by the monitor(s).

All forms must be completed using a digital pen, and must be legible. Errors must be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the Principal Investigator, co-investigator, or study nurse.

6.1.3.2 Database management and quality control

All data from the CRF will be entered into the database twice, by two different individuals.

The entered data will be systematically checked by the sponsor or CRO staff, using error messages printed from validation programs and database listings. Errors with obvious corrections will be corrected and communicated to the site. Data clarification requests will be entered on Data Clarification Forms, which will be returned to the investigational site for resolution. A copy of the signed Data Clarification Form is to be kept with the CRFs, and, once received at the sponsor or CRO, the resolutions will be entered into the clinical database.

A second review of the data will be performed by medically trained staff.

Quality control audits of the database will be made before study closure.

Laboratory samples will be processed centrally through Quest and the results will be sent electronically to the sponsor.

After the database has been declared complete and accurate, the database will be locked. Any changes to the database after that time may only be made by joint written agreement between the Clinical Trial Leader and the Trial Statistician.

6.1.4 Recording of data and retention of documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, and the study data to be subsequently verified. These documents are to be classified into two different categories: investigator's file, and patient clinical source documents.

The investigator's file will contain the protocol/ and all protocol amendments, the FDA form 1572 for studies conducted under a US IND, a financial disclosure form, the CRFs and data clarification and query forms, EC/IRB and Health Authority approval with correspondence, informed consent, drug records, staff curricula vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence in accordance with ICH GCP and local regulations.

Patient clinical source documents include, but are not limited to, hospital/clinic records, physicians' and nurses' notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, etc.

These two categories of documents must be kept on file by the investigator for as long as is necessary to comply with national and international regulations (generally 2 years after either discontinuation of clinical development, or the last marketing approval, of the investigational drug). No study document should be destroyed without prior written approval from the sponsor. Should the investigator wish to assign the study records to another party, or move them to another location, the sponsor must be notified in advance.

When source documents are required for the continued care of the patient, appropriate copies should be made for storing off site.

6.1.5 Audit

The sponsor's Global Quality Management Department may conduct audits of clinical research activities in accordance with internal standard operating procedures (SOPs) to evaluate compliance with the principles of GCP- and ICH-related guidelines.

Health Authorities may also wish to conduct an inspection (during the study or after its completion). Should an inspection be requested by a Health Authority, the investigator must inform the sponsor immediately that such a request has been made.

The investigator must permit such audits by the sponsor or Health Authorities, and must facilitate them by providing access to the relevant source documents.

6.1.6 Handling of study drug(s)

The sponsor will supply all study drug(s) to the site according to local regulations. Drug supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the drug labels. The site must maintain an accurate record of the shipment and dispensing of study drug(s) on an accountability form, which must be given to the monitor at the end of the study. An accurate record of the date and amount of study drug(s) dispensed to each patient must be available for inspection at any time.

All drug supplies are to be used only in accordance with this protocol, and not for any other purpose. The responsible person must not destroy any drug labels, or unused drug supply. On termination of the study, the monitor will collect used and unused patient kits,

which will be sent to the warehouse, where the sponsor or its deputy will check drug accountability. In certain circumstances, used and unused drug containers may be destroyed at the site once drug accountability is final and has been checked by the sponsor or its deputy, and written permission for destruction has been obtained from the sponsor.

6.1.7 Publication and reporting of study results

Study results will be documented in a clinical study report that will be signed by representatives of the sponsor and by the Coordinating Investigator.

In accordance with standard editorial and ethical practice, the results of the study will be published. Results from multicenter studies must be published or presented at congresses only in their entirety and not as individual center data, except for ancillary studies.

The Coordinating Investigator and the Steering Committee will have the opportunity to review the analysis of the data and to discuss with the sponsor the interpretation of the study results prior to publication.

Any study-related article or abstract written independently by investigators must be submitted to the sponsor for review at least 60 days prior to submission for publication or presentation.

The list of authors of any formal publication or presentation of study results may include, as appropriate, representatives of the sponsor, and will be determined by mutual agreement.

6.1.8 Disclosure and confidentiality

By signing this protocol, the investigator agrees to keep all information provided by the sponsor in strict confidence, and to request similar confidentiality from his or her staff and the EC/IRB. Study documents provided by the sponsor (including Investigator's Brochures, protocols, CRFs and other protocol-related documents) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorization from the sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

6.1.9 Premature termination or suspension of the study

Both the sponsor and the investigator reserve the right to terminate the study at any time.

If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators, the ECs/IRBs and Health Authorities, as appropriate, and provide the reasons for the termination or suspension.

If the study is prematurely terminated or suspended for any reason, the investigator in agreement with the sponsor must promptly inform all enrolled patients, and ensure their appropriate treatment and follow-up.

In addition, if the investigator terminates or suspends a study without prior agreement from the sponsor, the investigator must promptly inform the sponsor and the EC/IRB, and must provide the sponsor and the EC/IRB with a detailed written explanation of the termination or suspension.

If the EC/IRB terminates or suspends its approval/favorable opinion of a study, the investigator must promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

Any premature termination or suspension of the study must be discussed with the DMC, and Steering Committee, as appropriate.

6.2 Good Clinical Practice

6.2.1 Ethics and Good Clinical Practice

The investigator will ensure that this study is conducted in full compliance with the principles of the 'Declaration of Helsinki' (as amended in Tokyo, Venice, Hong Kong, Somerset West, Edinburgh and Seoul), and with the laws and regulations of the country in which the clinical research is conducted. A copy of the Declaration of Helsinki will be provided to each investigational site.

All studies must follow ICH GCP Guidelines and, if applicable, the US Code of Federal Regulations. In other jurisdictions in which GCP Guidelines exist, the investigators will ensure strict adherence to the stated provisions.

6.2.2 Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the patient (such as patient information used to obtain informed consent) to an EC or IRB. Approval from the committee must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval. A list of members participating in the meeting must be provided, including the functions of these members. If study staff were present, it must be clear that none of these persons voted.

Modifications made to the protocol after receipt of the EC/IRB approval must also be submitted as amendments by the investigator to the EC/IRB in accordance with local procedures and regulations (see Section [6.1.1](#)).

6.2.3 Informed consent

It is the responsibility of the investigator to obtain informed consent according to GCP and local regulations from each individual participating in this study, after adequate

explanation of the aims, methods, objectives and potential hazards of the study. The investigator must also explain to the patients that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason. Appropriate forms for documenting informed consent will be provided to the sites prior to the study.

The Informed Consent and Patient Information will be provided in the local language.

6.2.4 Compensation to patients and investigators

The sponsor provides insurance in order to indemnify (with both legal and financial coverage) the investigator/center against claims arising from the study, except for claims that arise from malpractice and/or negligence.

Compensation of the patient in the event of study-related injuries will comply with applicable regulations.

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Appendix 1 Actelion Guidelines for 6MWT

1. 6-minute walk test (6MWT)

1.1. General procedures [[ATS 2002](#)]

- **The 6MWT is a non-encouraged test** the same tester at the same location and the same time of the day to minimize intraday variability throughout the study should administer it.
- **The 6MWT should be performed** along a long, flat, straight corridor that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The use of treadmill is forbidden.
- **The corridor used for the test should be 30 meters in length (100 feet).** The length of the corridor should be marked every 3 meters (10 feet). The turnaround point should be marked with a cone. A starting line, which marks the beginning and the end of each 60-m lap, should be marked on the floor using brightly colored tape.
- **The required equipment** is: a countdown timer (or stop watch), a mechanical lap counter, 2 small cones for the turnaround points, a chair (easily moved along the walking course), a worksheets on a clipboard, a sphygmomanometer, an automated electronic defibrillator and, a source of oxygen.
- **The tester** should stand near the starting line during the test. **Do not walk with the patient!** Intermittent rest periods are allowed if the patient can no longer continue. If the patient needs to rest briefly, he/she may stand or sit and resumes walking when he/she is sufficiently rested. But the clock must continue to run. The tester can at any moment immediately stop the 6MWT in case the patient complains of having chest pain, intolerable dyspnea, leg cramps, looking pale or ashen appearance...

• Study-specific requirements:

The two 6MWTs at Screening and Baseline (Visit 1) must be performed within 14 days and on 2 separate days.

1.2 Instructions to the patient

Patients will be instructed that the preceding meal should be light, have rested at least 20 minutes before the test starts. Patients should receive their usual medication on the day of the test. If the patient is used to taking bronchodilators before a walk, he/she should take them 5-30 min before the test. Also if the patient is on chronic oxygen therapy, oxygen should be given at their standard rate during the test. Patients should be told to wear comfortable clothing and appropriate walking shoes. **Patients using walking aids (cane, walker, etc) should not be enrolled in the study.**

The person administering the test will use the following exact dialog with the patient:

“The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able to.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I’m going to show you. Please watch the way I turn without hesitation”. (*The tester demonstrates the walking and pivots around a cone briskly*).

“Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line.

Remember the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don’t run or jog. I will tell you when 2 minutes, 4 minutes have elapsed. Keep walking when I talk.”

After these instructions are given to the patient, the person administering the test will then ask:

“Do you have any questions about the test?”

“Please explain what you are going to do.”

“Are you ready?”

“Start now, or whenever you are ready”

The tester will then start the timer and write down the clock time of the test start.

The tester will tell the patient the time elapsed by saying:

“You have 4 minutes to go.”

“You have 2 minutes to go.”

When the timer is 15 seconds from completion, the tester says:

“In a moment I’m going to tell you to stop. When I do, just stop right where you are and I will come to you”.

When the timer alarm rings the tester says:

“Stop!”

The tester walks over to the patient, marks the spot where the patient stopped.

No other instruction or encouragement will be given during the test. Eye contact and body language signaling to the patient to speed up should be avoided during the test.

- Heart rate and blood pressure are checked **before** and **right after** the test.
- Total distance walked should be recorded in the worksheet at the end of 6MWT.

2. Borg dyspnea index

Following the walk test, the person administering the test will obtain a rating of dyspnea using the Borg Scale.

The tester will use the following dialog:

“I would like to use the following scale to indicate the maximal shortness of breath you had during the walk test (indicate the Borg scale). If there was no shortness of breath at all you would point to 0; if the shortness of breath was not very great you would choose from 0.5 to 2; if you were somewhat more short of breath you would select 3; and if the breathing was getting very difficult, you would choose 4 to 9, depending on just how hard it was; 10 represents the greatest shortness of breath you have ever experienced in your life.”

Appendix 2 Borg dyspnea index (Borg scale)

0	NOTHING AT ALL
0.5	VERY, VERY SLIGHT (just noticeable)
1	VERY SLIGHT
2	SLIGHT (light)
3	MODERATE
4	SOMEWHAT SEVERE
5	SEVERE (heavy)
6	
7	VERY SEVERE
8	
9	
10	VERY, VERY SEVERE (maximal)

Appendix 3 Modified NYHA/WHO classification of functional status of patients with PH

- Class I** Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
- Class II** Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
- Class III** Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
- Class IV** Patients with pulmonary hypertension who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

Adapted from [Rich 1998] Rich S. Primary pulmonary hypertension: executive summary. Evian, France. World Health Organization 1998.

Appendix 4 CAMPHOR questionnaire

CAMPHOR

Cambridge Pulmonary Hypertension Outcome Review

Please read this carefully

On the following pages you will find some statements that have been made by people who have Pulmonary Arterial Hypertension.

Please read each statement carefully.

We would like you to put a tick in the box ☒ next to 'Yes' if you feel it applies to you and a tick in the box ☒ next to 'No' if it does not

Please choose the response that applies best to you
at the moment

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Symptoms

Please read each statement carefully and decide whether it applies to you **at the moment**

1. My stamina levels are low	Yes ☐
	No ☐
2. I have to rest during the day	Yes ☐
	No ☐
3. I feel worn out	Yes ☐
	No ☐
4. I get tired very quickly	Yes ☐
	No ☐
5. I'm tired all the time	Yes ☐
	No ☐
6. I feel very weak	Yes ☐
	No ☐
7. I feel completely exhausted	Yes ☐
	No ☐
8. I want to sit down all the time	Yes ☐
	No ☐
9. I soon run out of energy	Yes ☐
	No ☐

10. Everything is an effort Yes ☐
No ☐

11. I get out of breath when I stand up Yes ☐
No ☐

12. When I talk I get out of breath Yes ☐
No ☐

Please read each statement carefully and decide whether it applies to you
at the moment

13. When I walk I get out of breath Yes ☐
No ☐

14. I get breathless if I bend Yes ☐
No ☐

15. I get breathless going up one step Yes ☐
No ☐

16. I get breathless walking up a slight slope Yes ☐
No ☐

17. I get breathless without doing anything Yes ☐
No ☐

18. I get breathless climbing a flight of stairs Yes ☐
No ☐

19. I have mood swings Yes ☐
No ☐

20. I get very down Yes ☐
No ☐

21. I seldom feel happy Yes ☐
No ☐

Please read each statement carefully and decide whether it applies to you
at the moment

22. I've forgotten what it's like to enjoy myself Yes ☐
No ☐

23. I feel hopeless Yes ☐
No ☐

24. It does get me down Yes ☐
No ☐

25. I often feel anxious Yes ☐
No ☐

please turn over

Activities

Please put a tick in the box ☒ under the response which best describes your abilities at the moment. Please respond to all 15 statements.

**Please describe your ability without the use of aids or assistance.
However, do describe your ability taking into account oxygen if you use it.**

Please mark only one box.

Able to do on own without difficulty	Able to do on own with difficulty	Unable to do on own

1. Cut your toenails	☐	☐	☐
2. Have an all over wash	☐	☐	☐
3. Get dressed	☐	☐	☐
4. Walk around inside the house (not including climbing stairs)	☐	☐	☐
5. Walk short distances on level ground	☐	☐	☐
6. Walk longer distances on level ground	☐	☐	☐
7. Walk up a slight incline	☐	☐	☐
8. Climb a flight of stairs	☐	☐	☐
9. Bend down to pick objects up from the floor	☐	☐	☐
10. Stand for a short time	☐	☐	☐
11. Stand for a long time	☐	☐	☐
12. Lift heavy items	☐	☐	☐
13. Carry heavy items	☐	☐	☐
14. Do light jobs around the house or garden	☐	☐	☐
15. Do heavy jobs around the house or garden	☐	☐	☐

Quality of Life

Please read each statement carefully and put a tick ☒ next to the response that applies best to you *at the moment*

1. I have to talk very quietly	True	☐
	Not True	☐
2. I can't stay away from home	True	☐
	Not True	☐
3. I've lost interest in food	True	☐
	Not True	☐
4. I can't put energy into my close relationships	True	☐
	Not True	☐
5. Walking for pleasure is out of the question	True	☐
	Not True	☐
6. My condition puts a strain on my close relationships	True	☐
	Not True	☐
7. I feel very isolated	True	☐
	Not True	☐
8. I can't do things on the spur of the moment	True	☐
	Not True	☐
9. I feel vulnerable when I'm on my own	True	☐
	Not True	☐

10. It feels like my body has let me down True ☐
Not True ☐

11. I feel as if I'm not in control of my life True ☐
Not True ☐

12. I feel dependent on other people True ☐
Not True ☐

Please remember to put a tick in **only one** of the alternative responses for each of the statements

13. .Sometimes it's too much effort to speak True ☐
Not True ☐

14. I feel as if I am a burden to people True ☐
Not True ☐

15. Travelling distances is a problem True ☐
Not True ☐

16. I don't like to be seen like this True ☐
Not True ☐

17. I feel that I'm losing my role in life True ☐
Not True ☐

18. I worry that I neglect people close to me True ☐
Not True ☐

Please read each statement carefully and decide whether it applies to you **at the moment**

19. I feel guilty asking for help	True	☐
	Not True	☐
20. My condition limits the places I can go	True	☐
	Not True	☐
21. I dislike having to rely on other people	True	☐
	Not True	☐
22. I don't want to talk to anybody	True	☐
	Not True	☐
23. I feel as if I let people down	True	☐
	Not True	☐
24. I am reluctant to leave the house	True	☐
	Not True	☐
25. I'm unable to join in activities with my family and friends	True	☐
	Not True	☐

Thank you for taking the trouble to fill in this questionnaire.

Please check all the pages to make sure that you have
answered every statement.

Table 1 **List of global protocol amendments**

Document Date	Global Amendment	Changes
11 March 2010	Amendment 1, and the resulting Global Protocol Version 2	The amendment was based on the recommendations received from the US FDA after a Special Protocol Assessment procedure. Since time to clinical worsening was considered to be a clinically more relevant endpoint than change from baseline in 6MWD in PAH patients, the co-primary endpoint “time to first clinical worsening” (co-primary endpoint for the pool of the identical studies AC-065A301 [never initiated] and AC-065A302) remained the primary efficacy endpoint. In addition, for the analysis of the time to clinical worsening, patients without clinical worsening event were to be censored 7 days after study treatment discontinuation. The primary endpoint of “change from baseline to Week 16 in 6MWD” was moved to the secondary endpoints and slightly changed to be assessed at Week 26 instead of Week 16. Also, all other secondary endpoints were to be assessed at Week 26 instead of Week 16. Imputation methods were modified to reflect this change. As a consequence of the above-mentioned modifications, the two studies AC-065A301 and AC-065A302 were merged into one study. The protocol for study AC-065A302/GRIPHON 2 was amended and renamed AC-065A302/GRIPHON (the present study). Study AC-065A301 was withdrawn. Prior to the issuance of Amendment 1 (11 March 2010), AC-065A302/ GRIPHON 2 was already approved in 9 countries (Belgium, Czech Republic, Denmark, France, Israel, Singapore, Spain, Sweden, and the UK), 3 sites had been initiated, and 1 patient had been enrolled. Overall, 19 patients at 10 sites had been enrolled in these countries under GRIPHON 2 Protocol version 1 before GRIPHON Protocol version 2 (the present study) was implemented. All references in the text to the “pool of studies AC-065A301 and AC-065A302” were removed. For the primary efficacy endpoint of “time to first clinical worsening up to 7 days after last study drug intake”, instead of 203 events, 202 events were required to detect with 90% power the hazard ratio of 0.5729, at two-sided 0.01 significance level, by means of the log-rank test. With an increase in sample size, from 544 to 670 patients, 202 events were expected within a maximum of 3.5 years. Sample size adaptation to be implemented if required was increased from a maximum of 750 to 1150 patients. After determination of MTD for each patient at Week 12, the dose was to be kept stable for the next 14 weeks, i.e., up to Week 26 (time point for assessment of the secondary efficacy endpoints). Changes from baseline to Week 16 in 6MWD measured at trough and Borg dyspnea index, and absence of worsening from baseline to Week 16 in NYHA/WHO functional class, were added to the list of the

Document Date	Global Amendment	Changes
		exploratory efficacy endpoints. The exploratory endpoint on CAMPHOR questionnaire was modified to be consistent with the defined secondary endpoint on CAMPHOR (i.e., use of the sub-scale “breathlessness” of the “symptom” score and use of the “symptom” score instead of the global CAMPHOR score). In addition, the Week 16 endpoints on CAMPHOR questionnaire were moved to the exploratory endpoints. The safety and tolerability endpoints of treatment-emergent AEs, SAEs, and MLAs were modified from up to 3 days after discontinuation of study drug to up to 7 days after the last intake of study drug. The date of the “last study drug intake” referred to the date of the actual last study drug intake reported in the CRF during the treatment period. For patients who prematurely discontinued due to an adjudicated clinical worsening event, and who continued in study AC-065A303/GRIPHON OL, the treatment-emergent AEs, ECGs and MLAs were to be counted until the last intake of study drug during AC-065A302/ GRIPHON treatment period. EOS was to be derived from the date of EOS Visit as recorded in the CRF. Due to the changes in the definition of the endpoints, the definition of the study periods was refined. To avoid double reporting in the AC-065A302/GRIPHON and AC-065A303/GRIPHON OL studies, the AE/SAE reporting procedure was clarified. The inclusion criterion on 6MWT was modified to exclude patients only on the basis of the screening test and not on the basis of the repeat test at baseline. In addition, all 6MWT assessments (except at screening and baseline) were to be performed at trough. The following inclusion/exclusion criteria were clarified or modified: – an upper age limit of 75 years was defined – In order to minimize the risk of including patients with other forms of PH than PAH (e.g., PH related to COPD or left heart disease), an upper age limit was defined, and the lower limit of resting PVR was increased from 240 to 400 dyn·s·cm⁻⁵. – Since no effect on blood pressure was observed in previous Phase 1 and 2a studies, the exclusion criterion regarding hypotensive patients (systemic systolic BP < 100 mmHg) at Screening was considered clinically not relevant and hence removed. – In accordance with the definition, the exclusion criterion regarding moderate/severe obstructive lung disease was modified from FEV₁/FVC < 70% or FEV₁ < 65% of predicted value after bronchodilator administration to FEV₁/FVC < 70% and FEV₁ < 65% of predicted value after bronchodilator administration. – Exclusion criterion regarding restrictive lung disease was clarified to exclude patients with restrictive lung disease. The upper limit of the Total Lung Capacity was increased to < 70% of predicted value from < 60% of predicted value. – Exclusion criterion regarding clinically relevant left ventricular dysfunction was re-worded from ‘patients with clinically relevant left ventricular

Document Date	Global Amendment	Changes
		dysfunction' to 'patients with documented left ventricular dysfunction (e.g., ejection fraction < 45%)'. – Exclusion criterion regarding patients with body weight < 40 kg was replaced by BMI < 18.5 kg/m². – Exclusion criterion added in Amendment 1: patients participating in a rehabilitation program based on exercise training were excluded from the study. The procedure for re-initiation of study drug up-titration in the event of study drug interruption of more than 3 days, and after Week 26, was clarified. Information on the initiation, and changes in dosage of PAH-specific therapies, as well as the investigator's rationale for altering these therapies was to be documented in the CRF: – For allowed concomitant PAH-specific therapies, 'the dose was to be stable for at least 1 month prior to Baseline visit and up to Week 16' was modified to 'the dose was to be stable for at least 3 months prior to Baseline visit and up to Week 26'. – Diuretic therapy was added in the allowed concomitant medications in Amendment 1. In order to properly characterize the PK of selexipag and its metabolite in the target population, additional time points for PK sampling were included. Information about clinical worsening event and study drug discontinuation was clarified: study drug was required to be discontinued permanently after the adjudication of a clinical worsening event. Change in study team was listed. ICF was amended to reflect the changes introduced by the amendment.
20 Dec 2010	Amendment 2, and the resulting Global Protocol Version 3	In order to strengthen ECG monitoring, the FDA recommended inclusion of two additional ECGs after study drug intake. Thus, at Month 12 (Visit 6), two ECGs at 2 h and 4 h post-dose were added. The inclusion criterion on sun exposure was removed based on the results of a Phase 1 study (AC-065-102) that did not indicate a clinically relevant phototoxic potential of selexipag at doses of 800 and 1200 µg b.i.d. after UV-A and UV-B irradiation in healthy male subjects. Following the request of the FDA, the information provided for the sample size adaptation was clarified. Also, a typographical error concerning the definition of the type 2 error was corrected, i.e., $\beta = 0.100$ (power = 90%). Change in study team was listed.
11 May 2011	Amendment 3, and the resulting Global	Due to a non-malignant thyroid hyperplasia finding in a 2-year carcinogenicity study in mice, additional safety assessments to monitor thyroid function were included. All newly enrolled patients were to be monitored for changes in thyroid hormone levels (free T₃, free T₄, and

Document Date	Global Amendment	Changes
	Protocol Version 4	TSH) at baseline and thereafter. Due to tortuosity and dilation of retinal vessels findings at Week 104 in a long-term toxicity study in rats (although not accompanied by histopathological findings), additional safety assessments to monitor retinal function were included. At selected sites, newly enrolled patients were to have an ophthalmological assessment (fundoscopy with digital pictures) at baseline, Month 12, and EOS visits. The maximum tolerated dose was to be analyzed as a categorical variable and not as a continuous variable. Information on laboratory assessments to be analyzed locally and centrally at screening was clarified. Information on the sequential process followed for entering AC-065A303/GRIPHON OL study was clarified. It was clarified that any change in dose of the allowed concomitant medications was to be recorded in the CRF. The term ‘end of study drug’ was changed to ‘study drug discontinuation’ for consistency. The statement about hormone replacement therapy was removed in the definition of a woman of non-childbearing potential. Based on the amendment, three ICFs were created. One ICF for the patients already enrolled in the study, a second one for newly enrolled patients who were to perform the thyroid assessments, and a third ICF for newly enrolled patients at selected sites for the ophthalmological assessments.
10 Aug 2011	Amendment 4, and the resulting Global Protocol Version 5	Global Amendment 4 (and the resulting Global Protocol Version 5), dated 10 Aug 2011 was submitted on 16 Aug 2011 to the FDA first. Following comments received from the FDA it was decided not to submit Global Amendment 4 to any other Health Authority. Based on the comments received for Global Amendment 4 submitted to the FDA, the Global Amendment 5 and the Local Amendment A (USA), dated 14 Dec 2011 were issued.

Document Date	Global Amendment	Changes
14 Dec 2011	Amendment 5, and the resulting Global Protocol Version 6	The following statistical changes were introduced: In order to eliminate any concern that the protocol change (based on Global Amendment 4) could be considered informed, the CEC-confirmed clinical worsening (morbidity/mortality) events observed until 16 Aug 2011 (date on which the amendment was submitted to the FDA) were not to be included in the primary endpoint analysis. The assumed hazard ratio of 0.5729 for the primary efficacy endpoint “time to first clinical worsening up to 7 days after last study drug intake” was based on data from previous PAH monotherapy studies conducted in patients with NYHA FC III and IV, not II and III. Since the majority of the patients randomized in the ongoing PAH trial were not treatment naïve, but on PAH-specific background therapies, and were mainly in NYHA functional class II and III, the assumed hazard ratio was modified to 0.650 in order to achieve 90% power for a smaller but still clinically relevant treatment effect. To reflect the increased assumed hazard ratio of 0.65 in the analysis of the primary endpoint, without changing the protocol requirements for the type-I and type-II error rates, an increase in the required number of primary events to 332 was made. In order to observe 332 primary events in approximately 3.5 years (initially planned treatment duration), the sample size was increased from 670 to 1150 patients (from 335 to 575 patients per group). Also, the duration of treatment for patients receiving study treatment up to Study closure was expected to be between 1.2–4.3 years. Due to the considerable increase in sample size, the possibility of early stopping of the trial for efficacy or futility was incorporated into the study design. It was planned to perform an interim analysis by an independent DMC after observing 202 primary events, corresponding to approximately 61% of the required number of events in the primary endpoint analysis. The DMC charter was updated accordingly. For the interim analysis, the type-I error was set to 0.0001 (1-sided) according to the Haybittle-Peto [Error! Reference source not found.] stopping rule. Efficacy and futility boundaries (Z-scores and estimated hazard ratios) were defined for early stopping of the trial for efficacy or futility. To increase precision and power, and reduce bias, the log-rank test stratified by WHO functional class I/II and III/IV at baseline was added as a sensitivity analysis. The alternative hypothesis (H1) was clarified and the type-II error was modified, from $\beta = 0.100$ (power = 90%) to $\beta < 0.10$ (power of at least 90%). The main sensitivity analysis of the primary endpoint to be performed on 378 events (including the censored events up to 16 Aug 2011). Primary and sensitivity analyses of the primary endpoint and statistical

Document Date	Global Amendment	Changes
		methods to be applied for treatment comparison were clarified. The secondary endpoints to be analyzed at the 0.005 1-sided level (equivalent to 0.01 2-sided). Other changes that were introduced: Due to withdrawal of sitaxentan from the market, it was removed from the list of currently approved agents for the treatment of PAH. The footnote associated with the inclusion criterion regarding PAH diagnosis and exclusion of other forms of PH was clarified. The procedure for plasma NT pro-BNP sampling was amended as per laboratory manual. RHC historical information was to be collected for all patients (including patients enrolled before the amendment) at screening. These included the hemodynamic results of the latest RHC performed. Information on 30-day follow-up was clarified: the safety follow-up (via telephone) was only applicable for patients who did not enter the open-label study within 30 days after study drug discontinuation. The safety follow-up phone call was to be documented in the patient chart. The safety reporting and follow-up procedure for patients was clarified: the procedure was dependent on the participation or not of a patient to the open-label study after study drug discontinuation. In addition, heart catheterization was removed from the list of the study-mandated procedures. The safety set was removed from the list of analysis sets defined for the study, instead the All-treated set to be used for safety evaluation. Changes in sponsor and other CRO contact details were listed. ICF was amended to reflect the changes introduced by the amendment. In addition, information about contraception methods was clarified.

Document Date	Global Amendment	Changes
23 Jan 2013	Amendment 6, and the resulting Global Protocol Version 7	The amendment was based on the recommendations made by the GRIPHON Steering Committee. To ensure consistency with new data from a recently completed clinical study in PAH with a similar primary endpoint, the ‘clinical worsening event’ was replaced by ‘morbidity and mortality (MM) event’, to reflect the overall objective of the study and the primary efficacy endpoint. The change was implemented throughout the protocol. A distinction between ‘adjudicated’ (i.e., morbidity and/or mortality event submitted to CEC) versus ‘confirmed’ (i.e., validated as event by the CEC) was made throughout the protocol. To collect additional clinical data until Study closure in all patients who prematurely discontinued study drug, a post-treatment observation period was added. This was defined as the period between the EOS visit (excluded) and the post-treatment observation closure visit (included), following Study closure announcement by the Sponsor. During the post-treatment observation period, site visits and telephone calls were performed alternatively every 3 months. To allow sufficient time in the planning of the Study closure visit for all patients after sponsor’s announcement, the period of 14 days was extended to 4 weeks. Two new committees were added: an ophthalmology safety board, and a committee with two PAH experts, who reviewed in a blinded fashion baseline PAH characteristics of all patients included in the study. Pre-defined criteria for hospitalization for PAH worsening and chronic oxygen therapy were clarified. Concomitant medications were collected during the treatment extension period. A single administration of medications such as i.v./inhaled prostacyclin analogs or inhaled nitric oxide or oral sildenafil was allowed for acute vasodilator testing during a RHC procedure preceding randomization into the study. For MM events adjudication by CEC, two CEC responsibilities were added and the CEC process was clarified: – the CEC was also to adjudicate each individual component of a MM event and its associated date. – the CEC was to assess the cause of death (due to PAH versus not due to PAH) A clarification that randomization was stratified by site was added. A clarification that compliance with study treatment was based on drug accountability was added. Patient management in case of Child-Pugh B or C liver impairment: If a patient developed or progressed to Child-Pugh B liver impairment, it was the responsibility of the investigator to assess the benefit-risk of

Document Date	Global Amendment	Changes
		maintaining the patient on study drug. If a patient developed or progressed to Child-Pugh C liver impairment, study drug was to be discontinued. This change was triggered by the results of the hepatic impairment Phase 1 study in which a 400 µg dose of selexipag resulted in a 4-fold increase in plasma exposure in Child-Pugh B subjects. Since 6MWT assessment was not performed during the post-treatment observation period, the endpoint component ‘disease progression’ could not be analyzed. Therefore, a MM event (excluding disease progression) based on the remaining components was used for the period. Based on this, the following exploratory endpoints were added/modified/clarified: – time from randomization to first CEC-confirmed MM event (excluding disease progression) up to Study closure. – time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to 7 days after last intake of study drug in the treatment period. – time from randomization to CEC-confirmed death due to PAH up to 7 days after last intake of study drug in the treatment period. – time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study closure. – time from randomization to first CEC-confirmed MM event up to Study closure. – time from randomization to CEC-confirmed death due to PAH up to Study closure. – CEC-confirmed (potentially recurrent) hospitalization due to worsening of PAH up to Study closure. – time course of CEC-confirmed (potentially recurrent) MM events hospitalization due to worsening of PAH, initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH, and death up to Study closure. – change from baseline to Week 16 in Borg dyspnea index was modified to Borg dyspnea index at Week 16 – change from baseline to EOS in Borg dyspnea index was modified to Borg dyspnea index at EOS. A safety endpoint quantifying retinal arterial tortuosity was added. Analysis of plasma samples from the 1800 µg b.i.d. dose (Day 3) of study AC-065-101 in healthy male subjects identified 10 metabolites other than ACT-333679. The structures of these 10 metabolites were determined, and none of these exceeded 3% of total drug-related material. Therefore, the reference to the measurement of other metabolites was removed from the protocol. The following clarifications were made in the statistical analysis section: – ICH terminology was used for the analysis sets, indicating roles of the analysis sets. – detailed censoring rules. – a rounding error that led to inconsistent statements in the group-sequential part was removed. A supplementary statistical analysis to be performed after

Document Date	Global Amendment	Changes
		study termination was added. – the probabilities for stopping the study at the interim analysis. – significance and confidence levels for the statistical analyses of secondary endpoints were aligned. – clarification for the handling of laboratory data. – information on the statistical analysis of the pharmacoeconomic endpoints. – clarifying the role of the independent Statistical Analysis Center generating the unblinded outputs for DMC review. The following modifications were made in the statistical analysis section (SAP to be finalized prior to the interim analysis): – statistical methods for handling missing data in the analyses were to be described in the SAP and were therefore removed from the protocol. – the PK analysis set was added. – the null and alternative hypotheses for the primary efficacy endpoint were specified in statistical terms and made directional. – one-sided type-I-error probability at the interim analysis (planned with 202 events) was fixed to 0.00005. – further supportive statistical analyses for the primary efficacy endpoint were added. – for statistical analysis of ordinal secondary efficacy endpoints, non-parametric ANCOVA with baseline value as covariate was used instead of the Wilcoxon rank sum test. – statistical analyses for additional exploratory efficacy endpoints introduced by the expanded data collection were added. – statistical analysis of the (ophthalmological) safety endpoint was added. At the time of randomization, the investigator was to confirm that treatment-naïve patients had no access to or could not tolerate PAH-specific therapy and that Functional Class IV patients could not be treated with i.v. prostanoid. In addition, throughout the course of the study, it was recommended to regularly discuss with patients whether new PAH therapy became available to them. Re-screening was occasionally accepted, but no more than one re-screening per patient was to be allowed. Examples of acceptable reasons for re-screening were: insufficient time window as defined in the protocol (PAH treatment stability period for ERA and PDE-5 inhibitor for at least 3 months), institution of a reliable method of contraception, and progression of disease severity over a reasonable period of time.



Statistical Analysis Plan (SAP)

Purpose of Analysis:	Interim Analysis and Clinical Study Report
Investigational Drug:	Selexipag
Protocol Number:	AC-065A302 / GRIPHON AC-065A303 / GRIPHON OL
Document Number:	D-12.232
Document Status / Version Number	Final 1.0
Date:	10 April 2013

AC-065A302 AND AC-065A303: STATISTICAL ANALYSIS PLAN FOR INTERIM ANALYSIS AND CLINICAL STUDY REPORT

MULTICENTER CLINICAL INVESTIGATIONS TO EVALUATE EFFICACY AND SAFETY OF SELEXIPAG IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-Minute walk distance
6MWT	6-Minute walk test
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
b.i.d.	<i>bis in die</i> / twice daily
BMI	Body mass index
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CEC	Critical Event Committee
CI	Confidence interval
CRF	Case Report Form
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
dPAP	Diastolic pulmonary arterial pressure
ECG	Electrocardiogram
EMA	European Medicines Agency
EOS	End of Study
EOTE	End-of-Treatment-Extension
ERA	Endothelin receptor antagonist
FAS	Full Analysis Set
FC	Functional class
FDA	Food and Drug Administration
HR	Hazard ratio
ICH	International Conference on Harmonisation
i.v.	Intravenous
IWRS/IVRS	Interactive Web / Voice Response System
KM	Kaplan-Meier
LVEDP	Left ventricular end diastolic pressure
MAR	Missing at random
MCMC	Markov Chain Monte Carlo

MedDRA	Medical Dictionary for Regulatory Activities
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
MTD	Maximum tolerated dose
NT pro-BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OL	Open label
PAH	Pulmonary arterial hypertension
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
PDE-5	Phosphodiesterase 5
PDE5-I	PDE-5 inhibitor
PK	Pharmacokinetic
PPS	Per-Protocol Set
PT	Preferred Term
PTOCV	Post-Treatment Observation Closure Visit
PV	Protocol violation
PVR	Pulmonary vascular resistance
Q1	First Quartile
Q3	Third Quartile
QoL	Quality of Life
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RCI	Repeated confidence interval
RHC	Right heart catheterization
SAC	Statistical Analysis Center
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
sc	Subcutaneous
SD	Standard deviation
SDTM	Study Data Tabulation Model
SI	Standardized International
SMQ	Standard MedDRA Query

SOC	System Organ Class
sPAP	Systolic pulmonary arterial pressure
SVO ₂	Mixed venous oxygen saturation
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes statistical analysis methods planned for

- the efficacy and safety interim analysis of studies AC-065A302 and AC-065A303; performed by the Statistical Analysis Center (SAC) and provided to the independent Data Monitoring Committee (DMC), see more details in Section [3.1](#)
- the final analysis of study AC-065A302 and study AC-065A303 up to the analysis cut-off date; performed by Actelion Biostatistics for the Clinical Study Report, see more details in Section [3.2](#).

The analysis of data from the Treatment-Extension Period of study AC-065A302 [see Section [2.1](#)] will be covered by a separate SAP.

2 STUDY DESIGN AND FLOW

2.1 Study design AC-065A302

Study AC-065A302 is designed as a multicenter, randomized, double-blind, parallel group, placebo-controlled, group-sequential Phase 3 study to compare efficacy, safety, tolerability of selexipag (administered at the individual maximum tolerated dose [MTD] in the range of 200 to 1600 µg twice daily [b.i.d.]) versus placebo. The randomization scheme is stratified by site, using permuted blocks and an allocation ratio of 1:1.

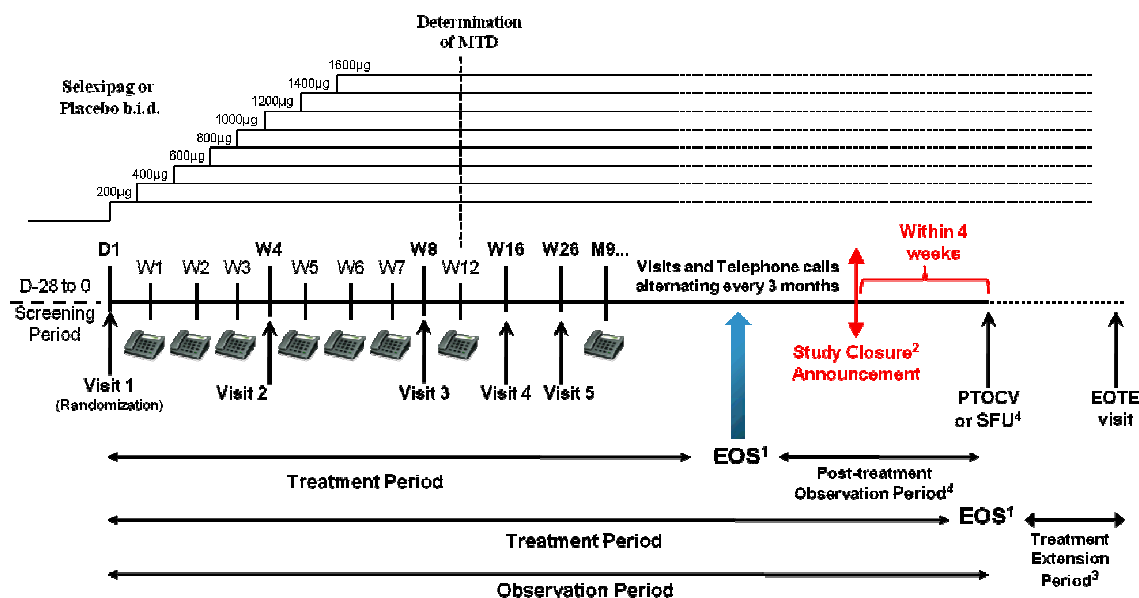
The study has the following periods:

- **Screening Period** starting with the patient signing the informed consent form and ending with the randomization, for eligible patients.
- **Treatment Period** starting with the Baseline Visit (Day 1) and ending with the End Of Study (EOS) Visit
 - Due to the fact that patients are to take their first dose of study medication on the evening of the Baseline Visit, this day is called Day 1.
 - Study closure is announced by the sponsor either following the recommendation of the DMC or when approximately 331 morbidity/mortality events (with onset date as per the Critical Event Committee [CEC] later than 16 August 2011¹) have been confirmed by the CEC. All patients still on study drug at study closure must have an EOS Visit within 4 weeks. Patients who have prematurely discontinued the study drug in AC-065A302 may enter the AC-065A302 Post-Treatment Observation Period, see below. However, patients who declined to enter the AC-065A302 Post-Treatment Observation Period may be contacted at the time of Study Closure to record their vital status.
- **Post-Treatment Safety Follow-Up Period for serious adverse events (SAEs):** SAEs must be reported up to 30 days after last study drug intake or until administration of the first dose of selexipag in study AC-065A303, whichever comes first.
- **Post-Treatment Observation Period:** starting with the EOS Visit (for patients with premature discontinuation of study drug in AC-065A302) and ending with the Post-Treatment Observation Closure Visit (PTOCV) within 4 weeks following announcement of Study Closure by the sponsor. Patients with premature discontinuation of study drug in AC-065A302 may enter the AC-065A302 Post-Treatment Observation Period irrespective of whether they enter study AC-065A303.
- **Treatment-Extension Period:** starting with the EOS Visit following Study Closure and ending with the End-Of-Treatment-Extension (EOTE) Visit following unblinding

¹ In order to eliminate any concern that the study protocol amendment could be considered informed, Actelion and the US Food and Drug Administration (FDA) agreed to right-censor events observed up to 16 August 2011 in the primary endpoint analysis (more details are given in subsequent sections of this SAP).

of the database by the sponsor. Once the unblinding of the database is announced by the sponsor, the patients must have the EOTE Visit shortly thereafter (within 14 days). This period will be covered by a separate SAP.

Figure 1 Design of study AC-065A302



- 1 EOS Visit for an individual patient may occur before Study Closure or within 4 weeks after announcement of Study Closure. Patients who discontinue study drug before announcement of Study Closure must have an EOS Visit and a Post-treatment Safety Follow-Up phone call.
- 2 Study Closure will be announced either after interim analysis or when the target number of CEC-confirmed morbidity/mortality events has been reached.
- 3 In case study AC-065A303 is approved by the national Health Authority, patients who are on study drug in AC-065A302 at Study Closure and who wish to enter study AC-065A303 must enter the Treatment-Extension Period of study AC-065A302.
- 4 Patients who prematurely discontinued study drug in AC-065A302 before Study Closure may enter the Post-Treatment Observation Period of AC-065A302, irrespective of whether they enter study AC-065A303 or not. When Study Closure is announced by the sponsor, a Post-Treatment Observation Closure Visit (PTOCV) is scheduled within 4 weeks. Patients not consenting to participate in the AC-065A302 Post-Treatment Observation Period may be contacted at the time of Study Closure to record their vital status.

Table 1 Visit and assessment schedule in study AC-065A302

	Screening	Visit 1	Tel. ^a W1	Tel. ^a W2	Tel. ^a W3	Visit 2	Tel. ^a W5	Tel. ^a W6	Tel. ^a W7	Visit 3	Tel. ^a W12	Visit 4	Visit 5 & onwards	Tel. ^a M9 & every 6 M ± 7d	Morbidity Mortality Event ^b	EOS Visit ^k	Safety Follow-up ^a 30 days after drug discontin. ^o	EOTE visit ^m
	≤ 28 days before Day 1	BL D 1 Randomization	Day 8 ± 3 d	Day 15 ± 3 d	Day 22 ± 3 d	Week 4 ± 3 d	Week 5 ± 3 d	Week 6 ± 3 d	Week 7 ± 3 d	Week 8 ± 3 d	Week 12 ± 3 d	Week 16 ± 3 d	W26 (M6) & every 6M ± 7 days					
Written informed consent	X ^t																	
Inclusion/exclusion crit. (incl. hemodynamics)	X	Re-confirm																
Med. history incl. PAH	X	X																
Concomitant medications	X	X				X				X		X	X	X	X	X		X
Mod. NYHA/WHO FC	X	X				X				X		X	X		X	X		
Physical examination	X	X				X				X		X	X		X	X		
Weight and height ^h	X	X				X				X		X	X		X	X		
Vital signs	X	X				X				X		X	X		X	X		
12-lead ECG		X				X				X		X	X ^p		X	X		
6-minute walk test	X ^c	X								X		X	X		X	X		
Borg dyspnea score	X ^c	X								X		X	X		X	X		
CAMPBOR (subset)		X										X	X ^f			X		
Pregnancy test (if appl.) ⁱ	X	X				X				X	X	X	X			X		X
Laboratory test ^d	X	X				X				X		X	X		X	X		
Plasma NT pro-BNP		X				X				X		X	X			X		
PK sampling		X				X				X		X ⁿ	X ^e			X		
Ophthalmol (subset)		X ^q											X ^r			X ^s		
Study drug dispensing		X				X				X		X	X					
First dose of study drug		X pm																
Dose titration			X	X	X	X	X	X	X		X ^g							
Drug accountability						X				X		X	X			X		X
(Serious) adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital status																X ^l		
Addendum to written ICF																X ^u		

a: Tel. = Scheduled telephone call. **b:** In case of suspected clinical worsening. **c:** Conducted ≤ 14 days before Day 1. **d:** Laboratory test (hematology and blood chemistry). **e:** On Visit 5 (Week 26, Month 6) & Visit 6 (Month 12) only. **f:** On Visit 5 (Week 26, Month 6), Visit 6 (Month 12) and Visit 8 (Month 24) only. **g:** Confirmation of MTD. **h:** Height measured only at screening. **i:** Serum pregnancy test to be performed at screening and urine pregnancy tests monthly until 1 month after study drug discontinuation. **k:** In case of premature discontinuation of study drug and for all patients on study drug at Study Closure. **l:** Survival follow-up phone call at Study Closure for patients with premature EOS not entering the Post-Treatment Observation Period. **m:** The End of Treatment Extension visit must be performed only for patients still on study drug at Study Closure and who wish to enter study AC-065A303 (if approved by the national Health Authority in the country). **n:** Two PK samplings will be taken at this visit, one pre-dose and one post-dose. **o:** For patients who will enter study AC-065A303, SAEs must be followed-up until the first dose of ACT-293987 in study AC-065A303. **p:** At Visit 6 (Month 12), two additional ECGs will be performed 2 and 4 hours after study drug intake. **q:** Performed at Baseline/Randomization Visit (Visit 1) (or within the screening period [28 days before Day1]) **r:** Only at Visit 6 (Month 12). **s:** Performed at EOS Visit or within 2 weeks before or after the scheduled EOS Visit. (* 6 months corresponds to 26 weeks). **t:** Confirm that treatment-naïve patients cannot tolerate or have no access to PAH-specific therapy and that NYHA FC IV patients cannot be treated with i.v. prostanoïd. Throughout the course of the study, it is recommended to regularly discuss with the patient whether new PAH therapy is becoming available. **u:** applies to patients who will enter the Post-Treatment Observation Period after approval of amendment 6 while under study drug.

Table 2 Visit and assessment schedule in the AC-065A302 Post-Treatment Observation Period

	Site visits for patients in the AC-065A302 Post-Treatment Observation Period	Phone calls for patients in the AC-065A302 Post-Treatment Observation Period	Unscheduled visit in case of PAH worsening	Post-Treatment Observation Closure Visit (within 4 weeks after Study Closure announcement)
	<u>Site visit</u> ² : 6 months after EOS visit and every 6 months thereafter	<u>Phone call</u> : 3 months after EOS Visit/first site visit ³ and every 6 months thereafter		
Addendum to Written Informed Consent Form	X if not already signed at EOS			
Concomitant medications for PAH ¹ (incl. O ₂ therapy)	X	X	X	X
Mod. NYHA/WHO functional class	X		X	X
Hospitalization for PAH worsening since last visit		X		
Morbidity/mortality event details (excluding “disease progression”) ⁴	X		X	X
Vital status	X	X		X

¹ Concomitant medications for PAH include ERA, PDE5-I, prostanoid and chronic O₂ therapy (change in dose will not be collected)

² For patients who had their EOS visit prior to approval of amendment 6, the first site visit of the Post-Treatment Observation Period may be scheduled more than 6 months after EOS visit. In such case, a retrospective data collection covering the entire period since EOS visit will be done.

³ For patients who had their EOS visit prior to approval of amendment 6, the first phone call will be three months after the first site visit

⁴ Morbidity/mortality event form records clinical information needed for the adjudication of the event (e.g. hospitalization for PAH worsening, PAH worsening resulting in need of lung transplantation/atrial septostomy, symptoms of PAH worsening, ...).

2.2 Study design AC-065A303

The study is designed as an open-label, uncontrolled, multicenter study to assess long-term safety and tolerability in:

- patients experiencing a CEC-confirmed morbidity event during study AC-065A302, and
- patients who have completed study AC-065A302 as scheduled, i.e., without premature end of study drug.

Patients entering study AC-065A303 following a CEC-confirmed morbidity event during study AC-065A302 are transferred without knowledge of their previous study drug allocation (selexipag or placebo) to preserve the integrity of study AC-065A302. These patients enter the AC-065A303 Titration Period and start with a selexipag dose of 200 µg b.i.d. with subsequent up-titration to identify their individual MTD of selexipag (but maximum 1600 µg b.i.d.). During the AC-065A303 Maintenance Period they will receive selexipag at their MTD.

Patients entering AC-065A303 immediately after their AC-065A302 End-of-Treatment-Extension visit are transferred with knowledge of their previous study drug allocations (selexipag or placebo). Therefore:

- patients who have received selexipag in study AC-065A302 start with the AC-065A303 Maintenance Period continuing with their same selexipag dose as they ended in study AC-065A302
- patients who have received placebo in study AC-065A302 start the AC-065A303 Titration Period with a selexipag dose of 200 µg b.i.d. with subsequent up-titration to identify their individual MTD of selexipag (but maximum 1600 µg b.i.d.). During the AC-065A303 Maintenance Period they receive selexipag at their MTD.

Table 3 Visit and assessment schedule in study AC-065A303 for patients starting selexipag with up-titration

	Visit ² 1	TITRATION PERIOD ¹										MAINTENANCE PERIOD			Safety follow up ⁴ 30 days after EOS
		Tel. ⁴ W1	Tel ⁴ W2	Tel ⁴ W3	Visit 2	Tel ⁴ W5	Tel ⁴ W6	Tel ⁴ W7	Visit 3	Tel ⁴ W12	Visit 4	Visit 5	Tel ⁴	EOS Visit	
	Day 1	Day 8 ± 3 days	Day 15 ± 3 days	Day 22 ± 3 days	Week 4 ± 3 days	Week 5 ± 3 days	Week 6 ± 3 days	Week 7 ± 3 days	Week 8 ± 3 day	Week 12 ± 3 days	Week 16 ± 3 days	Month 6* and every 6 months ± 7 days	Month 9 and every 6 months ± 7 days		
Written informed consent ⁷	X														
Concomitant medications	X				X				X		X	X		X	
Vital signs	X				X				X		X	X		X	
Body weight	X				X				X		X	X		X	
Laboratory tests ⁵	X				X				X		X	X		X	
Physical examination ⁶	X				X				X		X	X		X	
Pregnancy test ³	X				X				X	X	X	X	X	X	X
Dispensing of study drug	X				X				X		X	X			
Drug accountability					X				X		X	X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

¹ Only for patients who were on placebo or patients who experienced an adjudicated morbidity event during AC-065A302; ² Visit 1 should correspond to the last visit in the double-blind study or, if not possible, must be at the latest within 2 weeks (14 days). When Visit 1 is performed the same day as the last visit of the double-blind study, assessments that are common to both studies are not to be repeated. Results are to be reported on CRF pages of both studies; ³ Monthly urine pregnancy test for women of childbearing potential until 1 month after study drug discontinuation; ⁴ Scheduled telephone call; ⁵ Hematology and blood chemistry tests to be performed at Visit 1 only if the last assessment in AC-065A302 was performed more than 4 weeks ago, and then at every visit until EOS. ⁶ Physical examination results will not be collected in the CRF. ⁷ Throughout the course of the study, it is recommended to regularly discuss with the patient whether new PAH therapy is becoming available. * 6 months correspond to 26 weeks.

Table 4 Visit and assessment schedule in study AC-065A303 for patients starting selexipag without up-titration

	Visit ¹ 1	TITRATION PERIOD ²	MAINTENANCE PERIOD				EOS Visit	Safety follow up ⁴
		NA	Tel ⁴ W12	Visit 5	Tel ⁴			
	Day 1	NA	Week 12 ± 3 days	Month 6* and every 6 months ± 7 days	Month 9 and every 6 months ± 7 days			30 days after EOS
Written informed consent ⁷	X	NA						
Concomitant medications	X	NA		X		X		
Vital signs	X	NA		X		X		
Body weight	X	NA		X		X		
Laboratory tests ⁵	X	NA		X		X		
Physical examination ⁶	X	NA		X		X		
Pregnancy test (if appl.) ³	X	NA	X	X	X	X		X
Dispensing of study drug	X	NA		X				
Drug accountability		NA		X		X		
Adverse events	X	NA	X	X	X	X		
Serious adverse events	X	NA	X	X	X	X		X

¹ For patients on study drug until unblinding of AC-065A302, Visit 1 should correspond to the last visit in the double-blind study AC-065A302 or, if not possible, must be at latest within 2 weeks (14 days); ² Not applicable, patient will switch directly from Visit 1 to Week 12 phone call and Visit 5; ³ Monthly urine pregnancy test for women of childbearing potential until 1 month after study drug discontinuation; ⁴ Scheduled telephone call. ⁵ Hematology and blood chemistry tests to be performed at Visit 1 only if the last assessment in AC-065A302 was performed more than 4 weeks ago, and then at every visit until EOS. ⁶ Physical examination results will not be collected in the CRF. ⁷ Throughout the course of the study, it is recommended to regularly discuss with the patient whether new PAH therapy is becoming available.

* 6 months correspond to 26 weeks.

CRF = Case Report Form; EOS = End of Study; NA = Not applicable.

3 INTERIM AND FINAL ANALYSES

3.1 Interim analysis by DMC

The interim efficacy and safety analysis includes efficacy, safety and tolerability data from study AC-065A302 as well as safety data from patients in study AC-065A303.

Cut-off dates for the interim analysis

- 22 January 2013 for safety data
- 22 January 2013 for efficacy data other than those related to morbidity/mortality events
- 25 March 2013 for confirmation of morbidity/mortality events by the Critical Event Committee (CEC).

The interim analysis includes efficacy data only from the Treatment Period of study AC-065A302. Efficacy data from the AC-065A302 Post-Treatment Observation Period is not available due to the timing of AC-065A302 Protocol Amendment 6 (dated 23 January 2013) and the timing of the interim analysis.

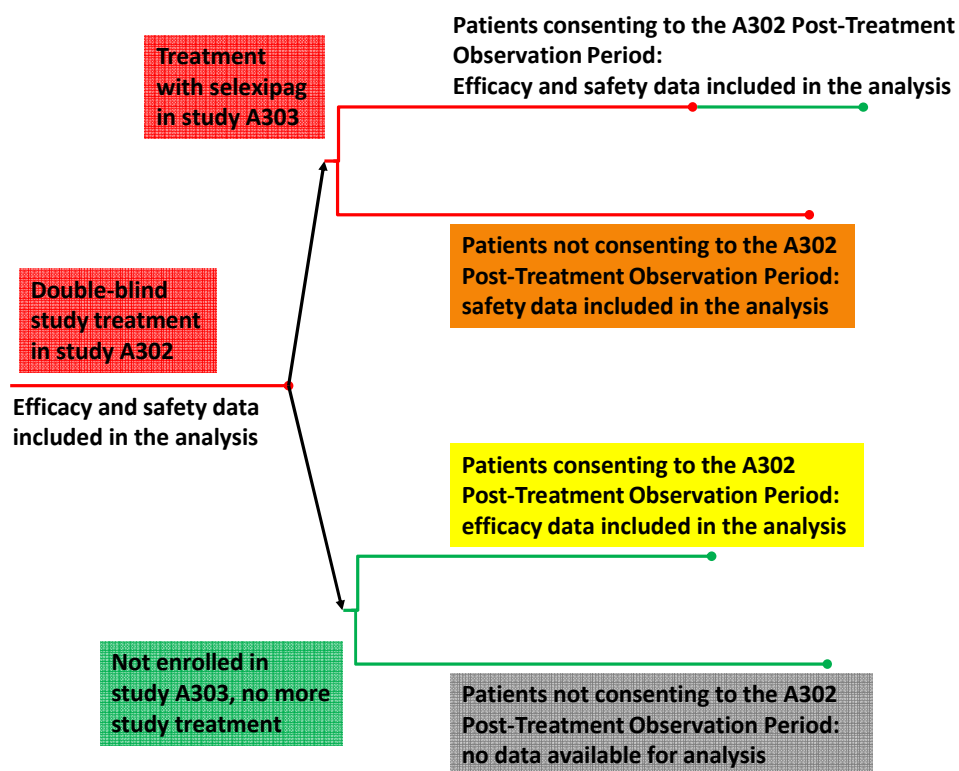
The detailed selection of endpoints and statistical methods for the interim analysis are provided below:

- Sections 19, 20 and 22 (including competing risk analysis)
- Sections 23.1 and 23.2
- Sections 24.2 and 24.4
- efficacy analyses only for the Full Analysis Set, not for the Per Protocol Set
- safety analyses same as for regular DMC meetings described in the DMC SAP (based on Safety Analysis Set but with study treatments as randomized and not as treated).

3.2 Final analysis

The final analysis covers all data from study AC-065A302 including all data from the AC-065A302 Post-Treatment Observation Period but excluding data from the Treatment-Extension Period. In addition, the final analysis includes all safety data (up to an analysis cut-off date) from patients who participate in study AC-065A303.

Figure 2 Inclusion of data for the final analysis²



Data sources to generate Study Data Tabulation Model (SDTM) datasets are the following:

- Interactive Web / Voice Response System (IWRS/IVRS) data (provided by ICON)
- Case Report Form (CRF) data (including coding where applicable)
- Protocol violation data (provided by the Clinical Trial Team)
- Critical Event Committee (CEC) data
- Central blinded expert review of PAH characteristics at Baseline
- Central laboratory data, central ECG data, etc

² red lines indicate study treatment, green lines indicate no study treatment

recording survival status at time of AC-065A302 Study Closure is not included in the figure for simplicity.

4 STUDY OBJECTIVES

4.1 Primary objective (study AC-065A302)

The primary objective is to determine whether selexipag has a favorable effect (relative to placebo) on time to first morbidity/mortality event in patients with pulmonary arterial hypertension (PAH).

4.2 Secondary objectives

Secondary objectives are:

- to evaluate the effects of selexipag (relative to placebo) on exercise capacity and other secondary and exploratory efficacy endpoints in patients with PAH (objective for study AC-065A302).
- to evaluate the safety and tolerability of selexipag in patients with PAH (objective for study AC-065A302 and study AC-065A303).

5 ANALYSIS SETS

Patients are only included in any of the analysis sets described below if signed informed consent for study AC-065A302 has been documented.

5.1 Full analysis set

The Full Analysis Set (FAS) includes all randomized patients in study AC-065A302.

All main statistical analyses of all efficacy endpoints are based on the FAS. In order to adhere to the intention-to-treat principle as much as possible:

- patients are evaluated according to the study drug they have been randomized to (which may be different from the study drug they have received)
- all available efficacy data is included.

5.2 Per-protocol set

The Per-Protocol Set (PPS) comprises data from all patients included in the FAS who

- were at least 18 years old at screening (based on CRF data)
- belonged to one of the subgroups of the Dana Point Updated Clinical Classification Group 1 mentioned in AC-065A302 inclusion criterion #3 at screening (protocol violation [PV] code 112M)
- received at least one dose of study drug (PV code 153C)
- did not interrupt intake of study drug (according to drug log CRF) for a total of at least 50% of the time between first and last study drug intake in AC-065A302 (based on CRF data)
- has not been off-treatment for at least 4 weeks at any point between first and last dosing of study drug in study in AC-065A302 (based on CRF data)
- had a valid Baseline 6-minute walk test (6MWT), with “valid” defined as
 - 6MWT performed prior to first intake of study drug (PV code 498M)
 - 6MWT not interrupted for reason not related to PAH (PV code 500MM)

and up to the occurrence of any of the following events:

- start of any forbidden treatment for PAH
 - initiation of PDE5 inhibitor or ERA or prostacyclin or prostacyclin analogs after randomization without a documented worsening of PAH (a switch within a drug class is not considered for exclusion) (PV code 277MM)
 - relevant dose increase of the same drug for an existing PAH therapy (PDE5 inhibitor or ERA) (PV code 497MM)
- intake of study drug in AC-065A302 other than which they were randomized to (PV codes 201, 424 to 434)
- individual unblinding of study drug to the investigator.

Patients are evaluated according to the study drug they have been randomized to.

The statistical analyses of the primary and secondary efficacy endpoints based on the PPS supplement those based on the FAS and assess the robustness of treatment effects.

5.3 Safety analysis set

The safety analysis set includes all randomized patients who received at least one dose of study drug in study AC-065A302. All statistical safety analyses are based on the safety analysis set.

Patients are evaluated according to the study drug they have received (which may be different from the study drug to which they have been randomized), defined as:

- if a patient has taken at least one dose of selexipag in study AC-065A302 and no dose of selexipag in study AC-065A303, then she/he is assigned to the AC-065A302 selexipag treatment group
- if a patient has taken only placebo in study AC-065A302 and no dose of selexipag in study AC-065A303, then she/he is assigned to the AC-065A302 placebo treatment group
- if a patient has taken at least one dose of selexipag in each of the studies AC-065A302 and AC-065A303, then she/he is assigned to the selexipag/selexipag treatment group
- if a patient has taken only placebo in study AC-065A302 and at least one dose of selexipag in study AC-065A303, then she/he is assigned to the placebo/selexipag treatment group.

Unless otherwise stated (e.g., for SAEs), the safety analysis set comprises all available safety data up to minimum(maximum[date of last study drug intake in AC-065A302 Treatment Period plus 7 days, date of last study drug intake in AC-065A303 plus 3 days], analysis cut-off date).

5.4 PK analysis set

The PK analysis set includes all patients in the FAS who received at least one dose of the study drug in AC-065A302 and had at least one PK sample collected after initiation of study drug in AC-065A302.

5.5 QoL analysis set

The QoL analysis set includes all patients in the FAS for whom a suitable language of the CAMPHOR questionnaire for study AC-065A302 has been available at his/her site.

5.6 Use of statistical analysis sets

Table 5 provides an overview of the use of the different analysis sets for the final analysis.

Table 5 Overview of the different analysis sets and their usage

	Full analysis set	Per-protocol set	QoL analysis set	Safety analysis set	PK analysis set
Baseline and disease characteristics	✓		✓		
Previous and concomitant therapies	✓				
Treatment exposure	✓			✓	
Primary and secondary efficacy endpoints (except CAMPHOR related efficacy endpoints)	✓	✓			
Exploratory efficacy endpoints (except CAMPHOR related efficacy endpoints)	✓				
CAMPHOR-related efficacy endpoints			✓		
Pharmacoeconomic endpoints	✓				
Safety endpoints				✓	
Listings	✓				
PK trough analysis					✓

6 PATIENT CHARACTERISTICS

6.1 Demographics

Demographics of the patients are sex, race, country, geographical region, age categorized as continuous variable as well as < 65 years and ≥ 65 years, weight (kg), height (cm), and BMI, all at AC-065A302 screening. BMI is categorized as <25 , $25\text{--}30$, >30 kg/m².

Geographical regions are defined as follows (numbers are the first 2 digits of the center number):

Asia includes any country with the center number starting with 14 (China), 29 (Singapore), 45 (Taiwan), 65 (India), 66 (Malaysia), 71 (South Korea), or 72 (Thailand)

Eastern Europe includes any country with the center number starting with 16 (Czech Republic), 26 (Poland), 27 (Slovakia), 38 (Serbia), 39 (Hungary), 49 (Turkey), 61 (Belarus), 69 (Romania), 70 (Russia), or 73 (Ukraine)

Latin America includes any country with the center number starting with 60 (Argentina), 62 (Chile), 63 (Colombia), 67 (Mexico), or 68 (Peru)

North America includes any country with the center number starting with 13 (Canada) or 31 (USA)

Western Europe + Australia includes any country with the center number starting with 10 (Australia), 11 (Austria), 12 (Belgium), 17 (Denmark), 19 (France), 20 (Germany), 23 (Italy), 32 (Spain), 33 (Sweden), 34 (Switzerland), 35 (Great Britain), 40 (Israel), 41 (Netherlands), 50 (Ireland), or 64 (Greece).

6.2 Baseline disease characteristics

Definition of Baseline is provided in Section [29.5](#).

Baseline disease characteristics are:

- time from PAH diagnosis confirmed by Right Heart Catheterization (RHC) to randomization
- RHC data (separately for patients with RHC within 3 months before randomization and for patients with RHC more than 3 months before randomization) (i.e., sPAP, dPAP, mPAP PVR, mRAP, Mean PCWP, Mean LVEDP, Cardiac Index, Cardiac Output and SVO₂)
- etiology of PAH
- modified NYHA/WHO functional class at Baseline
- systolic blood pressure, diastolic blood pressure, heart rate at Baseline
- 6-minute walk distance (6MWD) at Baseline
- Borg dyspnea index at Baseline.

6.3 Definition of subgroups

The following subgroups, classifying patients according to relevant AC-065A302 demographic characteristics and disease characteristics at Baseline, are considered for the evaluation of efficacy and/or safety:

- concomitant specific PAH therapy groups at Baseline [see Section [8.2](#)]
- PAH diagnosis within 6 months prior to randomization versus PAH diagnosis more than 6 months prior to randomization
- NYHA/WHO functional class at Baseline: I/II versus III/IV
- sex (male versus female)
- race/ethnicity: Caucasian/Hispanic versus Asian versus Black versus Hispanic versus other
- age at time of randomization: < 65 years versus $\geq$ 65 years
- PAH etiology at Baseline: (idiopathic, heritable, drug or toxin induced, associated with HIV infection) versus associated with connective tissue disease versus associated with congenital heart disease with systemic-to-pulmonary shunts
- geographical regions [see Section [6.1](#)]

7 EXPOSURE TO STUDY DRUG

Exposure to study drug is defined for study AC-065A302 (selexipag and placebo) in Section 7.2 and for study AC-065A303 (selexipag) in Section 7.3.

7.1 Reason for discontinuation of study drug

The following rules are applied to identify patients who discontinued study drug (separately for studies AC-065A302 and AC-065A303):

- EOS visit date present and preferred term for “Reason for End Date” of the last chronological interval in the study drug CRF different from “END OF DOUBLE-BLIND TREATMENT” or “UP-TITRATION”
- EOS visit date not present and preferred term for “Reason for End Date” equal to “DEATH” or “LOST TO FOLLOW UP” or “WITHDRAWAL OF CONSENT”.

The reason for discontinuation of study drug is collected in the last record (chronological order by start date) of the study drug CRF pages.

7.2 Exposure to study drug in AC-065A302

Exposure to study drug in study AC-065A302 is defined as date of last intake of study drug minus date of first intake of study drug plus 1.

If the date of last study drug intake is missing, the analysis cut-off date is used – unless the patient has the EOS visit date or died prior to the analysis cut-off date. In this case, minimum(EOS visit date, date of death) is used.

7.2.1 Study drug Titration and Maintenance Periods in study AC-065A302

The AC-065A302 study drug Titration Period starts at date of first intake of study drug and ends at AC-065A302 Study Day 87 (or earlier, if selexipag is discontinued before). The AC-065A302 study drug Maintenance Period starts at AC-065A302 Study Day 88 and ends at the date of last intake of study drug in study AC-065A302.

Study drug dose at the end of the AC-065A302 Titration Period is defined as the dose taken by the patient at AC-065A302 Study Day 87 (0 for patients with study drug discontinuation prior to AC-065A302 Study Day 87).

For each patient, the following study drug doses are defined:

- maximum and weighted-average³ study drug dose in the AC-065A302 Titration Period
- maximum and weighted-average study drug dose in the AC-065A302 Maintenance Period (for patients who entered this period)
- maximum and weighted-average study drug dose in the entire AC-065A302 Treatment Period.

³ weighting is done on the amount of time exposed to each study drug dose according to the drug log CRF

7.2.2 Maximum tolerated dose in study AC-065A302

For a patient with last study drug intake after AC-065A302 Study Day 87, her/his AC-065A302 MTD is defined as the study drug dose to which she/he was exposed for the longest duration in study AC-065A302.

For a patient with last study drug intake before AC-065A302 Study Day 88, her/his AC-065A302 MTD is defined as the highest dose that did not lead to study drug discontinuation or down-titration in study AC-065A302.

7.3 Exposure to selexipag in study AC-065A303

Exposure to selexipag in study AC-065A303 is defined as date of last intake of selexipag (up to the analysis cut-off date) in study AC-065A303 minus date of first intake of selexipag in study AC-065A303 plus 1.

7.3.1 Selexipag Titration and Maintenance Periods in study AC-065A303

The AC-065A303 selexipag Titration Period starts at date of first intake of selexipag in study AC-065A303 and ends at AC-065A303 Study Day 87 (or earlier, if selexipag is discontinued before). The AC-065A303 selexipag Maintenance Period starts at AC-065A303 Study Day 88 and ends at the date of last intake of selexipag in study AC-065A303.

Selexipag dose at the end of the AC-065A303 Titration Period is defined as the selexipag dose taken by the patient at AC-065A303 Study Day 87 (0 for patients with study drug discontinuation prior to AC-065A303 Study Day 87).

For each patient, the following selexipag doses are defined:

- maximum and weighted-average selexipag dose in the AC-065A303 Titration Period
- maximum and weighted-average selexipag dose in the AC-065A303 Maintenance Period (for patients who entered this period)
- maximum and weighted-average selexipag dose in the entire AC-065A303 Treatment Period.

7.3.2 Maximum tolerated dose in study AC-065A303

For patients without death before AC-065A303 Study Day 88, the AC-065A303 MTD is defined as the selexipag dose to which the patient was exposed for the longest duration in study AC-065A303.

For a patient with last study drug intake after AC-065A303 Study Day 87, her/his AC-065A303 MTD is defined as the study drug dose to which she/he was exposed for the longest duration in study AC-065A303.

For a patient with last study drug intake before AC-065A303 Study Day 88, her/his AC-065A303 MTD is defined as highest dose that did not lead to study drug discontinuation or down-titration in study AC-065A303.

8 PREVIOUS AND CONCOMITANT MEDICATIONS

8.1 Non-PAH medication

This includes any non-PAH medication/therapy reported.

Previous non-PAH medication

A previous non-PAH medication is defined as any non-PAH medication/therapy with end date prior to the AC-065A302 study drug start date.

Non-PAH medication concomitant at Baseline

Non-PAH medication concomitant at Baseline is defined as any non-PAH medication/therapy with start date before the AC-065A302 study drug start date and end date after or on the AC-065A302 study drug start date.

Concomitant non-PAH medication

Concomitant non-PAH medication is defined as any non-PAH medication/therapy with start date on or after the AC-065A302 study drug start date and on or before the study drug discontinuation date in study AC-065A303 (or AC-065A302 for patients who have not entered study AC-065A303).

8.2 PAH medication

This includes any PAH concomitant medication reported. The following subgroups of patients are defined (separately for studies AC-065A302 and AC-065A303):

- patients treated with Endothelin Receptor Antagonists (ERAs) monotherapy – identified by the following preferred terms (“Ambrisentan” OR “Bosentan” OR “Sitaxentan”) AND NOT (“Sildenafil” OR “Tadalafil” OR “Vardenafil”)
- patients treated with PDE5-Inhibitors (PDE5-I) monotherapy – identified by the following preferred terms (“Sildenafil” OR “Tadalafil” OR “Vardenafil”) AND NOT (“Ambrisentan” OR “Bosentan” OR “Sitaxentan”)
- patients treated with combination of both ERAs and PDE5-Inhibitors – identified by the following preferred terms (“Ambrisentan” OR “Bosentan” OR “Sitaxentan”) AND (“Sildenafil” OR “Tadalafil” OR “Vardenafil”)
- patients treated with prostacyclin/analogues (irrespective of ERAs or PDE5-Is) – identified by the following preferred terms “Iloprost” OR “Epoprostenol” OR “Treprostinil” OR “Beraprost” (this group of patients is not necessarily mutually exclusive to the other patient groups defined here; it is expected to be small as prostacyclin/analogues are not allowed to be co-administered according to the study protocol)
- patients without any such concomitant medication defined in the bullet points above.

Previous PAH medication

Previous PAH medication is any PAH medication/therapy with end date prior to the AC-065A302 study drug start date.

PAH medication concomitant at Baseline

PAH medication concomitant at Baseline is defined as any PAH medication/therapy with start date prior to the AC-065A302 study drug start date and end date after or on the AC-065A302 study drug start date.

Concomitant PAH medication

Concomitant PAH medication is defined as any PAH medication/therapy with start date on or after the AC-065A302 study drug start date and on or before the study drug discontinuation date in study AC-065A303 (or AC-065A302 for patients who have not entered study AC-065A303).

Subsequent PAH medication

Subsequent PAH medication is defined as any PAH medication/therapy with start date after the study drug discontinuation date in study AC-065A303 (or AC-065A302 for patients who have not entered study AC-065A303).

9 PRIMARY ENDPOINT DEFINITION

For the primary efficacy endpoint, the following morbidity/mortality events occurring up to 7 days after last study drug intake in the AC-065A302 Treatment Period and confirmed by the CEC are considered:

- death (all-cause mortality)
- hospitalization for worsening of PAH based on criteria defined in the study protocol
- worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy
- initiation of parenteral (subcutaneous or intravenous) prostanoid therapy or chronic oxygen therapy due to worsening of PAH
- disease progression (patients in modified NYHA/WHO functional class II or III at Baseline) confirmed by a decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) and worsening of NYHA/WHO functional class
- disease progression (patients in modified NYHA/WHO functional class III or IV at Baseline) confirmed by a decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) and need for additional PAH specific therapy.

Date of the first CEC-confirmed morbidity/mortality event (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is defined as the first event onset date provided by the CEC.

Time to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as date of the first CEC-confirmed morbidity/mortality event (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) minus date of randomization plus 1.

Censoring rules

For a patient without a CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in the AC-065A302 Treatment Period, time to first CEC-confirmed morbidity/mortality event (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is defined as

- for randomized patients with at least one intake of study drug and not consented for the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, EOS visit date, date of last contact, analysis cut-off date) minus date of randomization plus 1
- for randomized patients with at least one intake of study drug and consented for the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, date of last contact, analysis cut-off date) minus date of randomization plus 1

- for randomized patients without any intake of study drug: minimum(maximum[EOS visit date, randomization date], date of last contact, analysis cut-off date) minus date of randomization plus 1.

These constitute right-censored observations.

CEC-confirmed morbidity/mortality events with onset date (as per CEC) up to 16 August 2011 are considered as censored⁴ at event onset date in the primary statistical analysis.

⁴ In case a patient with a CEC-confirmed morbidity/mortality event with onset date up to 16 August 2011 has a subsequent CEC-confirmed morbidity/mortality event with onset date after 16 August 2011, then the first event is disregarded and the second event counts as event in the statistical analysis.

10 SECONDARY ENDPOINTS DEFINITIONS

10.1 Absolute change from Baseline in 6MWD at trough at Week 26

The absolute change from Baseline in 6MWD at trough level of study drug at Week 26 is defined as the difference between Week 26 value and Baseline value.

A 6MWT at Week 26 is defined as “at trough” if the date of last selexipag administration prior to the 6MWT at Week 26 is before the date of the 6MWT at Week 26.

For patients for whom the 6MWT at Week 26 was not performed at trough, the result of the 6MWT at Week 26 is set to “invalid” and considered as missing data in the analysis.

In a supportive analysis, all available 6MWT data at Week 26 will be included (irrespective whether the test was performed at trough or not).

10.2 Absence of worsening from Baseline to Week 26 in modified NYHA/WHO functional class

Worsening is defined as any increase in functional class level as compared to modified NYHA/WHO functional class at Baseline.

10.3 Borg dyspnea index at Week 26

The Borg dyspnea index at Week 26 is directly taken from the CRF.

10.4 Time from randomization to death up to Study Closure

Time from randomization to death up to Study Closure is defined as date of death minus date of randomization plus 1.

Censoring rules

For patients not known to be deceased, time from randomization to death is defined as

- for patients who did not consent for the AC-065A302 Post-Treatment Observation Period and did not consent to the survival follow-up at Study Closure: minimum(EOS visit date, date of last contact, analysis cut-off date) minus date of randomization plus 1
- for patients who did not consent for the AC-065A302 Post-Treatment Observation Period but consented to the survival status follow-up at Study Closure: minimum(date of last contact, analysis cut-off date) minus date of randomization plus 1
- for patients who consented for the AC-065A302 Post-Treatment Observation Period: minimum(maximum[PTOCV date, EOS visit date], date of last contact, analysis cut-off date) minus date of randomization plus 1.

These constitute right-censored observations. Deaths up to 16 August 2011 are considered as right-censored at date of death.

10.5 Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)

The details on the CAMPHOR questionnaire administration, score/subscale calculations and rules for missing items are described in the CAMPHOR Guidelines for Users, [[Galen Research 2004](#)].

CAMPHOR questionnaire was administered only in selected centers by availability of validated questionnaire in local language.

10.5.1 Absolute change from Baseline to Week 26 in sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’

The sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ is defined as the sum of the ‘Breathlessness’ items 11 to 18. It will range from 0 (good) to 8 (poor).

Absolute change from Baseline to Week 26 in sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ is defined as the difference between the Week 26 value and the Baseline value.

10.5.2 Absolute change from Baseline to Week 26 in CAMPHOR ‘Symptoms’ score

The CAMPHOR ‘Symptoms’ score is defined as the sum of the ‘Symptoms’ items 1 to 18. It will range from 0 (good) to 18 (poor).

Absolute change from Baseline to Week 26 in CAMPHOR ‘Symptoms’ score is defined as the difference between the Week 26 value and the Baseline value.

11 EXPLORATORY ENDPOINTS DEFINITIONS

Table 6 Overview of exploratory efficacy endpoints

Exploratory efficacy endpoints related to morbidity/mortality	
11.1	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure
11.2	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period
11.3	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure
11.4	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period
11.5	Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period
11.6	Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period
11.7	Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study Closure
11.8	Time from randomization to first CEC-confirmed morbidity/mortality event up to Study Closure
11.9	Time from randomization to CEC-confirmed death due to PAH up to Study Closure
11.10	CEC-confirmed (potentially recurrent) hospitalizations due to worsening of PAH up to Study Closure
11.11	Time course of CEC-confirmed (potentially recurrent) hospitalization due to worsening of PAH, initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH, and death up to Study Closure
Exploratory efficacy endpoints related to 6MWD	
11.12	Absolute changes in 6MWD at trough from Baseline to all scheduled visits other than Week 26
11.12	Absolute change in 6MWD at trough from Baseline to EOS

Exploratory efficacy endpoints related to modified NYHA/WHO functional class	
11.13	Absence of worsening from Baseline at scheduled visits other than Week 26
11.13	Absence of worsening from Baseline to EOS
Exploratory efficacy endpoints related to Borg dyspnea index	
11.14	Borg dyspnea index at scheduled visits other than Week 26
11.14	Borg dyspnea index at EOS
Exploratory efficacy endpoints related to plasma NT pro-brain natriuretic peptide	
11.15	Absolute change in plasma NT pro-BNP from Baseline at scheduled visits
11.15	Absolute change in plasma NT pro-BNP from Baseline to EOS
Exploratory efficacy endpoints related to CAMPHOR	
11.16	Absolute changes in CAMPHOR sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' from Baseline at scheduled visits other than Week 26
11.16	Absolute changes in CAMPHOR 'Symptoms' score from Baseline at scheduled visits other than Week 26
11.16	Absolute change in CAMPHOR sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' from Baseline to EOS
11.16	Absolute change in CAMPHOR 'Symptoms' score from Baseline to EOS

11.1 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding "disease progression") up to Study Closure

The following four CEC-confirmed morbidity/mortality events are considered:

- death (all-cause mortality)
- hospitalization for worsening of PAH based on predefined criteria
- worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy
- initiation of parenteral (subcutaneous or intravenous) prostanoid therapy or chronic oxygen therapy due to worsening of PAH.

Date of the first CEC-confirmed morbidity/mortality event (excluding "disease progression") up to Study Closure is defined as the onset date provided by the CEC.

Time to first CEC-confirmed morbidity/mortality event (excluding "disease progression") up to Study Closure is defined as the date of the first CEC-confirmed morbidity/mortality event (excluding "disease progression") minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed morbidity/mortality event (other than “disease progression”), time to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure is defined as

- for patients who did not consent for the AC-065A302 Post-Treatment Observation Period: minimum(EOS visit date, date of last contact, analysis cut-off date) minus date of randomization plus 1
- for patients who consented for the AC-065A302 Post-Treatment Observation Period: minimum(maximum[PTOCV date, EOS visit date], date of last contact, analysis cut-off date) minus date of randomization plus 1 for all other patients.

These constitute right-censored observations. CEC-confirmed morbidity/mortality events (other than “disease progression”) with onset date (as per CEC) up to 16 August 2011 are considered as right-censored at date of event onset in the main analysis.

11.2 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period

The same four CEC-confirmed morbidity/mortality events as mentioned in Section [11.1](#) are considered.

Date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as the onset date provided by the CEC.

Time to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as the date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression”) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed morbidity/mortality event (other than “disease progression”), time to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as

- for randomized patients with at least one intake of study drug and not consented for the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, EOS visit date, date of last contact, analysis cut-off date) minus date of randomization plus 1
- for randomized patients with at least one intake of study drug and consented for the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, date of last contact, analysis cut-off date) minus date of randomization plus 1

- for all randomized patients without any intake of study drug: minimum(maximum[EOS visit date, randomization date], date of last contact, analysis cut-off date) minus date of randomization plus 1.

These constitute right-censored observations. CEC-confirmed morbidity/mortality events (other than “disease progression”) with onset date (as per CEC) up to 16 August 2011 are considered as right-censored at date of event onset in the main analysis.

11.3 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure

The following three CEC-confirmed morbidity/mortality events are considered:

- death (all-cause mortality)
- hospitalization for worsening of PAH based on predefined criteria
- worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy.

Date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure is defined as the onset date provided by the CEC.

Time to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure is defined as the date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed morbidity/mortality event (other than “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH), time to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure is defined as

- for patients who did not consent for the AC-065A302 Post-Treatment Observation Period: minimum(EOS visit date, date of last contact, analysis cut-off date) minus date of randomization plus 1
- for patients who consented for the AC-065A302 Post-Treatment Observation Period: minimum(maximum[PTOCV date, EOS visit date], date of last contact, analysis cut-off date) minus date of randomization plus 1.

These constitute right-censored observations. CEC-confirmed morbidity/mortality events (other than “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) with onset date (as per CEC) up to 16 August 2011 are considered as right-censored at date of event onset in the main analysis.

11.4 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period

The same three CEC-confirmed morbidity/mortality events as mentioned in Section 11.3 are considered.

Date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as the onset date provided by the CEC.

Time to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as the date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed morbidity/mortality event (other than “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH), time to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as

- for randomized patients with at least one intake of study drug and not consented for the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, EOS visit date, date of last contact, analysis cut-off date) minus date of randomization plus 1
- for randomized patients with at least one intake of study drug and consented for the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, date of last contact, analysis cut-off date) minus date of randomization plus 1
- for all randomized patients without any intake of study drug: minimum(maximum[EOS visit date, randomization date], date of last contact, analysis cut-off date) minus date of randomization plus 1.

These constitute right-censored observations. CEC-confirmed morbidity/mortality events (other than “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) with onset date (as per CEC) up to 16 August 2011 are considered as right-censored at date of event onset in the main analysis.

11.5 Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period

The following two CEC-confirmed morbidity/mortality events are considered:

- hospitalization for worsening of PAH based on predefined criteria
- death due to PAH.

Date of the first CEC-confirmed hospitalization due to PAH worsening or death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as the onset date provided by the CEC.

Time to first CEC-confirmed hospitalization due to PAH worsening or death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is defined as the date of the first CEC-confirmed hospitalization due to PAH worsening or death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed hospitalization due to PAH worsening or death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period), time to first CEC-confirmed hospitalization due to PAH worsening or death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is defined as

- for patients with at least one administration of study drug and who deceased (but not due to PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period: date of death
- for patients with at least one administration of study drug and who did not consent for the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, EOS visit date, date of last contact, analysis cut-off date) minus date of randomization plus 1
- for patients with at least one administration of study drug and who consented for the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, date of last contact, analysis cut-off date) minus date of randomization plus 1
- for randomized patients without any administration of study drug: minimum(maximum[EOS visit date, randomization date], date of last contact, analysis cut-off date) minus date of randomization plus 1.

These constitute (potentially informative) right-censored observations. CEC-confirmed hospitalizations due to PAH worsening and deaths due to PAH with dates (as per CEC) up to 16 August 2011 are considered as censored at event onset date in the main analysis.

11.6 Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period

Date of CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as the date of death provided by the CEC.

Time to first CEC-confirmed death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is defined as the date of death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period), time to death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is defined as

- for patients with at least one administration of study drug and who deceased (not due to PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period: date of death
- for patients with at least one administration of study drug and who did not consent for the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, EOS visit date, date of last contact, analysis cut-off date) minus date of randomization plus 1
- for patients with at least one administration of study drug and who consented for the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, date of last contact, analysis cut-off date) minus date of randomization plus 1
- for randomized patients without any administration of study drug: minimum(maximum[EOS visit date, randomization date], date of last contact, analysis cut-off date) minus date of randomization plus 1.

These constitute (potentially informative) right-censored observations. CEC-confirmed deaths due to PAH (as per CEC) up to 16 August 2011 are considered as censored at date of death in the main analysis.

11.7 Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study Closure

The following two CEC-confirmed morbidity/mortality events are considered:

- hospitalization for worsening of PAH based on predefined criteria
- death due to PAH.

Date of the first CEC-confirmed hospitalization due to PAH worsening or death due to PAH up to Study Closure is defined as the onset date provided by the CEC.

Time to first CEC-confirmed hospitalization due to PAH worsening or death due to PAH (up to Study Closure) is defined as the date of the first CEC-confirmed hospitalization due to PAH worsening or death due to PAH (up to Study Closure) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed hospitalization due to PAH worsening or death due to PAH, time to first CEC-confirmed hospitalization due to PAH worsening or death due to PAH up to Study Closure is defined as

- date of death for patients deceased (not due to PAH) up to Study Closure and for all other patients defined as
- minimum(EOS visit date, date of last contact, analysis cut-off date) minus date of randomization plus 1 for patients who did not consent for the AC-065A302 Post-Treatment Observation Period
- minimum(maximum[PTOCV date, EOS visit date], date of last contact, analysis cut-off date) minus date of randomization plus 1 for all other patients.

These constitute right-censored observations. CEC-confirmed hospitalizations due to PAH worsening and deaths due to PAH with dates (as per CEC) up to 16 August 2011 are considered as censored at event onset date in the main analysis.

11.8 Time from randomization to first CEC-confirmed morbidity/mortality event up to Study Closure

The components of this endpoint are the same as for the primary efficacy endpoint described in Section 9.

Date of the first CEC-confirmed morbidity/mortality event up to Study Closure is defined as the onset date provided by the CEC.

Time to first CEC-confirmed morbidity/mortality event up to Study Closure is defined as the date of the first CEC-confirmed morbidity/mortality event minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed morbidity/mortality event, time to first CEC-confirmed morbidity/mortality event up to Study Closure is defined as

- minimum(EOS visit date, date of last contact, analysis cut-off date) minus date of randomization plus 1 for patients who did not consent for the AC-065A302 Post-Treatment Observation Period

- $\text{minimum}(\text{maximum}[\text{PTOCV date, EOS visit date}], \text{date of last contact, analysis cut-off date}) - \text{date of randomization} + 1$ for all other patients.

These constitute right-censored observations. CEC-confirmed morbidity/mortality events with onset date (as per CEC) up to 16 August 2011 are considered as right-censored at date of event onset in the main analysis.

11.9 Time from randomization to CEC-confirmed death due to PAH up to Study Closure

Date of CEC-confirmed death due to PAH up to Study Closure is defined as the date of death due to PAH provided by the CEC.

Time to CEC-confirmed death due to PAH up to Study Closure is defined as the date of death due to PAH (up to Study Closure) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed death due to PAH, time to CEC-confirmed death due to PAH up to Study Closure is defined as

- date of death for patients deceased (not due to PAH) up to Study Closure and for all other patients defined as
- $\text{minimum}(\text{EOS visit date, date of last contact, analysis cut-off date}) - \text{date of randomization} + 1$ for patients who did not consent for the AC-065A302 Post-Treatment Observation Period
- $\text{minimum}(\text{maximum}[\text{PTOCV date, EOS visit date}], \text{date of last contact, analysis cut-off date}) - \text{date of randomization} + 1$ for all other patients.

These constitute right-censored observations. CEC-confirmed deaths due to PAH with dates (as per CEC) up to 16 August 2011 are considered as censored at death date in the main analysis.

11.10 CEC-confirmed (potentially recurrent) hospitalizations due to worsening of PAH up to Study Closure

Data on CEC-confirmed recurrent hospitalizations due to worsening of PAH up to Study Closure is arranged in the counting process structure [[Therneau 2000](#)]: one record (row) for each time interval a patient is at risk for a hospitalization due to worsening of PAH. The first record starts with the date of randomization. Time intervals ending with hospitalization due to worsening of PAH are indicated by the event/censoring variable taking the value 1; intervals ending without hospitalization due to worsening of PAH are indicated by the event/censoring variable taking the value 0.

Patients are off-risk for hospitalization due to worsening of PAH during the time when they are already hospitalized due to worsening of PAH.

Example: Patient 1 was never hospitalized and observation ended at Day 475; Patient 2 was hospitalized at Day 60 due to worsening of PAH and discharged at Day 75, hospitalized at Day 180 due to worsening of PAH and discharged at Day 190, and observation ended without further hospitalizations at Day 560. This would result in following counting process data representation:

	Event-risk period		Event (1)/ Censoring (0)
	Start day	Stop day	
Patient 1	1	475	0
Patient 2	1	60	1
	75	180	1
	190	560	0

11.11 Time course of CEC-confirmed (potentially recurrent) hospitalization due to worsening of PAH, initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH, and death up to Study Closure

Multistate processes $(X_t)_{t \geq 0}$ are considered where X_t denotes the state a patient is at time t . Four states are defined as follows:

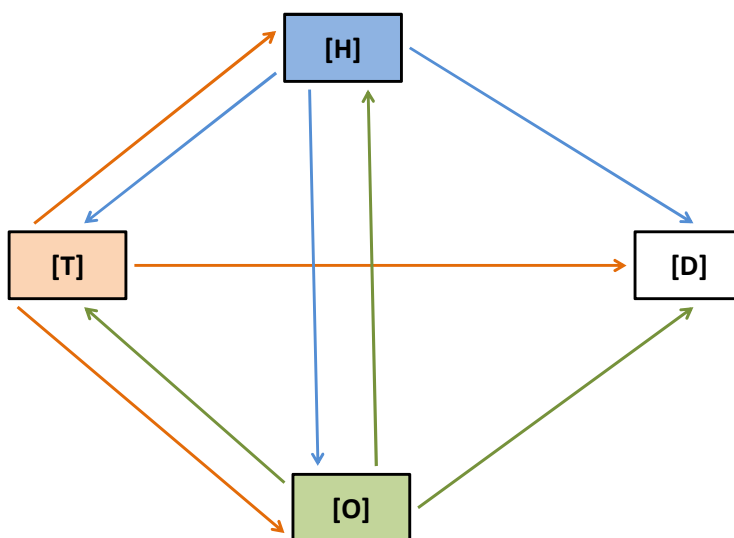
- [T] parenteral (subcutaneous or intravenous) prostanoid treatment or chronic oxygen therapy
- [H] hospitalization for worsening of PAH based on predefined criteria
- [D] death (all-cause mortality)
- [O] other (none of [T], [H], [D])

In case of parenteral prostanoid treatment or chronic oxygen therapy during hospitalization, the state [H] is used.

[D] is an absorbing state (a state out of which transitions are not possible) whereas all other 3 states are transient states (states out of which transitions are modeled).

According to the study protocol patients are expected to be in state [O] at time of randomization ($t=0$). States and possible transitions between states are illustrated by [Figure 3](#) below followed by some examples of the stochastic process over time for individual patients.

Figure 3 Multi-state model with possible transitions



	Occupied state from start day	to stop day	Transition to state at day	Event (1)/ Censoring (0)
Patient 1	[O] other		[D] death	1
	1	300	301	
	[D] death		not applicable	not applicable
	301	Study closure		
Patient 2	[O] other		[H] hospitalization	1
	1	60	61	
	[H] hospitalization		[O] other	1
	61	70	71	
	[O] other		[H] hospitalization	1
	71	110	111	
	[H] hospitalization		[T] therapy	1
	111	116	117	
	[T] therapy		not applicable	0
	117	294		
Patient 3	[O] other		not applicable	0
	1	460		

11.12 Exploratory endpoints related to 6MWD

Absolute changes in 6MWD at trough from Baseline to all scheduled visits other than Week 26

The definition is analogous to the absolute change from Baseline to Week 26 described in Section [10.1](#).

Absolute change in 6MWD at trough from Baseline to EOS

The definition is analogous to the absolute change from Baseline to Week 26 described in Section [10.1](#).

11.13 Exploratory endpoints related to modified NYHA/WHO functional class

Absence of worsening from Baseline at scheduled visits other than Week 26

The definition is analogous to the absence of worsening from Baseline at Week 26 described in Section [10.2](#).

Absence of worsening from Baseline to EOS

For patients alive at EOS, the definition is analogous to the absence of worsening from Baseline at Week 26 described in Section [10.2](#).

11.14 Exploratory endpoints related to Borg dyspnea index

Borg dyspnea index at scheduled visits other than Week 26

The Borg dyspnea index at scheduled visits other than Week 26 is directly taken from the CRF.

Borg dyspnea index at EOS

For patients alive at EOS, the Borg dyspnea index at EOS is directly taken from the CRF.

11.15 Exploratory endpoints related to plasma NT pro-brain natriuretic peptide

Absolute change in plasma NT pro-BNP from Baseline at scheduled visits

The absolute change from Baseline in plasma NT pro-BNP is defined as the differences between the values at scheduled visits and the Baseline value.

Absolute change in plasma NT pro-BNP from Baseline to EOS

For patients alive at EOS, the absolute change from Baseline to EOS in plasma NT pro-BNP is defined as the difference between the value at EOS and the Baseline value.

11.16 Exploratory endpoints related to CAMPHOR

Absolute changes in CAMPHOR sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' from Baseline at scheduled visits other than Week 26

The definition is analog to the absolute change from Baseline to Week 26 described in Section [10.5.1](#).

Absolute changes in CAMPHOR ‘Symptoms’ score from Baseline at scheduled visits other than Week 26

The definition is analog to the absolute change from Baseline to Week 26 described in Section [10.5.2](#).

Absolute change in CAMPHOR sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ from Baseline to EOS

For patients alive at EOS, the definition is analog to the absolute change from Baseline to Week 26 described in Section [10.5.1](#).

Absolute change in CAMPHOR ‘Symptoms’ score from Baseline to EOS

For patients alive at EOS, the definition is analog to the absolute change from Baseline to Week 26 described in Section [10.5.2](#).

12 PHARMACO-ECONOMIC ENDPOINTS DEFINITIONS

All-cause hospitalizations are taken from AE CRF in which hospital admission dates are documented.

PAH-related hospitalizations are defined as hospitalizations associated with AEs coded by the following MedDRA Preferred Terms: “acute right ventricular failure”, “right ventricular failure”, “cardiac failure”, “pulmonary arterial hypertension”, “pulmonary hypertension”, “cardiac failure chronic”, “cor pulmonale acute”, “cardiac failure congestive”, “right ventricular dysfunction”, “syncope”, “loss of consciousness”, “dyspnoea”, “dyspnoea at rest”, “hypoxia”, “pulmonary oedema”, “oedema peripheral”, “atrial fibrillation”, “atrial flutter”, “cardio-respiratory arrest”, “cardiopulmonary failure”.

12.1 Annualized number of all-cause and PAH-related hospitalizations up to the EOS visit

The number of hospitalizations initiated after randomization up to the EOS visit is annualized by multiplying with 365.25 days divided by (EOS visit date minus randomization date + 1). In case there is no EOS visit available for a patient, the date of last contact is used.

Occurrence of recurrent hospitalizations (all-cause and PAH-related) up to the EOS visit is analyzed as well.

12.2 Annualized number of days spent in hospital up to the EOS visit

For each hospitalization, the number of days in hospital is calculated as discharge date minus admission date plus 1. For each patient, the number of days spent in hospital is the sum of the number of days in hospital for all his/her hospitalizations up to the EOS visit. In case there is no EOS visit available for a patient, the date of last contact is used.

The number of days spent in hospital for all causes is annualized by multiplying with 365.25 days divided by (EOS visit date minus randomization date + 1).

12.3 Annualized number of days spent in hospital for PAH-related causes up to the EOS visit

For each hospitalization for PAH-related causes, the number of days in hospital is calculated as discharge date minus admission date plus 1. For each patient, the number of days spent in hospital for PAH-related causes is the sum of the number of days in hospital for all his/her hospitalizations for PAH-related causes up to the EOS visit. In case there is no EOS visit available for a patient, the date of last contact is used.

The number of days spent in hospital for PAH-related causes is annualized by multiplying with 365.25 days divided by (EOS visit date minus randomization date + 1).

13 PHARMACODYNAMIC AND PHARMACOKINETIC ENDPOINTS DEFINITIONS

Trough plasma concentrations of ACT-293987 (selexipag) and ACT-333679 are measured at Baseline, Week 4, Week 8, Week 16, Week 26 (Month 6), Week 52 (Month 12), and EOS.

The PK endpoints are trough plasma concentrations of ACT-293987 (selexipag) and ACT-333679 after start of study drug. For this purpose, “trough” is defined as the plasma sample taken before the morning dose, with the last study drug administration one day prior to the PK sampling. If the date of last study drug administration prior to PK sampling is more than one calendar day before or on the same calendar day as the actual PK sampling the measurement is excluded from the statistical analysis.

The population PK analysis of all plasma concentrations (trough concentrations and concentrations of post-dose samples at Visit 4) and the population PK/PD analysis are described in a separate document.

14 SAFETY AND TOLERABILITY ENDPOINTS DEFINITIONS

Both interim and final analyses are based on the most recent MedDRA version, and System Organ Class (SOC) / Preferred Term (PT) / Standard MedDRA Query (SMQ) definitions are taken from there.

14.1 Definition of treatment-emergent events

For safety events (e.g., AEs, lab abnormalities, ECG abnormalities, etc.) the term “treatment-emergent” is defined as follows:

- for patients who did not discontinue study drug in the AC-065A302 Treatment Period prior to the analysis cut-off date (for interim or final analysis, respectively): all safety events that are new or worsening compared to Baseline with
 - event (onset) date after first dose of study drug in AC-065A302 AND
 - event (onset) date not later than analysis cut-off date
- for patients who discontinued study drug in the AC-065A302 Treatment Period prior to the analysis cut-off date (for interim or final analysis, respectively) AND did not enter study AC-065A303: all safety events that are new or worsening compared to Baseline with
 - event (onset) date after first dose of study drug in AC-065A302 AND
 - event (onset) date not later than minimum[date of last study drug intake in AC-065A302 + 7 days, analysis cut-off date]
- for patients who entered study AC-065A303 prior to the analysis cut-off date (for interim or final analysis, respectively): all safety events that are new or worsening compared to Baseline with
 - event (onset) after first dose of study drug in AC-065A302 AND
 - event (onset) not later than minimum[date of last study drug intake in AC-065A303 + 3 days, analysis cut-off date].

14.2 Adverse events

14.2.1 Treatment-emergent adverse events

Treatment-emergent AEs are events documented on the AE CRF page that fulfill the definition in Section [14.1](#).

14.2.2 AEs leading to premature discontinuation of study drug

AEs leading to the permanent discontinuation of study drug are those for which the AE CRF tick box ‘Permanently discontinued’ of ‘Action taken with study drug’ has been marked.

14.2.3 Treatment-emergent SAEs

A treatment-emergent SAE is any treatment-emergent AE for which the AE CRF tick box ‘Yes’ of the ‘Serious’ question has been marked.

14.2.4 Treatment-emergent AEs of special interest

14.2.4.1 Eye disorders

Treatment-emergent AEs of special interest “Eye disorders” are defined as treatment-emergent AEs with PTs belonging to the SOC “Eye disorder”.

They are presented for the entire safety set and for the following subgroups defined by use of potentially confounding concomitant medications or medical history events:

- high level class “ANTITHROMBOTIC AGENTS” (B01) or “ACETYLSALICYCLIC ACID”
- “ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS” (M01)
- PDE5-Inhibitors [PDE5-I] identified by the following preferred terms (“Sildenafil” OR “Tadalafil” OR “Vardenafil”)
- medical history events with PTs belonging to SOC “Eye disorder”
- none of these potential confounding concomitant medications or medical histories.

Within the first two subgroups, patients are further assigned to one of two groups:

- patients with last “Eye disorder” AE onset before administration of any of the above described medication start
- patients with at least one “Eye disorder” AE started after administration of any of the above described medications.

A specific ophthalmology sub-study has been set up; its endpoint and analysis is described in Sections [14.6](#) and [28.8](#).

14.2.4.2 Retinal disorders

Treatment-emergent AEs of special interest “Retinal disorders” are defined as treatment-emergent AEs with PTs belonging to the SMQ “Retinal disorders” (including both narrow and broad PTs).

They are presented for the entire safety set and for the following subgroups defined by use of potentially confounding concomitant medications or medical history events:

- high level class “ANTITHROMBOTIC AGENTS” (B01) or “ACETYLSALICYCLIC ACID”
- “ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS” (M01)
- PDE5-Inhibitors [PDE5-I] identified by the following preferred terms (“Sildenafil” OR “Tadalafil” OR “Vardenafil”)
- medical history events with PTs belonging to SMQ Retinal disorders (including both narrow and broad PTs)
- none of these potential confounding concomitant medications or medical histories.

Within the first two subgroups, patients are further assigned to one of two groups:

- patients with last “Retinal disorder” AE onset before administration of any of the above described medication start
- patients with at least one “Retinal disorder” AE started after administration of any of the above described medications.

A specific ophthalmology sub-study has been set up; its endpoint and analysis is described in Sections 14.6 and 28.8.

14.2.4.3 Hemorrhage

Treatment-emergent AEs of special interest “Hemorrhage” are defined as treatment-emergent AEs with PTs listed in the SMQ Haemorrhage (excluding laboratory terms).

They are presented for the entire safety set and for the following subgroups defined by use of potentially confounding concomitant medications or medical history events:

- high level class “ANTITHROMBOTIC AGENTS” (B01) or “ACETYLSALICYCLIC ACID”
- high level class “ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS” (M01)
- medical history events with PTs belonging to the SMQ Haemorrhage (excluding laboratory terms)
- PAH associated with connective tissue disease.

Within the subgroup of patients with at least one of the potentially confounding concomitant medications, patients are further assigned to one of two groups:

- patients with last “Hemorrhage” AE onset before administration of any of the above described concomitant medication start
- patients with at least one “Hemorrhage” AE started after administration of any of the above described concomitant medications.

14.2.4.4 Gastrointestinal hemorrhage

Treatment-emergent AEs of special interest “Gastrointestinal hemorrhage” are defined as treatment-emergent AEs with PTs listed in the SMQ Gastrointestinal haemorrhage.

They are presented for the entire safety set and for the following subgroups defined by use of potentially confounding concomitant medications or medical history events:

- high level class “ANTITHROMBOTIC AGENTS” (B01) or “ACETYLSALICYCLIC ACID”
- high level class “ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS” (M01)
- high level class “CORTICOSTEROIDS FOR SYSTEMIC USE” (H02)
- medical history events with PTs belonging to the SMQ Gastrointestinal haemorrhage
- PAH associated with connective tissue disease.

Within the subgroup of patients with at least one of the potentially confounding concomitant medications, patients are further assigned to one of two groups:

- patients with last “Gastrointestinal hemorrhage” AE onset before administration of any of the above described concomitant medication start
- patients with at least one “Gastrointestinal hemorrhage” AE started after administration of any of the above described concomitant medications.

14.2.4.5 Thrombocytopenia

Treatment-emergent AEs of special interest “Thrombocytopenia” are defined as treatment-emergent AEs with PTs listed in at least one of the following SMQs:

- SMQ Haematopoietic thrombocytopenia (including both narrow and broad PTs)
- SMQ Haematopoietic cytopenias affecting more than one type of blood cell (narrow PTs only)

or with PT containing the string “Thrombocytop”.

They are presented for the entire safety analysis set and for the following subgroups of patients with/without medical history belonging to any of the above mentioned SMQs or PTs.

14.2.4.6 Hypotension

Treatment-emergent AEs of special interest “Hypotension” are defined as treatment-emergent AEs with PTs listed below:

- Blood pressure ambulatory decreased
- Blood pressure decreased
- Blood pressure diastolic decreased
- Blood pressure orthostatic decreased
- Blood pressure systolic decreased
- Diastolic hypotension
- Hypotension
- Mean arterial pressure decreased
- Orthostatic hypotension
- Procedural hypotension

14.2.4.7 Bone disorders

Treatment-emergent AEs of special interest “Bone disorders” are defined as treatment-emergent AEs with PTs listed in the following SMQs:

- SMQ Osteoporosis/osteopenia (including both narrow and broad PTs)
- SMQ Osteonecrosis (including both narrow and broad PTs)

or with PTs containing the string “fracture”.

They are presented for the entire safety analysis set and for the following subgroups:

- patients with/without medical history of any of the above mentioned SMQs or PTs
- patients with age at randomization < 65 years versus patients with age at randomization $\geq$ 65 years.

14.2.4.8 Gastrointestinal disorders

Treatment-emergent AEs of special interest “GI disorder” are defined as treatment-emergent AEs with PTs listed in the SOC Gastrointestinal disorders.

14.2.4.9 Thyroid disorders

Treatment-emergent AEs of special interest “Thyroid disorders” are defined as treatment-emergent AEs with PTs listed in at least one of the following SMQs:

- SMQ Hyperthyroidism (including both narrow and broad PTs)
- SMQ Hypothyroidism (including both narrow and broad PTs).

They are presented for the entire safety analysis set and for the subgroups of patients with/without medical history of belonging to the above mentioned SMQs.

14.2.4.10 Liver disorders

Treatment-emergent AEs of special interest “Liver disorders” are defined as treatment-emergent AEs with

- SOC, High Level Group Term, High Level Term or PT containing strings “hepat” or “liver ” (including a trailing space)
- PT containing strings “yellow skin”, “icter”, “jaundice”, “cirrhosis”, “hyperbilirubin”, “cholesta” or “blood alkaline phosphatase”.

They are presented for the entire safety analysis set and for patients with/without concomitant ERA (PTs “Ambrisentan”, “Bosentan” or “Sitaxentan”). Within the former subgroup, patients are further assigned to one of two groups:

- patients with last “Liver disorders” AE onset before start of any of the above mentioned concomitant medications
- patients with at least one “Liver disorders” AE started after start of any of the above mentioned concomitant medications.

14.3 Electrocardiogram

ECG results are reported by a central reader (Cardibase).

14.3.1 Treatment-emergent qualitative ECG abnormalities

Findings / original terms (tick boxes and free text) reported by CRO Cardibase are coded using the Actelion ECG dictionary and the latest study specific Coding Assignment version.

14.3.2 Absolute changes from Baseline in ECGs data

The change from Baseline in ECGs data is defined as the change from the last value assessed prior to the first study drug intake in AC-065A302 to patient's lowest / highest (as applicable) treatment-emergent value in study AC-065A302 (and for each visit in study AC-065A302) for heart rate and the intervals RR, PR, QRS, QT and QTcF.

14.3.3 QTcF categories

For QTcF, the following categories (according to [\[ICH 2005\]](#)) are used:

- QTcF > 450 ms
- QTcF > 480 ms
- QTcF > 500 ms
- QTcF increase from Baseline > 30 ms
- QTcF increase from Baseline > 60 ms

In addition, the following categories are used:

- QTcF > 450 ms and QTcF increase from Baseline > 30 ms
- QTcF > 450 ms and QTcF increase from Baseline > 60 ms

A patient is included in these categories based on its highest value assessed while on study drug (up to 7 days after last study drug intake).

14.4 Laboratory test results

Laboratory tests results are obtained by a central laboratory (Quest) and provided to Actelion in Standard International (SI) units together with Quest's laboratory test normal ranges. Only these data provided by Quest (and no transformations) are used for the statistical analysis and reporting.

14.4.1 Absolute change from Baseline in hematology test results

Hematology tests are hemoglobin, hematocrit, platelet count, leukocyte count and erythrocyte count from the central laboratory. The absolute change from Baseline is evaluated for patient's lowest/highest treatment-emergent value and for each scheduled assessment.

These endpoints are presented for the entire safety analysis set and for the subgroups of patients with/without concomitant ERA (preferred terms "Ambrisentan", "Bosentan" or "Sitaxentan") medication during the Treatment Period. For patients with concomitant ERA medications, the change in hematology test results after initiation of ERA is presented.

14.4.2 Absolute change from Baseline in chemistry test results

Chemistry tests are alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, direct bilirubin, serum creatinine, estimated creatinine clearance, urea, glucose, sodium, potassium and albumin. The absolute change from

Baseline is evaluated for patient's lowest/highest treatment-emergent value and for each scheduled assessment.

The endpoints related to ALT, AST, alkaline phosphatase, total bilirubin and direct bilirubin are to be presented for the entire safety analysis set and for the subgroups of patients with/without concomitant ERA (preferred terms "Ambrisentan", "Bosentan" or "Sitaxentan") medication during the Treatment Period. For patients with concomitant ERA medications, the change in the respective test results after initiation of ERA is presented.

14.4.3 Absolute change from Baseline in thyroid markers

Thyroid markers are triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH) for patients randomized under study protocol Amendment 3 or higher. The absolute change from Baseline is evaluated for patient's lowest/highest treatment-emergent value and for each scheduled assessment.

14.4.4 Absolute change from Baseline in bone turnover markers

Bone turnover markers include bone alkaline phosphatase and carboxy-terminal telopeptide. The absolute change from Baseline is evaluated for patient's lowest/highest treatment-emergent value and for each scheduled assessment.

14.4.5 Treatment-emergent laboratory abnormalities

A laboratory test abnormality is defined as any value outside the normal range as provided by the central laboratory Quest. The direction of the abnormality (below or above the normal range) is indicated using 'H' and 'L', if applicable.

A marked (alert) laboratory test abnormality is defined as any value that fulfills the applicable condition listed in [Table 7](#) below for LL / HH (or LLL / HHH, respectively).

Table 7 Definition of marked laboratory abnormalities

Parameter	LL Marked	LLL Alert	HH Marked	HHH Alert
Hemoglobin (g/L)	< 100	< 80	increase > 20 g/L above ULN or above BL if BL is >ULN	increase > 40 g/L above ULN or above BL if BL is above ULN
Hematocrit (l)	< 0.28 for females; < 0.32 for males	< 0.20	> 0.55 for females; > 0.6 for males	> 0.65
Platelet count (GI/L)	< 75	< 50	> 600	> 999
WBC count (GI/L)	< 3.0	< 2.0	> 20.0	> 100.0
AST (U/L)	NA	NA	> 3 ULN	> 5 ULN
ALT (U/L)	NA	NA	> 3 ULN	> 5 ULN
Total bilirubin (μmol/L)	NA	NA	> 2 ULN	> 5 ULN
Alkaline Phosphatase (U/L)	NA	NA	> 2.5 ULN	> 5 ULN
Creatinine (μmol/L)	NA	NA	> 1.5 ULN or 1.5 BL	> 3 ULN or 3 BL
Urea (mmol/L)	NA	NA	> 2.5 ULN	> 5 ULN
Albumin (g/L)	< 30	< 20	NA	NA
Protein total (g/L)	< 39	NA	> 101	NA
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0
Sodium (mmol/L)	NA	< 130	> 150	> 155

ULN refers to the upper limit of the central laboratory normal range.

Treatment-emergent abnormalities in liver function test results

Abnormalities in liver function tests are defined as (“and” conditions do not require concomitant values):

- $AST \geq 3 \times ULN$ or $ALT \geq 3 \times ULN$
- $AST \geq 8 \times ULN$ or $ALT \geq 8 \times ULN$
- $ALT \geq 3 \times ULN$ and total bilirubin $\geq 2 \times ULN$
- $ALT \geq 3 \times ULN$ and total bilirubin $\geq 2 \times ULN$ and $ALP \leq 2 \times ULN$
- $(AST \geq 3 \times ULN \text{ or } ALT \geq 3 \times ULN)$ and total bilirubin $\geq 2 \times ULN$
- $(AST \geq 3 \times ULN \text{ or } ALT \geq 3 \times ULN)$ and total bilirubin $\geq 2 \times ULN$ and $ALP \leq 2 \times ULN$.

14.5 Vital signs and body weight

14.5.1 Absolute change from Baseline in vital signs

Vital signs include blood pressure (systolic and diastolic) and heart rate. The absolute change from Baseline is evaluated for patient's lowest/highest treatment-emergent value and for each scheduled assessment.

The following summaries for systolic blood pressure (SBP) and diastolic blood pressure (DBP) are provided:

- number and percentage of female patients with SBP < 100 mmHg or DBP < 60mmHg
- number and percentage of male patients with SBP < 110 mmHg or DBP < 70 mmHg
- number and percentage of patients with a decrease of ≥ 20 mmHg in SBP or ≥ 10 mmHg in DBP relative to Baseline.

The same BP analyses will also be done in the subgroup of patients up to 50 years of age at Baseline versus patients of more than 50 years of age at Baseline.

14.5.2 Absolute change from Baseline in body weight

The absolute change from Baseline is evaluated for patient's lowest/highest treatment-emergent value and for each scheduled assessment.

14.6 Ophthalmologic sub-study

The absolute change from Baseline in retinal arterial tortuosity to all visits up to EOS in AC-065A302 is evaluated for patients participating in the ophthalmologic sub-study.

15 STATISTICAL ANALYSIS METHODS

This section describes the statistical analysis methods (models, tests, and point and interval estimation) which are applied to endpoints in the subsequent sections.

In general, data is listed and summarized by appropriate descriptive statistics (tables or figures), typically including:

- for continuous variables: number of non-missing observations, number of missing observations, mean, standard deviation (SD), standard error, minimum, Q1, median, Q3 and maximum
- time-to-event variables: number of events, number of censored observations and Kaplan-Meier estimates of the survival function
- categorical variables: number of non-missing observations, number of missing observations and frequency with percentage per category (percentages based on the number of non-missing observations).

15.1 Statistical analysis methods for event history endpoints

15.1.1 Kaplan-Meier estimation and display of survival distributions

A graphical estimate of the survival function for both treatment groups are obtained by the Kaplan-Meier (KM) product-limit method as implemented in SAS PROC LIFETEST.

The graphical presentation follows the recommendations from [[Pocock 2002](#)], in particular defining rules for KM curves going upwards or downwards, termination of the vertical and horizontal axes.

KM estimates with two-sided 95% confidence intervals (CI) at specific time points (Weeks 26, 52, 78) are provided and may be added to the plot. The CIs are constructed using Greenwood's formula [[Collett 1994](#)] for the standard error of the Kaplan-Meier estimate. If available, median time to event (as well as 25th and 75th percentiles) for each treatment group are provided along with two-sided CIs calculated using the method of [[Brookmeyer 1982](#)].

Standard statistics to be displayed with Kaplan-Meier graphs are given below.

Per treatment group:

- number of events and number of censored observations (reasons for censoring are provided in a separate listing)
- number of patients at risk for specific time points (Weeks 0, 26, 52, 78, 104, etc.)

For comparison of treatment groups:

- one-sided *p*-value of the (stratified, if relevant) log-rank test and list of stratification variables (if used)
- hazard ratio (HR) point estimate with two-sided CI based on Wald's method and list of list of stratification variables / covariates (if used).

See Sections 15.1.2 to 15.1.3 for details on these characteristics.

15.1.2 Log-rank tests

15.1.2.1 Unstratified log-rank test

Let $S_{\text{sel}}(t)$ and $S_{\text{pla}}(t)$ denote the survival functions for selexipag and placebo, respectively.

The null hypothesis

$H_0: S_{\text{sel}}(t) = S_{\text{pla}}(t)$ for all $t \geq 0$ “identical survival functions for both treatments”

is tested against the one-sided alternative hypothesis

$H_A: S_{\text{sel}}(t) \geq S_{\text{pla}}(t)$ for all $t \geq 0$ and $S_{\text{sel}}(t) > S_{\text{pla}}(t)$ for at least some $t > 0$
“survival function in the selexipag group superior to the survival function in the placebo group”

The unstratified log-rank test is conducted by SAS PROC LIFETEST where the STRATA statement includes only the treatment group variable (*treat*). The TIME statement includes a variable with times to event (*survtime*) and an indicator variable for right censoring (*censor*) with 0 representing censoring (additional options controlling the output may be added):

```
PROC LIFETEST DATA=dataset METHOD=KM;  
    TIME survtime*censor(0);  
    STRATA treat;  
RUN;
```

As an output of the procedure, the rank statistic S and variance $Var(S)$ are obtained. Under the null hypothesis, the test statistic $Z = S/\sqrt{Var(S)}$ is approximately normally distributed. The one-sided p -value is therefore obtained from normally distributed Z statistic and H_0 is rejected if the p -value does not exceed the (nominal) significance level assigned to the test.

15.1.2.2 Stratified log-rank test

Let $S_{\text{sel},k}(t)$ and $S_{\text{pla},k}(t)$ denote the survival functions for selexipag and placebo in stratum k , $k=1,\dots,K$, $K = m_1 \times m_2 \times \dots \times m_j$ where m_i denotes the number of categories for stratification factor i , $1 \leq i \leq j$, respectively. The null hypothesis

$H_0: S_{\text{sel},k}(t) = S_{\text{pla},k}(t)$ for all $t \geq 0$ and all k (“identical survival functions for both groups in each stratum”)

is tested against the one-sided alternative hypothesis

$H_A: S_{\text{sel},k}(t) \geq S_{\text{pla},k}(t)$ for all $t \geq 0$ and all $k=1,\dots,K$ and $S_{\text{sel},m}(t) > S_{\text{pla},m}(t)$ for at least some $t > 0$ and some m (“survival function in the selexipag superior to the survival in the placebo group in at least one stratum”)

Log-rank tests are performed for each of the strata separately, obtaining the rank statistic S_k and variance $Var(S_k)$ where $k=1, 2, \dots, K$. The stratified log-rank test statistic is

constructed as $Z = [S_I + \dots + S_K] / \sqrt{[Var(S_I) + \dots + Var(S_K)]}$. Under the null hypothesis, Z is approximately normally distributed. The one-sided stratified log-rank p -value is therefore obtained from normally distributed Z statistic and H_0 is rejected if p does not exceed the (nominal) significance level assigned to the test.

The stratified log-rank test is conducted with SAS PROC LIFETEST where the STRATA statement includes the j strata variables ($strat\_1, \dots, strat\_j$) and the GROUP option includes the treatment variable ($treat$). The TIME statement includes a variable with times to event ($survtime$) and an indicator variable for right censoring ($censor$) with 0 representing censoring (additional options controlling the output may be added):

```
PROC LIFETEST DATA=dataset METHOD=KM;  
  TIME survtime*censor(0);  
  STRATA strat_1 .. strat_j GROUP=treat;  
RUN;
```

15.1.3 Proportional hazards model

15.1.3.1 Unstratified unadjusted proportional hazards regression model

The unstratified unadjusted proportional hazards regression model and its assumptions are illustrated by:

$$h(t, x_{j1}, \beta_1) = h_0(t) \cdot \exp(x_{j1} \cdot \beta_1)$$

$h(.)$ hazard function as a function of time (relative to the start date), the patient's treatment and the unknown regression parameter

$h_0(t)$ unspecified baseline hazard function at time t

x_{j1} treatment for patient j coded as 0 (placebo) or 1 (selexipag); this coding leads to a hazard ratio < 1 if the estimated effect suggests a lower hazard in the selexipag group relative to the placebo group

β_1 unknown regression parameter for the treatment effect on the log-scale (the log hazard ratio).

The hazard ratio (HR) is a multiplicative constant $\lambda_1 = \exp(\beta_1)$ comparing the hazard function in the selexipag group relative to the hazard function in the placebo group (identical to the baseline hazard function). A $HR < 1$ indicates decreased hazard for the event of interest in the selexipag group compared to the placebo group.

SAS PROC PHREG (with the TIES=EXACT option for the "exact" handling of ties) is used to estimate the hazard ratio based on the partial maximum likelihood function; a Wald-test based two-sided CI is requested by the RISKLIMITS option (additional options controlling the output may be added):

```
PROC PHREG DATA=dataset;  
  MODEL survtime*censor(0)=treat / TIES=EXACT RISKLIMITS ALPHA=;  
RUN;  
  
* survtime represents variable containing event/censoring times;  
* censor represents censoring variable (0=censored, 1=event);  
* treat represents treatment group variable (0=placebo, 1=selexipag);
```

15.1.3.2 Stratified unadjusted proportional hazards regression

The stratified unadjusted proportional hazards regression model and its assumptions are described by:

$$h(t, x_{jk1}, \beta_1) = h_{0k}(t) \cdot \exp(x_{jk1} \cdot \beta_1)$$

$h(.)$ hazard function as a function of time (relative to the start date), the patient's stratum and treatment and the unknown regression parameter

$h_{0k}(t)$ unspecified baseline hazard function for stratum k at time t

x_{jk1} treatment for patient j in stratum k coded as 0 (placebo) or 1 (selexipag); this coding leads to a hazard ratio < 1 if the estimated effect suggests a lower hazard in the selexipag group relative to the placebo group

β_1 unknown regression parameter for the treatment effect on the log-scale (the log hazard ratio).

The hazard ratio is a multiplicative constant $\lambda_1 = \exp(\beta_1)$ comparing the hazard functions in the selexipag group relative to the hazard functions in the placebo group. The latter are allowed varying across strata. However, the hazard ratio is assumed to be common across strata. A HR < 1 indicates decreased hazard for the event of interest in the selexipag group compared to the placebo group.

SAS PROC PHREG (with the TIES=EXACT option for the "exact" handling of ties) is used to estimate the hazard ratio based on the partial maximum likelihood function; a Wald-test based two-sided CI is requested by the RISKLIMITS option (additional options controlling the output may be added):

```
PROC PHREG DATA=dataset;  
  MODEL survtime*censor(0)=treat / TIES=EXACT RISKLIMITS ALPHA=;  
  STRATA strat_1 .. strat_j;  
RUN;  
  
* survtime represents variable containing event/censoring times;  
* censor represents censoring variable (0=censored, 1=event);  
* treat represents treatment group variable (0=placebo, 1=selexipag);  
* strat_1 to strat_j represent stratification variables;
```


15.1.3.3 Stratified adjusted proportional hazards regression

The stratified adjusted proportional hazards regression model and its assumptions are illustrated by:

$$\begin{aligned} h(t, \mathbf{x}_{jk}, \boldsymbol{\beta}) &= h_{0k}(t) \cdot \exp(\mathbf{x}'_{jk} \cdot \boldsymbol{\beta}) \\ &= h_{0k}(t) \cdot \exp(x_{jk1} \cdot \beta_1 + \dots + x_{jkn} \cdot \beta_n) \end{aligned}$$

$h(.)$ hazard function as a function of time (relative to the start date), the patient's stratum and covariates, and the unknown vector of regression parameters

$h_{0k}(t)$ unspecified baseline hazard function for patients with covariate vector (0, ..., 0) for stratum k at time t

$\mathbf{x}_{jk}$ vector of Baseline covariates for patient j in stratum k , with x_{jk1} representing treatment coded as 0 (placebo) or 1 (selexipag)

$\boldsymbol{\beta}$: unknown regression parameter vector on the log-scale (β_1 represents the log hazard ratio for treatment).

The hazard ratio for the i -th covariate is a multiplicative constant $\exp(\beta_i)$ comparing the hazard functions between the levels of the i -th covariate. Baseline hazard functions are allowed varying across strata without any restrictions. However, the hazard ratio comparing a covariate (including treatment) is assumed to be common across strata. The estimates of β_i are adjusted for the other covariates in the model.

SAS PROC PHREG (with the TIES=EXACT option for the "exact" handling of ties) is used to estimate the hazard ratios based on the partial maximum likelihood function; a Wald-test based two-sided CI is requested by the RISKLIMITS option (additional options controlling the output may be added):

```
PROC PHREG DATA=dataset;
  MODEL survtime*censor(0)=treat cov_1 .. cov_k /
  TIES=EXACT RISKLIMITS ALPHA;
  STRATA strat_1 .. strat_j;
RUN;

* survtime represents variable containing event/censoring times;
* censor represents censoring variable (0=censored, 1=event);
* treat represents treatment group variable (0=placebo, 1=selexipag);
* cov_1 to cov_k represent covariates other than treatment group;
* strat_1 to strat_j represent stratification variables;
```

15.1.3.4 Examination of proportional hazards assumption

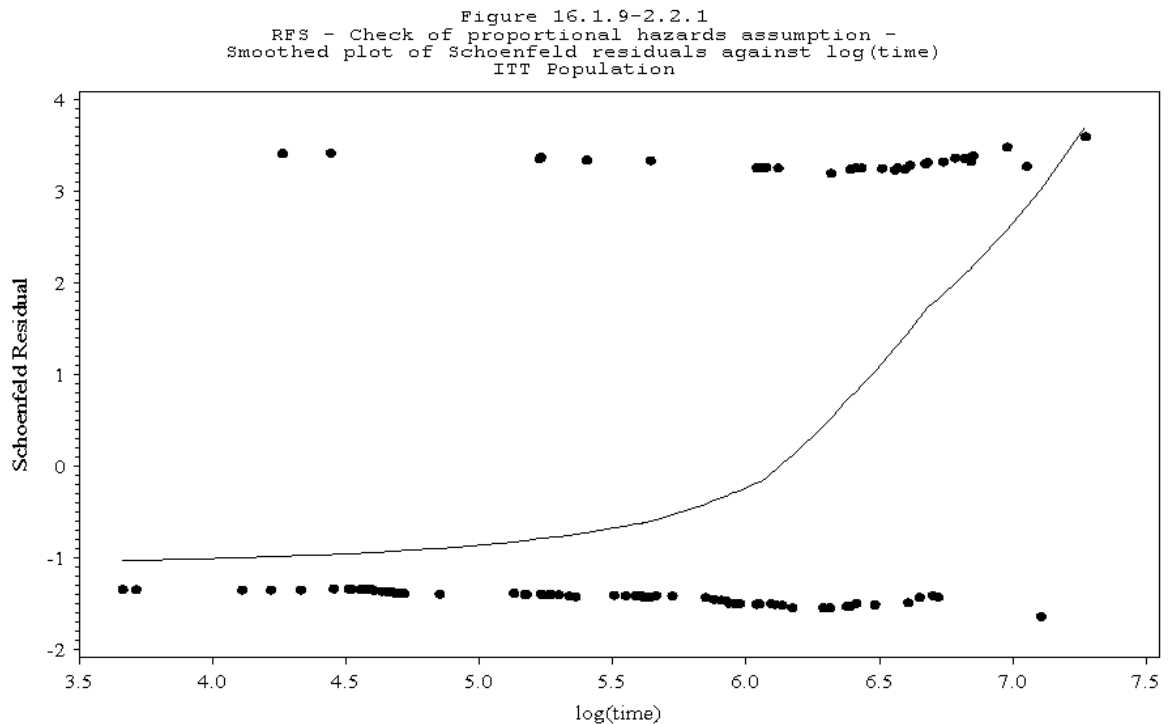
An investigation into the assumption of proportional hazards for treatment is performed informally using graphical means and more formally by a statistical test.

Using an output dataset from SAS PROC LIFETEST a plot of $\log(-\log[S(t)])$ against $\log(t)$ showing values for each treatment group separately is of help to identify the presence of non-proportional hazards. If the hazards are proportional over time the lines formed from joining up the values for each treatment group should be approximately parallel.

A smoothed plot (e.g., incorporating a LOESS curve) of scaled Schoenfeld residuals against time t , $\log(t)$ or some other transformation $g(t)$, can also indicate evidence of non-proportional hazards [Therneau 2000, chapter 6]. Within SAS PROC PHREG, the scaled Schoenfeld weighted residuals are obtained by using the keyword WTRESSCH within the OUTPUT statement. A linear regression line is fitted (e.g., by SAS PROC REG) to the plot along with a test of zero slope. Non-zero slope indicates non-proportional hazards. This formal test corresponds to testing an additional time-dependent variable $g(t)$ to the original model.

Figure 4 below is an example of a Schoenfeld residual plot with spline curve fitted showing definite non-proportional hazards with respect to the effect of treatment (active vs placebo). In this example the treatment effect appears fairly stable up to around one year ($\log(6)$) before decreasing notably afterwards.

Figure 4 Schoenfeld residuals plot



15.1.4 Competing risks analysis

Competing risks analysis is described below for the primary efficacy endpoint but the underlying method can be applied for time-to-event analysis for other composite endpoints as well.

15.1.4.1 Description of the underlying stochastic process

For each patient, a multistate stochastic process $(X_t)_{t \geq 0}$ is considered where X_t denotes the state a patient is at day t , $0 \leq t \leq \text{date of last study drug intake in the AC-065A302 Treatment Period plus 7 days}$. Five states are defined as follows:

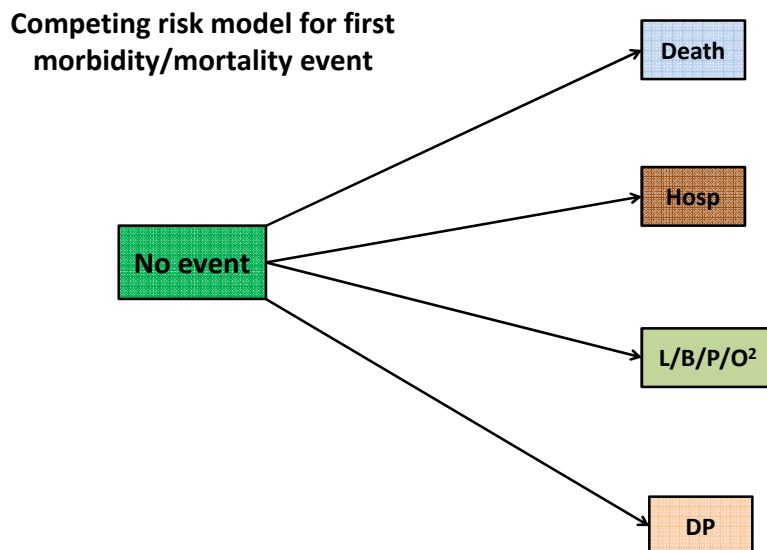
- [Death] death (all-cause mortality)
- [Hosp] hospitalization for worsening of PAH based on predefined criteria
- [L/B/P/O²] worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy, parenteral prostanoid treatment or chronic oxygen therapy
- [DP] disease progression
- [No event] no event

According to the study protocol patients start in state [No event] at time of randomization $t=0$, i.e. $P(X_0 = [\text{No event}]) = 1$. As the process $(X_t)_{t \geq 0}$ is discrete in time (days) it may

happen that that two states are associated with the same date, e.g., disease progression and hospitalization at the same day. In such cases, the state higher in the list above is used.

States and possible transitions between states are illustrated by Figure 5 below.

Figure 5 Multi-state competing risks model for primary efficacy endpoint



A transition probability from state [No event] at day s to state $[m]$ at day $t \geq s$ is defined as:

$$P_{[\text{No event}][m]}(s, t) := P(X_t = [m] | X_s = [\text{No event}])$$

A patient stays in state [No event] as long as none of the competing events have occurred; the competing risks process moves out of the [No event] state at time T , defined as

$$T := \inf\{t > 0 | X_t \neq [\text{No event}]\},$$

called the event time; X_T is the type of event, also called cause of failure.

Observation of the competing risks process are subject to right-censoring (assumed to be independent from the risk process), i.e., observation was stopped (for the primary efficacy endpoint typically 7 days after last study drug intake in the AC-065A302 Treatment Period) while the patient was still in state [No event].

Cause-specific hazard functions for each state $[m]$ are defined as

$$\begin{aligned} h_{[\text{No event}][m]}(t) &= \lim_{\Delta t \rightarrow 0^+} \frac{P(X_{t+\Delta t} = [m] | X_t = [\text{No event}])}{\Delta t} \\ &= \lim_{\Delta t \rightarrow 0^+} \frac{P(T \in [t + \Delta t[, X_T = [m] | T \geq t)}{\Delta t} \end{aligned}$$

and corresponding cumulative cause-specific hazard functions as

$$H_{[\text{No event}][m]}(t) = \int_0^t h_{[\text{No event}][m]}(u) du$$

The cause-specific hazards are assumed to completely determine the stochastic behavior of the competing risks process, and they sum-up to the all-cause hazard function

$$\begin{aligned} h(t) &= \lim_{\Delta t \rightarrow 0^+} \frac{P(X_{t+\Delta t} \neq [\text{No event}] | X_t = [\text{No event}])}{\Delta t} \\ &= \lim_{\Delta t \rightarrow 0^+} \frac{P(T \in [t + \Delta t[| T \geq t)}{\Delta t}, \end{aligned}$$

same as for the all-cause cumulative hazard function $H(t) = \int_0^t h(u) du$.

The cumulative cause-specific incidence function, i.e., the expected proportion of patients experiencing a specific competing event (here: one of the 4 states defined at the beginning of this section) over the course of time is defined as $P(T \leq t, X_T = [m])$. The equation⁵

$$P(T \leq t, X_T = [m]) = \int_0^t P(T > u^-) \cdot h_{[\text{No event}][m]}(u) du$$

demonstrates that cumulative cause-specific incidence functions depend on all cause-specific hazard functions through $P(T > u^-)$.

15.1.4.2 Non-parametric estimation

For both selexipag and placebo, the *cumulative* cause-specific hazard functions $H_{[\text{No event}][m]}(t)$ are estimated by Nelson-Aalen estimators, as this estimation is more straightforward as estimation of the cause-specific hazard functions $h_{[\text{No event}][m]}(t)$. The details of the Nelson-Aalen estimators (and point wise 95% CIs based on their asymptotically normal distributions) in the setting of competing risks are described in sections 4.1 and 4.2 of [Beyersmann 2012]⁶. These estimators are obtained with the R package mvna [Allignol 2008]; the all-cause cumulative hazard function $H(t)$ is estimated by the sum of the cause-specific Nelson-Aalen estimators.

As next step, the cumulative cause-specific incidence functions (and point wise 95% CIs) for selexipag and placebo are derived from the Nelson-Aalen estimators using the

⁵ $P(T > u^-)$ denotes the value of the survival function just prior to u .

⁶ The simple extension to more than 2 competing risks is described in section 7.1 of [Beyersmann 2012].

functional relationship between cumulative hazard and survival functions. This estimator (as given in formula (4.18) of [Beyersmann 2012]) is a special case of the Aalen-Johansen estimator for general time-inhomogeneous Markov multi-state processes [see Section 15.1.6.2] and is obtained with the R package etm [Allignol 2011].

15.1.4.3 Proportional cause-specific hazards models

The (general) stratified adjusted proportional cause-specific hazards regression model and its assumptions are illustrated by:

$$h_{[\text{No event}], [m]}(t, x_{jk}, \beta_{[\text{No event}], [m]}) = h_{[\text{No event}], [m]; 0k}(t) \cdot \exp(x'_{jk} \cdot \beta_{[\text{No event}], [m]})$$

$h_{[\text{No event}], [m]}(\cdot)$ cause-specific hazard functions as a function of time (relative to the randomization date), the patient's stratum and covariates, and the unknown vector of regression parameters

$h_{[\text{No event}], [m]; 0k}(t)$ unspecified cause-specific baseline hazard functions for patients with covariate vector (0, ..., 0) for stratum k at time t

x_{jk} vector of Baseline covariates for patient j in stratum k , with x_{jk1} representing treatment coded as 0 (placebo) or 1 (selexipag)

β : unknown regression parameter vector on the log-scale (β_1 represents the log hazard ratio for treatment).

The hazard ratio for the i -th covariate is a multiplicative constant $\exp(\beta_{[\text{No event}], [m]; i})$ comparing the hazard functions between the levels of the i -th covariate. Cause-specific baseline hazard functions are allowed varying across strata without any restrictions. The cause-specific hazard ratios for a covariate are assumed to be common across strata but are allowed to be different for different causes. The estimates of $\beta_{[\text{No event}], [m]; i}$ are adjusted for the other covariates in the model.

Estimation of the regression parameters is performed by maximizing partial likelihood function as described in section 5.2 of [Beyersmann 2012] and by using the R-package mstate [de Wreede 2011] where appropriate; CIs are derived on large sample properties of the maximum partial likelihood estimates.

15.1.5 Andersen-Gill model for recurrent events

Data on recurrent events is to be arranged in the counting process structure [Therneau 2000]. There is one record (row) for each time interval a patient is at risk to experience an event. In general, there is more than one of such time intervals per patient, so that each patient is represented by a series of records (rows of data). The first interval starts with the date of randomization (for an efficacy event) or the date of first study drug intake (for safety events). Intervals ending without an event are indicated by a censoring variable: 0 indicates censored, 1 indicates event. A time dependent covariate for study treatment (selexipag, placebo, none) may be added.

Example 1 Patient 1 experienced no event and observation ended at Day 450; Patient 2 had events at Day 87, 200, and 510 and observation ended without further events at Day 610. This would result in following counting process data representation:

	Event-risk period		Event (1)/ Censoring (0)
	Start day	Stop day	
Patient 1	1	450	0
Patient 2	1	87	1
	88	200	1
	201	510	1
	511	610	0

There may be types of events for which patients are off-risk for a number of days before they are back at risk. An example is the event of hospitalization: during the time when hospitalized a patient is not at risk for hospitalization.

Example 2 Patient 3 was never hospitalized and observation ended at Day 475; Patient 4 was hospitalized at Day 60 and discharged at Day 75, hospitalized at Day 180 and discharged at Day 190, and observation ended without further hospitalizations at Day 560. This would result in following counting process data representation:

	Event-risk period		Event (1)/ Censoring (0)
	Start day	Stop day	
Patient 3	1	475	0
Patient 4	1	60	1
	75	180	1
	190	560	0

The (stratified) Andersen-Gill model [[Andersen 1982](#)] for recurrent events is an extension of the (stratified) proportional hazards model. It can be described by:

$$\begin{aligned}\lambda_{jk}(t, x_{jk1}, \beta_1) &= \lim_{h \downarrow 0} \frac{1}{h} P(N_{jk}(t+h) - N_{jk}(t) = 1 | F_{jk}(t)) \\ &= Y_{jk}(t) \cdot h_{0k}(t) \cdot \exp(x_{jk1} \cdot \beta_1)\end{aligned}$$

$\lambda_{jk}(\cdot)$ intensity function depending on time (relative to the start date), the treatment of patient j in stratum k and the unknown regression parameter

$N_{jk}(\cdot)$ stochastic process counting the number of events for patient j in stratum k (right continuous process with jumps of height 1)

- $F_{jk}(t)$ Filtration (a collection of σ -algebras with $F_{jk}(s)$ subset of $F_{jk}(t)$ for all $0 \leq s \leq t$) containing all relevant information on patient j in stratum k collected up to time t
- $Y_{jk}(t)$ left continuous predictable stochastic process indicating patient j in stratum k is at risk, i.e., $Y_{jk}(t)=1$, or not, i.e., $Y_{jk}(t)=0$, for the event at time t
- $h_{0k}(t)$ unspecified baseline hazard function for stratum k at time t
- x_{jk1} treatment for patient j in stratum k coded as 0 (placebo) or 1 (selexipag); this coding leads to a hazard ratio < 1 if the estimated effect suggests a lower hazard in the selexipag group relative to the placebo group
- β_1 : unknown parameter for the treatment effect on the log-scale (the log hazard ratio).

The hazard ratio is a multiplicative constant $\exp(\beta_1)$ comparing the hazard functions in the selexipag group relative to the hazard functions in the placebo group. The latter are allowed varying across strata. However, the HR is assumed to be common across strata. A $HR < 1$ indicates decreased hazard for the event of interest in the selexipag group compared to the placebo group. Note that the model equation does not assume a change in the intensity function caused by an event and the argument of the baseline hazard function remains relative to the date of randomization, see [Kelly 2000].

Statistical analysis

The regression parameter β_1 is estimated by maximum likelihood method first ignoring possible correlation followed by a Wald test-based two-sided CI for the HR using a robust sandwich-type variance estimate taking into account correlation between recurrent events within a patient [Therneau 2000, sections 7.2 and 8.2.1].

SAS PROC PHREG using COVSANDWICH(AGGREGATE) option and the ID statement is used (additional options controlling the output may be added):

```
PROC PHREG DATA=dataset COVSANDWICH(AGGREGATE) ;
  MODEL (start stop)*censor(0)=treat
    / TIES=EXACT RISKLIMITS ALPHA=;
  ID subjid;
  STRATA strat_1 .. strat_j;
RUN;

* start represents the variable containing start day of event-risk periods;
* stop represents the variable containing stop day of event-risk periods;
* censor represents the censoring variable (0=censored, 1=event);
* treat represents the treatment group variable (0=placebo, 1=selexipag);
* subjid represents the patient identifier
* strat_1 .. strat_j represent stratification variables (if applicable);
```


15.1.6 Multi-state model

15.1.6.1 Model description

Multi-state models and statistical analysis related to them are described below for a specific exploratory efficacy endpoint but the underlying method can be applied for other similar endpoints (for example safety endpoints) as well.

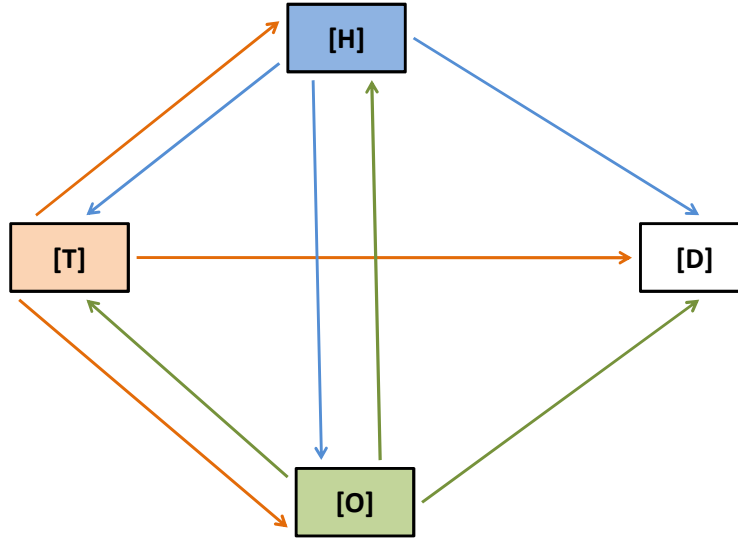
Multistate processes $(X_t)_{t \geq 0}$ are considered where X_t denotes the state a patient is at time t . For the exploratory efficacy endpoint “Time course of CEC confirmed (potentially recurrent) morbidity/mortality events hospitalization due to worsening of PAH, initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH, and death up to Study Closure” the following four states are defined:

- [D] death
- [H] hospitalization for worsening of PAH based on predefined criteria
- [T] parenteral (sc or i.v.) prostanoid treatment or chronic oxygen therapy
- [O] other (none of [T], [H], [D])

In case of parenteral prostanoid treatment or chronic oxygen therapy during hospitalization, the state [H] is used. State [D] constitutes an absorbing state (a state out of which transitions are not possible) whereas all other 3 states are transient states (states out of which transitions are possible and modeled). As the process $(X_t)_{t \geq 0}$ is discrete in time (days) it may happen that that two states are associated with the same date, e.g., hospitalization and death at the same day. In such cases, the state higher in the list above is used. According to the study protocol patients are expected to be in state [O] at time of randomization ($t=0$).

States and possible transitions between states are illustrated by [Figure 6](#) below.

Figure 6 Multi-state model with possible transitions



Patient-level examples of the stochastic process have been given in Section 11.11.

Transition probability from state $[k]$ at time s to state $[m]$ at time $t \geq s$ is defined as:

$$P_{[k][m]}(s, t) := P(X_t = [m] | X_s = [k], \text{Past})$$

where “Past” represents knowledge about the process’ history up to time s (it actually is the filtration generated by the process).

It is assumed that $(X_t)_{t \geq 0}$ fulfills the Markov property, i.e., for all states $[k]$ and $[m]$ and all times $s \leq t$ holds:

$$P(X_t = [m] | X_s = [k], \text{Past}) = P(X_t = [m] | X_s = [k]).$$

This means the transition probabilities depend on the past only via the current state. As the transition probabilities depend on the day since randomization, the process is called time-inhomogeneous Markov. For states $[k] \neq [m]$, transition hazard functions are defined as

$$h_{[k][m]}(t) = \lim_{\Delta t \rightarrow 0^+} \frac{P(X_{t+\Delta t} = [m] | X_t = [k])}{\Delta t}$$

and cumulative transition hazards up to time t as

$$H_{[k][m]}(t) = \int_0^t h_{[k][m]}(u) du .$$

15.1.6.2 Non-parametric estimation

For both selexipag and placebo, the *cumulative* transition hazard functions $H_{[k][m]}(t)$ are estimated by the Nelson-Aalen estimators $\hat{H}_{[k][m]}(t)$, as this estimation is more straightforward as estimation of the transition hazard functions. The details of the Nelson-Aalen estimators (and point wise CIs based on their asymptotically normal distributions) in the setting of time-inhomogeneous Markov multi-state models are described in section 9.1 of [Beyersmann 2012]⁷. Estimators and 95% point wise CIs are obtained with the R package mvna [Allignol 2008].

As next step, the 4x4 transition probability matrices $\mathbf{P}(s, t)$ are estimated by making use of the following relationship between and the cumulative transition hazard functions:

$$\mathbf{P}(s, t) \approx \prod_{n=1}^N (\mathbf{I} + \Delta \mathbf{H}(t_n))$$

where

$s = t_0 < t_1 < t_2 < \dots < t_{N-1} < t_N = t$ is a partition of the time interval $[s, t]$

$\mathbf{I}$ is the 4x4 identity matrix

$\Delta \mathbf{H}(t_n)$ is a 4x4 matrix with the (k, m) -th element defined as $H_{[k][m]}(t_n) - H_{[k][m]}(t_{n-1})$ and $H_{[k][k]} = -\sum_{[j] \neq [k]} H_{[k][j]}(t)$.

Plugging the Nelson-Aalen estimators in this relation results in the Aalen-Johansen estimator (also called “empirical transition matrix”):

$$\hat{\mathbf{P}}(s, t) = \prod_{u \in (s, t]} (\mathbf{I} + \Delta \hat{\mathbf{H}}(u)) ,$$

which is a finite matrix product over all event times u in $(s, t]$ and is obtained with the R package etm [Allignol 2011].

⁷ The simple extension to more than 2 competing risk is described in section 7.1 of [Beyersmann 2012].

15.1.6.3 Proportional transition hazard models

For the transition from state $[k]$ to state $[m]$, the proportional transition hazard model is defined by

$$h_{[k][m],i}(t; Z_i) = h_{[k][m],0}(t) \cdot \exp(\beta_{[k][m]} \cdot Z_i)$$

where

$\beta_{[k][m]}$ denotes the regression parameter vector (including the log hazard ratio for study drug)

Z_i denotes the covariate vector for patient i (including the study drug indicator)

$h_{[k][m],0}(t)$ denotes an unspecified non-negative baseline hazard function.

SAS PROC PHREG with data arranged in the counting process structure, see Section 15.1.5, and section 10.1 of [Beyersmann 2012], is used to estimate the hazard ratios for study drug and CIs. A robust sandwich variance estimate is accounting for the correlation of transitions in case the same patient experiences a certain transition for more than one time. The model may also include a stratification variable and a time-dependent covariate.

15.2 Statistical analysis methods for categorical endpoints

15.2.1 Unstratified analysis method for binary endpoints

Let π_{sel} and π_{pla} denote the unknown probabilities for an outcome of interest in the selexipag and placebo group, respectively.

The null hypothesis

$H_0: \pi_{sel} = \pi_{pla}$ “identical probabilities for an outcome in both treatment groups”

is tested against the one-sided alternative hypothesis

$H_A: \pi_{sel} > \pi_{pla}$ “probability for an outcome is higher in the selexipag group”

The Mantel-Haenszel test is used to test the null hypothesis: H_0 is rejected if the two-sided p -value is not exceeding the two-sided significance level assigned to the test (typically 0.01) and the observed proportions fulfill $p_{sel} > p_{pla}$.

The effect of selexipag relative to placebo is expressed by the odds ratio estimate and a two-sided CI.

SAS PROC FREQ is used (additional options controlling the output may be added):

```
PROC FREQ DATA=dataset;  
  TABLES treat*response / CHISQ MEASURE ALPHA=0.01;  
RUN;  
  
* response represents binary endpoint (outcome of interest in first column);  
* treat represents the treatment group (selexipag in first row);
```

15.2.2 Stratified analysis method for binary endpoints

Let $\pi_{sel,k}$ and $\pi_{pla,k}$, $k=1,\dots,K$, denote the unknown probabilities for an outcome of interest in stratum k for the selexipag and placebo group, respectively.

The null hypothesis

H_0 : $\pi_{sel,k} = \pi_{pla,k}$ for all $k=1,\dots,K$ “in all K strata the probabilities for an outcome are the same for both treatment groups”

is tested against the two-sided alternative hypothesis

H_A : $\pi_{sel,j} \neq \pi_{pla,j}$ for at least one stratum j with $1 \leq j \leq K$ “for at least one stratum the probabilities for an outcome are different between selexipag and placebo”.

The Cochran-Mantel-Haenszel test is used to test the null hypothesis: H_0 is rejected if the two-sided p -value is not exceeding the two-sided significance level assigned to the test (typically 0.01).

If the assumption of a common odds ratio is not rejected by the Breslow-Day test using a two-sided significance level of 0.05, the effect of selexipag relative to placebo is expressed by the common odds ratio estimate and a two-sided CI.

SAS PROC FREQ is used (additional options controlling the output may be added):

```
PROC FREQ DATA=dataset;  
    TABLES strata*treat*response / CMH ALPHA=0.01;  
RUN;  
  
* strata represents the stratification factor(s);  
* response represents the binary endpoint (e.g. yes/no);  
* treat represents the treatment group (selexipag as first row);
```

15.2.3 Analysis method for counts and rates

For statistical analysis of counts and rates (for example the annualized hospitalization rate), the following individual patient data is used:

- the patient's number of events (e.g., hospitalizations) up to the EOS visit
- the patient's length of observation expressed in years, defined as: [EOS visit date minus randomization date +1] divided by 365.25.

A generalized linear model with negative-binomial distribution for the number of events up to the EOS visit is assumed.

t_j denotes the length of observation (see above) for patient j

Y_j denotes the number of events for patient j during t_j

μ_j denotes the mean of the negative binomial distribution of Y_j .

The mean for the distribution of the annualized hospitalization rate for patient j , denoted by μ_j/t_j , is modeled by the following equation:

$$\log(\mu_j/t_j) = \mathbf{x}'_j \boldsymbol{\theta}, \quad \text{i.e., } \log(\mu_j) = \mathbf{x}'_j \boldsymbol{\theta} + \log(t_j), \quad \text{where}$$

$\mathbf{x}_j$ is the vector denoting treatment (and other Baseline covariates, if applicable) for patient j

$\boldsymbol{\theta}$ is the vector of unknown fixed model parameters (treatment and other Baseline covariates, if applicable).

Within the negative binomial regression model, the null hypothesis of no treatment effect ($\theta_{\text{treatment}} = 0$) is tested by a two-sided Wald-type test (typically at a two-sided significance level of 0.01). A two-sided Wald CI is calculated for the relative reduction in mean annualized event rate for selexipag compared to placebo.

15.3 Statistical analysis methods for endpoints with a continuous distribution

15.3.1 General linear mixed model for normally distributed endpoints measured repeatedly over time

The following general linear mixed model is used for an endpoint (repeatedly measured over time) following a normal distribution (at least approximately). The endpoint may be the actual measurement or, for example, the absolute change from Baseline.

The model equation (additional fixed effects defined by Baseline data can be added) is:

$$Y_{ijk} = \theta_0 \cdot y_{ij0} + T_i + V_k + TV_{ik} + s_{ij} + e_{ijk}$$

where

Y_{ijk} is the endpoint for the j^{th} patient of treatment group i at visit week k

y_{ij0} is the Baseline value for the j^{th} patient of treatment group i

θ_0 is the unknown fixed slope for the Baseline covariate

T_i is the unknown fixed effect of treatment i

V_k is the unknown fixed effect of visit week k

TV_{ik} is the unknown fixed interaction effect of treatment i and visit week k

s_{ij} is the random effect associated with the j^{th} patient of treatment i

e_{ijk} is the random error associated with the j^{th} patient of treatment i at visit week k

s_{ij} and e_{ijk} are assumed to be stochastically independent from each other and following a multivariate normal distribution. The covariance matrix for e is chosen to be block diagonal (with each block corresponding to a patient) with non-zero block diagonal elements following a spatial power law structure (which is a generalization of the autoregressive order one structure for unequally spaced data). The unstructured covariance matrix for e is considered as an alternative; Akaike's Information Criteria and Schwarz' Bayesian Criterion are used to assist in the selection process for the covariance structure.

One-sided hypotheses related to treatment are expressed as linear combinations of the fixed effect terms given above and tested by one-sided t-tests (typically at an one-sided significance level of 0.005). Point estimates and two-sided CIs are provided.

15.3.2 General linear model for normally distributed endpoint measured once

If the statistical analysis is reduced to a single post-Baseline time point, the model is

$$Y_{ij} = \theta_0 \cdot y_{ij0} + T_i + e_{ijk}$$

where

Y_{ij} is the endpoint for the j^{th} patient of treatment group i

y_{ij0} is the Baseline value for the j^{th} patient of treatment group i

θ_0 is the unknown fixed slope for the Baseline covariate

T_i is the unknown fixed effect of treatment i

e_{ijk} is the random error associated with the j^{th} patient of treatment i at visit week k

e_{ijk} assumed to be stochastically independent and following a multivariate normal distribution.

15.3.3 Nonparametric analysis of covariance for univariate endpoints

Non-parametric analysis of covariance (ANCOVA) similar as described in section 7.7 of [Stokes 2000] is performed.

Null hypothesis H_0 : “Distributions of the post-Baseline endpoint, adjusted for its Baseline value, are identical for selexipag and placebo”

is tested against the alternative hypothesis H_A : “Distribution of the post-Baseline endpoint, adjusted for its Baseline value, is more favorable for selexipag as compared to placebo”.

The non-parametric ANCOVA procedure incorporates three steps:

1. Transformation of Baseline and post-Baseline values for all patients (regardless of treatment groups) to standardized ranks (i.e., ranks divided by the number of patients ranked plus 1, mean ranks in case of ties)
2. Determination of residuals from the linear regression of the response variable standardized ranks on Baseline variable standardized ranks.
3. Application of the one-sided Wilcoxon-Mann-Whitney test to these residuals. The standardized test statistic with a continuity correction of 0.5 is asymptotically standard normally distributed under the null hypothesis. One-sided significance level of 0.005 is used.

SAS code for the analysis:

```
PROC RANK DATA=dataset TIES=MEAN NPLUS1 OUT=stdrank;  
    VAR base outcome;  
RUN;  
  
PROC GLM DATA=stdrank;  
    MODEL outcome=base / PREDICTED;  
    ODS OUTPUT PredictedValues=pred;  
    ID treat;  
RUN;  
  
PROC NPARIWAY DATA=pred WILCOXON;  
    CLASS treat;  
    VAR residual;  
RUN;  
  
* base represents the Baseline value of the endpoint;  
* outcome represents the post-Baseline endpoint;  
* treat represents the treatment group;
```

Further options to control the output may be added.

In case of a stratified non-parametric ANCOVA, the linear regression in step 2 is stratified, and in step 3 a two-sided stratified van Elteren test with two-sided significance level 0.01 is performed.

SAS code for the analysis:

```
PROC RANK DATA=dataset TIES=MEAN NPLUS1 OUT=stdrank;  
  BY strata;  
  VAR base outcome;  
RUN;  
  
PROC GLM DATA=stdrank;  
  BY strata;  
  MODEL outcome=base / PREDICTED;  
  ODS OUTPUT PredictedValues=pred;  
  ID treat;  
RUN;  
  
PROC FREQ DATA=pred SCORES=MODRIDIT;  
  TABLES strata*treat*residual / CMH2;  
RUN;  
  
* base represents the Baseline value of the endpoint;  
* outcome represents the post-Baseline endpoint;  
* strata represents the stratification variable(s);  
* treat represents the treatment group;
```

Further options to control the output may be added.

15.3.4 Nonparametric analysis of distribution shift

Non-parametric estimation of the distribution shift (between selexipag and placebo) for a univariate endpoint is performed by the Hodges-Lehmann method [Lehmann 1998, section 2.5]. Apart from the shift, the distributions for both treatment groups are assumed to be the same. Two-sided CIs for the location shift are provided with the method described in [SAS Institute Inc. 2009].

SAS code for the analysis:

```
PROC NPARIWAY DATA=dataset HL ALPHA=;  
  CLASS treat;  
  VAR outcome;  
RUN;  
  
* outcome represents the post-Baseline endpoint;  
* treat represents the treatment group;
```

Further options to control the output may be added.

15.3.5 Nonparametric comparative probabilities

As distributions may not simply differ by a shift, a further method is to express the difference (or similarity) by the terms $P(X_{\text{sel}} < X_{\text{pla}})$, $P(X_{\text{sel}} = X_{\text{pla}})$ and $P(X_{\text{sel}} > X_{\text{pla}})$. These quantities are estimated by comparing all n_{sel} to all m_{pla} observations, counting the pairs falling in each of the 3 categories and dividing by $n_{\text{sel}} \times m_{\text{pla}}$. For example, $P(X_{\text{sel}} > X_{\text{pla}})$ can be interpreted as the probability to achieve a larger result (e.g., 6MWD) for a randomly chosen patient treated with selexipag rather than treated with placebo.

16 STATISTICAL ANALYSES WITH MISSING DATA

16.1 Amount and reason for missing data

Missing data is expected due to the PAH patient population, some specific design features of studies AC-065A302 and AC-065A303 and general features of clinical studies:

- (D) patient died
- (E) patient with a CEC-confirmed morbidity event in study AC-065A302 entered the AC-065A302 Post-Treatment Observation Period with reduced efficacy data collection or was not followed-up any further (with the possible exception of survival status)
- (P) patient prematurely discontinued study drug in AC-065A302 without a CEC-confirmed morbidity/mortality event (e.g., because of intolerability or an administrative reason) entered the AC-065A302 Post-Treatment Observation Period with reduced efficacy data collection – or were not followed-up any further (with the possible exception of survival status)
- (L) at the analysis cut-off date the patient has not reached the visit for which an assessment is scheduled according to the study protocol (a feature more prominent for the interim analysis and for patients randomized during the final part of the recruitment phase)
- (W) patient withdrew informed consent or became lost to follow-up
- (M) assessment (may be a complete visit) could not be performed for a reason not covered by one of the reasons above.

Number and percentage (based on the number of randomized patients) of missing values and reasons (categories as defined above) are summarized by treatment and visit for each endpoint.

Censoring for time-to-event endpoints

For all time-to-event endpoints (including the primary efficacy endpoint), the censoring is defined in the respective SAP section for endpoint definitions. The analysis methods for time-to-event endpoints [see Section 15.1] are taking into account the censoring, typically assuming independent censoring but also allowing for sensitivity analyses where the assumption of independent censoring is doubtful and interpretation is difficult.

Number and percentage (based on the number of randomized patients) of censored observations and reasons (categories as defined above) are summarized by treatment for each time-to-event endpoint.

16.2 Pattern of missingness

The pattern of missingness is an important feature to determine a suitable statistical analysis method.

A dataset with variables $Y_1, Y_2, \dots, Y_p$ (in that order) is said to have a “monotone missing pattern” if a missing value for variable Y_j for a particular patient implies that all variables $Y_k, k > j$, are missing as well for that patient. Monotone missing patterns are generated by (D), (E), (P), (L) and (W), but in general not by (M). However, missing values because of (M) are expected to be far less frequent than missing values because of the other reasons. A richer set of methods exists for data sets with a monotone missing data pattern (as opposed to methods applicable to data sets with an arbitrary missing pattern). As it is expected that the data sets in studies AC-065A302 and AC-065A303 are close to monotone missingness (so that there are not many such imputations required to achieve monotone missingness) the general strategy is outlined as follows:

- (1) dataset is checked for its pattern of missingness
- (2) in case of non-monotone missingness
 - for a set of variables with continuous distributions, a Markov Chain Monte Carlo (MCMC) method is used to impute missing values to the data set to achieve a monotone missing pattern in the imputed data set
 - for a set of variables with discrete distributions, the method described in Section 16.6.1 is used to achieve a monotone missing pattern in the imputed data set
- (3) multiple imputation methods are used to analyze the dataset with monotone missing pattern (the specific method depends on the type of distribution for the endpoint at hand, see Sections 16.5 and 16.6).

16.3 Assumptions for statistical analyses with missing data

The methods described in the two subsequent sections assume that the missing values are “missing at random” (MAR); that is, the probability that an observation is missing may depend on the observed data, but not on the missing data. To be more precise: with $\mathbf{R}$ representing the $n \times p$ matrix of response indicators whose elements are 0 or 1 depending on whether the corresponding elements Y are missing or observed. Then the MAR assumption is that the distribution of $\mathbf{R}$ can depend on Y_{obs} but not on Y_{miss} :

$$P(\mathbf{R}|Y_{\text{obs}}, Y_{\text{miss}}) = P(\mathbf{R}|Y_{\text{obs}})$$

Further, they assume that the distribution of the endpoint and the distribution of the missing data indicator (whether or not the value is missing) are “distinct”, in the sense that knowledge about the distribution of the endpoint does not provide any additional information about the distribution of the missing data indicator, and vice versa.

If both MAR and distinctness assumptions are holding, the missing-data mechanism is said to be “ignorable”.

16.4 Multiple imputation method – the general approach

Multiple imputation methods replace each missing value with a set of plausible values that represent the uncertainty about the right value to impute. The multiply imputed datasets

are then analyzed by standard statistical procedures for complete data and combining the results from these analyses. Multiple imputation methods do not attempt to estimate each missing value through simulated values, but rather to represent a random sample of the missing values. Under the assumption of MAR this process results in valid statistical inferences that properly reflect the uncertainty due to missing values.

Multiple imputation methods involve three steps:

- the missing values are filled in m times to generate m complete data sets (using SAS PROC MI), see Sections 16.5.2 and 16.6.2 depending on the type of distribution
- the m complete datasets are analyzed by using standard statistical procedures, see Section 16.4.1
- the results from the m analyses are combined for statistical inference (using SAS PROC MIANALYZE), see Section 16.4.2.

16.4.1 Statistical analysis of complete datasets

The result of SAS PROC MI is an output dataset with $m=5$ replications of observed values but (in general) different imputations for the missing values; these now complete sets are indexed by variable `_imputation_`.

The output dataset is analyzed by an appropriate SAS analysis procedure according to the required statistical analysis for the endpoint as described in Sections 23 and 24. In such SAS analysis procedures a BY `_imputation_` statement is used to generate separate statistical analyses for each of the new complete sets. The output dataset of the SAS analysis procedure is again indexed by the variable `_imputation_` (the content of that output dataset depends on the specific SAS analysis procedure) and is subsequently used as input dataset for SAS PROC MIANALYZE for combining result for inference, see Section 16.4.2.

16.4.2 Combining results from imputed datasets for inference

The analyses of imputations are obtained by using SAS analysis procedures for complete data. No matter which complete-data analysis is used, the concept of combining results from different imputed data sets in SAS PROC MIANALYZE is the same (although technically different depending on the type of model and SAS procedure used for the complete data) and results in valid statistical inferences that properly reflect the uncertainty due to missing values.

SAS PROC MIANALYZE reads parameter estimates and associated standard errors or covariance matrices that are computed by the standard statistical procedure for each imputed set. SAS PROC MIANALYZE then derives valid univariate inference for these parameters.

With m (default 5) imputations, m different sets of point and variance estimates for a parameter Q are computed. With $\hat{Q}_i$ and $\hat{U}_i$ denoting the point and variance estimates from

the i -th imputed complete data set, $i=1, 2, \dots, m$. Then the point estimate for Q from multiple imputations is the average of the m complete-data estimates:

$$\bar{Q} = \frac{1}{m} \sum_{i=1}^m \hat{Q}_i.$$

Let $\bar{U}$ denote the average of the m complete-data variance estimates

$$\bar{U} = \frac{1}{m} \sum_{i=1}^m \hat{U}_i$$

and B the (between-imputation) variance of the point estimates

$$B = \frac{1}{m-1} \sum_{i=1}^m (\hat{Q}_i - \bar{Q})^2.$$

Then the variance estimate for the point estimate $\bar{Q}$ is

$$T = \bar{U} + \left(1 + \frac{1}{m}\right) B.$$

$\bar{Q}$ and T can be used for testing null hypotheses on Q and constructing CIs for Q . The use of SAS PROC MIANALYZE for various models is described in [Yuan 2011] and [SAS Institute 2009].

16.5 Statistical analysis with missing data for endpoints with continuous distributions

This section deals with the analysis of secondary / exploratory endpoints with (quasi-) continuous distributions (absolute change from Baseline in 6MWD, absolute change from Baseline in CAMPHOR ‘Symptoms’ score, absolute change from Baseline in sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ and absolute change from Baseline in plasma NT pro-BNP).

16.5.1 Imputation method to generate monotone missing data pattern for endpoints with continuous distributions

In case the observed missing data pattern is not monotone, a Markov chain Monte Carlo (MCMC) method is used to generate a monotone missing data pattern.

Within SAS PROC MI, the monotone MCMC method is requested by the option IMPUTE=MONOTONE in the MCMC statement. The resulting “Missing Data Patterns” table denotes the variables with missing values

- by “.” indicating that the variable is missing and will be imputed in this step
- “O” indicating that the variable is missing and will not be imputed in this step.

This monotone MCMC method consists of two steps: the imputation I-step and the posterior P-step.

The imputation I-step

Given an estimated mean vector and covariance matrix, the I-step simulates the missing values for each observation independently, i.e., when denoting the variables with observed values for patient j by $Y_{j(obs)}$ and the variables with missing values for patient j by $Y_{j(miss)} = (Y_{j(m1)}, Y_{j(m1)})$, where $Y_{j(m1)}$ is a subject of the missing variables that will cause a monotone missingness pattern when their values are imputed. Then the I-step draws values for $Y_{j(m1)}$ from a conditional distribution for $Y_{j(m1)}$ given $Y_{j(obs)}$.

The posterior P-step

Given a new sample (generated by the I-step) with a monotone missingness pattern, the P-step simulates the posterior population mean vector and covariance matrix with a non-informative Jeffreys prior distribution. These new estimates are then used in the next I-step.

These two steps are iterated long enough for the results to be reliable, i.e., the iterations converge to a stationary distribution and an approximately independent draw of the relevant missing values from this distribution can be obtained.

16.5.2 Multiple imputation method for monotone missingness patterns in endpoints with continuous distributions

A linear regression model is fitted using observations with observed values for the endpoint and further covariates (these may be Baseline covariates or measurements of the endpoint at earlier visits or others). Based on the fitted regression model, a new regression model is simulated from the Bayesian posterior predictive distribution of the regression parameters and is used to impute the missing values.

In detail, for a continuous variable Y_j with missing values, a regression model

$$Y_j = \beta_0 + \beta_1 \cdot X_1 + \beta_2 \cdot X_2 + \dots + \beta_k \cdot X_k$$

is considered where $X_1, X_2, \dots, X_k$ are covariates derived from preceding variables $Y_1, Y_2, \dots, Y_{j-1}$.

The following steps are used to impute missing values for Y_j at each imputation:

1. The regression model is fitted using observed values for the variable Y_j and its covariates $X_1, X_2, \dots, X_k$. The fitted model includes the regression parameter vector estimate $\hat{\beta} = (\hat{\beta}_0, \hat{\beta}_1, \dots, \hat{\beta}_k)$ and the associated covariance matrix $\hat{\sigma}_j^2 V_j$ where V_j is the $(X'X)^{-1}$ matrix derived from the intercept and covariates.
2. New regression parameters $\beta_* = (\beta_{*0}, \beta_{*1}, \dots, \beta_{*k})$ and σ_{*j}^2 are drawn from the Bayesian posterior prediction distribution of the regression parameters. [Yuan 2011] describes the details of the sampling procedure implemented in SAS PROC MI.

3. For each missing value, a predicted value $y_{i*} = \beta_{*0} + \beta_{*1}x_1 + \dots + \beta_{*k}x_k$ is computed with the covariate values $x_1, \dots, x_k$.
4. A set of k_0 observations whose corresponding predicted values are closest to y_{i*} is generated.
5. The missing value is then replaced by a value drawn randomly from these k_0 observations. An output dataset with m replications of observed values but (in general) different imputations for the missing values is generated; these now completed sets are indexed by variable `_imputation_`.

This method is called the “predictive mean matching method” and it requires the number k_0 of closest observations to be specified. A smaller k_0 tends to increase the correlation among the multiple imputations for the missing observation and results in a higher variability of point estimators in repeated sampling. A larger k_0 tends to lessen the effect from the imputation model and results in biased estimators.

The predictive mean matching method ensures that imputed values are plausible and may be more appropriate than the regression method (a similar method but without the steps 4 and 5 above) if Y_j is not normally distributed.

SAS PROC MI is used with following statements and options, see [Yuan 2011] and [SAS Institute 2009] (further statements or options to control the output may be used):

- PROC MI statement with option NIMPUTE=5 (which is the default in PROC MI and suggested in the literature) and providing a positive integer seed number with the SEED= option for reproduction purpose
- VAR statement lists the variables to be analyzed in the order of the monotone missingness pattern
- CLASS statement specifies categorical variables in VAR statement
- MONOTONE statement
 - specifies the imputation method (for datasets with monotone missingness): REGPREDMEANMATCH is selected for the predictive mean matching method described above
 - specifies the regression model in step 1 described above
 - specifies k_0 by the K= option (the default K=5 is used)
- TRANSFORM statement may be used to transform variables from the VAR statement, e.g., logarithmic, exponential, power transformation) before the imputation process.

16.6 Statistical analysis with missing data for endpoints with discrete distributions

This section deals with the analysis of secondary / exploratory efficacy endpoints with discrete (e.g., Bernoulli) distributions (absence of worsening in modified NYHA/WHO functional class, modified NYHA/WHO functional class, Borg dyspnea index).

16.6.1 Imputation method to generate monotone missing data pattern for endpoints with discrete distributions

In case the observed missing data pattern is not monotone, a monotone missing data pattern is generated by imputing missing values between two available values by the value of the earlier of the two available values.

16.6.2 Multiple imputation method for monotone missing data pattern for endpoints with discrete distributions

A logistic regression model is fitted using observations with observed values for the endpoint and further covariates (these may be Baseline covariates or measurements of the endpoint at earlier visits or others). Based on the fitted logistic regression model, a new logistic regression model is simulated from the Bayesian posterior predictive distribution of the regression parameters and is used to impute the missing values.

In detail, for a binary⁸ variable Y_j with missing values, a logistic regression model

$$\text{logit}(p_j) = \log\left(\frac{p_j}{1-p_j}\right) = \beta_0 + \beta_1 \cdot X_1 + \beta_2 \cdot X_2 + \dots + \beta_k \cdot X_k$$

is considered where $X_1, X_2, \dots, X_k$ are covariates derived from preceding variables $Y_1, Y_2, \dots, Y_{j-1}$ and $p_j = P(Y_j = 1 | X_1, X_2, \dots, X_k)$

The following steps are used to impute missing values for Y_j at each imputation:

1. The logistic regression model is fitted using observed values for the variable Y_j and its covariates $X_1, X_2, \dots, X_k$. The fitted model includes the regression parameter vector estimate $\hat{\beta} = (\hat{\beta}_0, \hat{\beta}_1, \dots, \hat{\beta}_k)$ and the associated covariance matrix V_j
2. New regression parameters $\beta_* = (\beta_{*0}, \beta_{*1}, \dots, \beta_{*k})$ and σ_{*j}^2 are drawn from the Bayesian posterior prediction distribution of the regression parameters
3. For patient i with missing Y_j and covariate values $x_{1i}, x_{2i}, \dots, x_{ki}$, the expected probability for $Y_j=1$ is computed as

$$p_{ij} = P(Y_j = 1 | X_1 = x_{1i}, X_2 = x_{2i}, \dots, X_k = x_{ki}) = \frac{\exp(\mu_{ij})}{1 + \exp(\mu_{ij})}$$

$$\text{with } \mu_{ij} = \beta_{*0} + \beta_{*1}x_{1i} + \beta_{*2}x_{2i} + \dots + \beta_{*k}x_{ki}$$

4. A random uniform variate, u , between 0 and 1 is drawn. If the value of u is less than p_{ij} , Y_j is imputed by 1; otherwise Y_j is imputed by 2.

⁸ For an ordinal categorical endpoint (with more than two response categories) the logistic regression model is extended.

17 STATISTICAL METHODS FOR SUBGROUP ANALYSIS

17.1 General remarks

Subgroup analyses are performed by

- (A) separate analyses for each of the respective subgroups using the same statistical methods, e.g.,
 - log-rank test and proportional hazards model for time-to-event endpoints
 - Cochran-Mantel-Haenszel test for binary endpoints
 - (non-parametric) ANCOVA for continuous endpointsas for the statistical analysis in the overall Full Analysis Set.
- (B) modified statistical models that allow incorporation of treatment-by-subgroup interaction of , e.g.,
 - proportional hazards model with study treatment, subgroup and treatment-by-subgroup interaction terms for time-to-event endpoints
 - logistic regression model with study treatment, subgroup and treatment-by-subgroup interaction terms for binary endpoints
 - (non-parametric) ANCOVA with study treatment, subgroup and treatment-by-subgroup interaction terms for continuous endpoints.

17.2 Display of subgroup analysis results

Point estimates and corresponding two-sided 99% CIs for treatment effect in each subgroup – method (A) described above – are presented in a forest-plot as descriptive evidence about consistency of estimated treatment effect across subgroups.

These plots are prepared with a vertical reference line displayed for the treatment effect in the overall Full Analysis Set, see [[Cuzick 2005](#)]. In addition the two-sided p-value for the respective test of treatment-by-subgroup interaction is displayed on the plots (no formal significance level is employed for the interaction test).

18 GROUP-SEQUENTIAL DESIGN AND ANALYSIS

18.1 Group-sequential design

Study AC-065A302 employs a group-sequential design for the primary efficacy endpoint with options to recommend stop for futility or for compelling and robust efficacy at the interim analysis.

18.1.1 Concept of alpha-spending functions

Group-sequential designs based on the concept of alpha-spending functions have been introduced by [Lan 1983] and are described in more detail in [DeMets 1995]. The alpha-spending function allocates some fractions of the pre-specified overall type-I-error probability (one-sided 0.005 in this study) to interim and final analyses over the course of the study. This is achieved by a mathematical function with certain properties; argument of such a function is the information fraction f observed at a particular analysis out of the total amount of information the study has been designed for. In other words, the information fraction f indicates how much of the study has been completed in terms of the accumulated information (observed mortality/morbidity events), and thus indicates how much of the overall α should be allocated up to (and including) that analysis.

Formally, the equation below defines the information fraction f :

$$f = \frac{\text{amount of information available at time of analysis}}{\text{amount of total information planned for the entire study}}$$

Any alpha spending function is equal to 0 at $f=0$ and equal to α at $f=1$, and it is non-decreasing in-between.

The alpha spending approach requires neither a specific number of interim analyses nor specific times when they have to occur. It does however require that the particular spending function is specified in advance and that the maximum information is specified at the design stage.

18.1.2 Application of the alpha-spending function principle in study AC-065A302

The alpha-spending function principle is applied in study AC-065A302 in a slightly modified fashion: the interim nominal significance level has been fixed in the study protocol rather than the type of alpha-spending function.

The design features are:

- the one-sided overall type-I-error probability is fixed to $\alpha = 0.005$
- the maximum information is specified as 331 morbidity/mortality events⁹ confirmed by the CEC
- the one-sided type-I-error probability at the interim analysis is fixed to 0.00005

⁹ Morbidity/mortality events in this section exclude events with CEC-determined onset date up to 16 Aug 2011

- the interim analysis is planned with 202 morbidity/mortality events (an information fraction of $f = 202/331 = 0.61$) confirmed by the CEC; however, if there are less or more events available for the interim analysis, the one-sided significance level used for the interim analysis is kept unchanged at 0.00005
- calculation of the one-sided type-I-error probability / required Z-score for the final analysis are performed once the number of morbidity/mortality events confirmed by the CEC at the interim analysis is known (this number together with the other characteristics described above determines the necessary characteristic of the alpha spending function in this modified approach).

The one-sided log-rank statistic Z (which fulfills the condition of independent increments) is used to test the null hypothesis for time to first morbidity/mortality event described in Section 15.1.2. In addition, a non-binding interim futility stopping rule is foreseen as outlined in Table 8 below.

Table 8 Summary of group-sequential design

Analysis stage (anticipated cumulative number of events ¹)	Efficacy			Futility		
	Cumulative alpha ² spent	Guidance ³ to reject H_0		Cumulative beta spent	Guidance ³ to accept H_0	
		p -value	Z-score		p -value	Z-score
Interim (202 events)	0.00005	≤ 0.00005	≥ 3.8906	0.0013	≥ 0.5	≤ 0
Final (331 events)	0.005	≤ 0.004991	≥ 2.5764	0.1	> 0.004991	< 2.5764

¹ If number of events observed at the interim analysis differs from 202, the interim boundaries are not to be changed.

² All significance levels (alpha) are one-sided.

³ The boundaries for the final analysis are definite whereas they are only guidelines for the DMC at the interim stage.

18.2 Group-sequential statistical analysis

In past experience with group-sequential studies FDA/EMA recommended not to modify efficacy boundaries because of the presence of any futility rules (from theoretical point of view, efficacy stopping boundaries (on the Z-scale) are affected slightly towards 0 by the presence of futility stopping rules). Therefore, the group-sequential analysis (with software East, currently version 5.3) is performed by using a design employing the stopping rule for a stopping philosophy outlined by [Haybittle 1971] but formally ignoring the stopping rule for futility. However, the DMC may apply the futility stopping rule as given in the table above.

At the interim and, if applicable, final analysis stage, the following statistics are calculated based on the methods described in Sections 15.1.2 and 15.1.3:

- Z statistic for the log-rank test
- point estimate and standard error of the log hazard ratio β from the proportional hazard model.

These quantities are entered in the East monitoring sheet and the following results are reported:

- a comparison of the observed Z-score to the efficacy boundary given in Table 8
- two-sided repeated 99% CI for the log hazard ratio β as well as for the hazard ratio $\exp(\beta)$.

If the observed Z-score is greater or equal the efficacy stopping boundary for rejection of the null hypothesis, the DMC may nevertheless recommend to continue the trial to its end, i.e., when 331 morbidity/mortality events have been confirmed by the CEC. In addition, also Actelion may decide to continue the trial to its end despite the DMC recommending to stop it at the interim stage.

18.2.1 Repeated CIs

In general, multiplicity introduced by interim analyses affects construction of CIs just as it affects significance levels of hypothesis tests. If naïvely using standard two-sided $(1-2\alpha)\times 100\%$ CIs like $\hat{\beta}(f_k) \pm z_{1-\alpha} \cdot SE(\hat{\beta}(f_k))$ for a parameter β of interest based on observations accumulated up to analysis stages $k = 1, \dots, K$ with information fractions $f_1, \dots, f_K$, then the overall coverage probability of all these K intervals would be less than $(1-2\alpha)\times 100\%$.

Following [Jennison 1989], a repeated CI (RCI) for β is defined as a sequence of intervals

$I(f_k) = \left(\beta(f_k), \beta(\bar{f}_k) \right)$, with $k = 1, \dots, K$, for which a simultaneous coverage probability is maintained at level $1-2\alpha$.

As both $\beta(f_k)$ and $\beta(\bar{f}_k)$ are random variables, the RCI definition can be formalized by

$$P_{\beta}(\beta \in I(f_k) \text{ for all } k = 1, \dots, K) = 1 - 2\alpha \quad \text{for all } \beta.$$

Hence, the RCI $I(f_k)$

- provides a statistical summary of the information about the parameter β available at the k -th analysis, adjusted to compensate for repeated (past, present and planned future) looks at the accumulating data
- is valid regardless of how the decision to stop the study may have reached, in particular if group-sequential stopping guidelines are or are not followed by the DMC.

Typically, two-sided repeated $(1-2\alpha)\times 100\%$ CIs are obtained from inverting a family of two-sided group-sequential tests (called parent test) with type-I-error probability 2α by using the familiar duality between CIs and hypothesis tests. Therefore, the construction of a sequence of RCIs depends on the group-sequential parent test (here the Wald-type test for the (log) hazard ratio) and the type-I-error probability available at the analysis stage.

This allows calculation of two-sided RCIs by replacing the standard normal quantile $z_\alpha = \Phi^{-1}(1-\alpha)$ in the formula for the unadjusted two-sided $(1-2\alpha)\times 100\%$ CI $\hat{\beta}(f_k) \pm z_\alpha \cdot SE(\hat{\beta}(f_k))$ by the critical value $c_\alpha(f_k)$ from the two-sided level 2α parent test: $I(f_k) = \hat{\beta}(f_k) \pm c_\alpha(f_k) \cdot SE(\hat{\beta}(f_k))$.

18.2.2 Supplementary statistical analysis after study termination

This section deals with the supplementary computation of p -values and estimates (including CIs) for log hazard ratio β and hazard ratio $\exp(\beta)$ after terminating the group-sequential trial, see [Whitehead 1986a], [Whitehead 1986b], [Kim 1987], [Kim 1989]. Computing these quantities ignoring that a sequential monitoring procedure with an option for an early stop is used, would fail to preserve the desired type-I-error probability of the significance test, the desired coverage probability of the CI and the lack of bias of the point estimate.

Rather, there is a need first to order the sample space to reflect the sequential nature of the test procedure, and then obtain p -values and CIs on the basis of this ordering. Software East is used to obtain supplementary statistical results by applying the stage-wise ordering, [Tsiatis 1984] and [Cytel 2009], of the sample space. This ordering is recommended because it does not require knowledge about the interim monitoring time-points that would have been adopted in the future, had the study not stopped early. In addition, stage-wise ordering ensures consistency between the p -value and the CI: the upper limit of the two-sided $(1-2\alpha)\times 100\%$ CI for the hazard ratio excludes 1 if and only if the corresponding one-sided p -value is smaller than α .

In case the study continues to its planned end the data observed before and after the interim analysis are compared [Friede 2009].

18.2.3 Analyses when statistical stopping guidance has been overruled

If the study has been continued despite the statistical efficacy guidance boundary having been crossed, the overall p -values, overall CIs and point estimates adjusted for the original group-sequential design are not valid anymore [Jennison 1989]. Instead, the more conservative repeated CI is used for reporting.

18.2.4 Over-running and under-running

If Actelion and the Steering Committee decide – without having any access to unblinded results restricted to the DMC – that the study is not to be continued to its planned end, then

all the remaining alpha, i.e., $\alpha - \alpha(t_{j-1})$ is spent for this now final analysis. An example for such reasons would be lack of ethical justification for randomized assignment of placebo caused by approval of another treatment with demonstrated superiority over placebo.

Using all the remaining alpha is thereby a way to deal with the problems of

- “**under-running**”, i.e., reaching the final analysis with less than 331 events, at the cost of statistical power;
- “**over-running**”, i.e., performing the final analysis with more than 331 events.

The latter scenario is not to be confused by the fact that there is additional data (therefore also more events) obtained within the timeframe from the interim analysis cut-off date to the date when an ultimate decision to close the study is communicated to investigators. [CHMP 2007] states that “in such a situation, it is accepted regulatory practice to base decision making on the final results of the trial (not the interim analysis). This is also in accordance with the intention to treat principle that all randomized patients¹⁰ should be analyzed. Obviously, overrunning patients need to be treated and observed according to the protocol and due attention should be given to this at the planning stage of the trial.”

Estimates of the treatment effects in- and excluding such extra information is provided in the Clinical Study Report.

18.3 Required number of events and power

In order to determine sample size and power, the following assumptions have been made in addition to the group-sequential design features described in Section 18.1:

- Constant hazard rate of 0.2231 per year for placebo
- Constant hazard rate of 0.145 per year for selexipag (hazard ratio of 0.65)
- Constant hazard rate of 0.051 per year for drop-out (end of study without a morbidity/mortality event) in both treatment groups

These lead to a total of 331 morbidity/mortality events confirmed by the CEC in order to obtain an overall power of 90% for rejection of the null hypothesis.

Under these assumptions, the probability to (correctly) reject the null hypothesis already at the interim stage is approximately 19%, and to (falsely) accept the null hypothesis at the interim stage is less than 0.2%.

If the true hazard ratio is 1, then the probability of (correctly) accepting the null hypothesis at the interim stage is approximately 50%.

¹⁰ and all available data from these patients

19 STATISTICAL ANALYSIS OF PATIENT DISPOSITION

The numbers of subjects included in each analysis set (described in Section 5) are presented. Reasons for excluding patients from analysis sets are summarized by frequency tables and listed.

Protocol violations are summarized by treatment group. Two further categories are displayed: violations of eligibility criteria and violations during the study conduct.

Screening failures, together with the reason for screening failure, are listed (information stored in IWRS data).

20 STATISTICAL ANALYSIS OF DEMOGRAPHIC AND BASELINE DISEASE CHARACTERISTICS

Demographic characteristics and disease characteristics (including 6MWD) at Baseline are summarized by treatment group and by geographical region.

Previous and concomitant diseases at Baseline are summarized by presenting, for each treatment group, the number and percentage of patients having a disease in each SOC, and having each individual disease (preferred term).

21 OVERVIEW OF ANALYSES FOR EFFICACY ENDPOINTS

Primary efficacy endpoint:

Time to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in the AC-065A302 Treatment Period (defined in Section 9)

General statistical methods for this endpoint are described in Sections 15.1 and 18, specifics in Section 22.

Primary analysis: group-sequential unstratified log-rank test on the FAS (overall one-sided significance level 0.005)

Supportive analyses (on the FAS if not otherwise specified):

- unstratified proportional hazards model
- log-rank test and proportional hazards model stratified by geographical region
- log-rank test and proportional hazards model stratified by PAH etiology
- log-rank test and proportional hazards model stratified by modified NYHA / WHO functional class at Baseline (classes I/II versus classes III/IV)
- log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline (no/yes)
- log-rank test and proportional hazards model stratified by modified NYHA / WHO functional class at Baseline and concomitant PAH medication at Baseline
- models attempting to address potential informative censoring, with the following circumstances identified as potentially informative censoring for the morbidity/mortality event:
 - morbidity/mortality events not confirmed by the CEC but study drug prematurely discontinued because of this event
 - patient lost-to follow-up
- log-rank tests and proportional hazards models ignoring all data up to 16 August 2011
- log-rank tests and proportional hazards models handling morbidity/mortality events confirmed by the CEC with onset date up to 16 August 2011 as events
- competing risk analysis as described in Section 15.1.4
- subgroup analyses as specified in Sections 6.3 and 17
- unstratified log-rank test and proportional hazards model based on the PPS
- unstratified log-rank test and proportional hazards model for time to first morbidity/mortality event (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) reported by the investigator (irrespective of confirmation by the CEC)

Secondary efficacy endpoints

In case the primary statistical analysis of the primary efficacy endpoint leads to rejection of the related null hypothesis, the null hypotheses for the secondary efficacy endpoints are tested in a conditional sequential manner (sequence as given below): a null hypothesis is rejected if and only if the main analysis of the endpoint and all main analyses of preceding secondary efficacy endpoints result in rejection of respective null hypotheses (using one-sided alpha of 0.005 or two-sided alpha of 0.01, respectively).

Secondary efficacy endpoint:

Absolute change from Baseline at Week 26 in 6MWD at trough (defined in Section 10.1)

General statistical methods for this endpoint are described in Sections 15.3.3 to 15.3.5, specifics in Section 23.1.

Main analysis: non-parametric ANCOVA (covariate: 6MWD at Baseline)

Supportive analyses (on the FAS if not otherwise specified):

- non-parametric ANCOVA with additional stratification for geographical region
- non-parametric ANCOVA with additional stratification for PAH etiology
- non-parametric ANCOVA with additional stratification for modified NYHA / WHO functional class at Baseline
- non-parametric ANCOVA with additional stratification for concomitant PAH medication at Baseline
- subgroup analyses as specified in Sections 6.3 and 17

All these analyses are also performed irrespective of the timing of dosing and 6MWT at Week 26.

In addition: non-parametric ANCOVA on the PPS excluding patients randomized to selexipag with an intake of study drug on the same day prior to the 6MWT at Week 26.

Secondary efficacy endpoint:

Absence of worsening from Baseline to Week 26 in modified NYHA/WHO functional class (defined in Section 10.2)

General statistical methods for this endpoint are described in Section 15.2, specifics in Section 23.2.

Main analysis: Cochran-Mantel-Haenszel test stratified by modified NYHA/WHO functional class at Baseline

Supportive analyses (on the FAS if not otherwise specified):

- common odds ratio estimate¹¹ and a two-sided 99% CI
- Cochran-Mantel-Haenszel test and two-sided 99% CI for common odds ratio with additional stratification for geographical region

¹¹ if assumption of common odds ratio is not rejected by a Breslow-Day test

- Cochran-Mantel-Haenszel test and two-sided 99% CI for common odds ratio with additional stratification for PAH etiology
- Cochran-Mantel-Haenszel test and two-sided 99% CI for common odds ratio with additional stratification for concomitant PAH medication at Baseline
- subgroup analyses as specified in Sections 6.3 and 17
- Cochran-Mantel-Haenszel test, common odds ratio estimate and two-sided 99% CI based on the PPS

Secondary efficacy endpoint:

Borg dyspnea index at Week 26 (defined in Section 10.3)

General statistical methods for this endpoint are described in Sections 15.3.3 to 15.3.5, specifics in Section 23.3.

Main analysis: non-parametric ANCOVA (covariate: Borg dyspnea index at Baseline)

Supportive analyses (on the FAS if not otherwise specified):

- non-parametric ANCOVA with additional stratification for geographical region
- non-parametric ANCOVA with additional stratification for PAH etiology
- non-parametric ANCOVA with additional stratification for modified NYHA / WHO functional class at Baseline
- non-parametric ANCOVA with additional stratification for concomitant PAH medication at Baseline
- subgroup analyses as specified in Sections 6.3 and 17
- non-parametric ANCOVA on the PPS

Secondary efficacy endpoint:

Time from randomization to death up to Study Closure (defined in Section 10.4)

General statistical methods for this endpoint are described in Section 15.1, specifics in Section 23.4.

Main analysis: unstratified log-rank test

Supportive analyses (on the FAS if not otherwise specified):

- unstratified proportional hazards model
- log-rank test and proportional hazards model stratified by geographical region
- log-rank test and proportional hazards model stratified by PAH etiology
- log-rank test and proportional hazards model stratified by modified NYHA / WHO functional class at Baseline
- log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline
- log-rank tests and proportional hazards models handling morbidity/mortality events confirmed by the CEC with onset date up to 16 August 2011 as events

- log-rank tests and proportional hazards models ignoring all data up to 16 August 2011
- subgroup analyses as specified in Sections 6.3 and 17
- log-rank test and proportional hazards model based on the PPS

Secondary efficacy endpoint:

Absolute change from Baseline to Week 26 in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score (defined in Section 10.5.1)

General statistical methods for this endpoint are described in Sections 15.3.3 to 15.3.5, specifics in Section 23.5.

Main analysis: non-parametric ANCOVA (covariate: sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score at Baseline) on the QoL analysis set

Supportive analyses (on the QoL analysis set):

- non-parametric ANCOVA with additional stratification for geographical region
- non-parametric ANCOVA with additional stratification for PAH etiology
- non-parametric ANCOVA with additional stratification for modified NYHA / WHO functional class at Baseline
- non-parametric ANCOVA with additional stratification for concomitant PAH medication at Baseline
- subgroup analyses as specified in Sections 6.3 and 17

Secondary efficacy endpoint:

Absolute change from Baseline to Week 26 in CAMPHOR 'Symptoms' score (defined in Section 10.5.1)

General statistical methods for this endpoint are described in Sections 15.3.3 to 15.3.5.

Main analysis: non-parametric ANCOVA (covariate: CAMPHOR 'Symptoms' score at Baseline)

Supportive analyses: same as for previous secondary efficacy endpoint.

Exploratory efficacy endpoints (all analyses are exploratory by definition)	
Endpoint	Statistical methods
Exploratory efficacy endpoints related to morbidity/mortality (defined in Sections 11.1 to 11.11)	
Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure	same as for primary efficacy endpoint (except for the group-sequential method), see also Section 15.1
Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period	same as for primary efficacy endpoint (except for the group-sequential method), see also Section 15.1
Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure	same as for primary efficacy endpoint (except for the group-sequential method), see also Section 15.1
Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period	same as for primary efficacy endpoint (except for the group-sequential method), see also Section 15.1
Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period	same as for primary efficacy endpoint (except for the group-sequential method), see also Section 15.1
Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period	same as for primary efficacy endpoint (except for the group-sequential method), see also Section 15.1
Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study closure	same as for primary efficacy endpoint (except for the group-sequential method), see also Section 15.1

Time from randomization to first CEC-confirmed morbidity/mortality event up to Study Closure	same as for primary efficacy endpoint (except for the group-sequential method), see also Section 15.1
Time from randomization to CEC-confirmed death due to PAH up to Study Closure	same as for primary efficacy endpoint (except for competing risk and group-sequential method), see Section 15.1
CEC-confirmed (potentially recurrent) hospitalizations due to worsening of PAH up to Study Closure	Andersen-Gill model, see Section 15.1.5
Time course of CEC-confirmed (potentially recurrent) hospitalization due to worsening of PAH, initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH, and death up to Study Closure	Multi-state Markov model analysis, see Section 15.1.6
Exploratory efficacy endpoints related to 6MWD (defined in Section 11.12)	
Absolute changes in 6MWD at trough from Baseline to all scheduled visits other than Week 26	• non-parametric ANCOVAs (covariate: 6MWD at Baseline) • separate non-parametric ANCOVAs with additional stratification for geographical region / PAH etiology / modified NYHA/WHO functional class at Baseline / concomitant PAH medication at Baseline
Absolute change in 6MWD at trough from Baseline to EOS	descriptive summary

Exploratory endpoints related to modified NYHA/WHO functional class (defined in Section 11.13)	
Absence of worsening from Baseline at scheduled visits other than Week 26	• Cochran-Mantel-Haenszel test stratified by modified NYHA/WHO functional class at Baseline • common odds ratio estimate and a two-sided 99% CI • separate Cochran-Mantel-Haenszel tests and two-sided 99% CIs for common odds ratio with additional stratification for geographical region / PAH etiology / concomitant PAH medication at Baseline • transition table from Baseline visit to post-Baseline visits
Absence of worsening from Baseline to EOS	descriptive summary
Exploratory efficacy endpoints related to Borg dyspnea index (defined in Section 11.14)	
Borg dyspnea index at scheduled visits other than Week 26	• non-parametric ANCOVA (covariate: Borg dyspnea index at Baseline) • separate non-parametric ANCOVAs with additional stratification for geographical region / PAH etiology / modified NYHA/WHO functional class at Baseline / concomitant PAH medication at Baseline
Borg dyspnea index at EOS	descriptive summary
Exploratory efficacy endpoints related to plasma NT pro-brain natriuretic peptide (defined in Section 11.15)	
Absolute change in plasma NT pro-BNP from Baseline at scheduled visits	descriptive summary and optionally a repeated measures mixed model with covariate plasma NT pro-BNP at Baseline
Absolute change in plasma NT pro-BNP from Baseline to EOS	descriptive summary

Exploratory efficacy endpoints related to CAMPHOR (defined in Section 11.16)	
Absolute change from Baseline to scheduled visits other than Week 26 in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score	• non-parametric ANCOVA (covariate: sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score at Baseline) • separate non-parametric ANCOVAs with additional stratification for geographical region / PAH etiology / modified NYHA/WHO functional class at Baseline / concomitant PAH medication at Baseline
Absolute change from Baseline to EOS in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score	descriptive summary
Absolute change from Baseline to scheduled visits other than Week 26 in CAMPHOR 'Symptoms' score	• non-parametric ANCOVA (covariate: CAMPHOR 'Symptoms' score at Baseline) • separate non-parametric ANCOVAs with additional stratification for geographical region / PAH etiology / modified NYHA/WHO functional class at Baseline / concomitant PAH medication at Baseline
Absolute change from Baseline to EOS in CAMPHOR 'Symptoms' score	descriptive summary

22 STATISTICAL ANALYSES OF THE PRIMARY EFFICACY ENDPOINT

See also Section 21 for an overview.

22.1 Hypotheses

Hypotheses are formulated in terms of “survival” functions $S_{m/m}(t)$, i.e., the probability that time to first morbidity/mortality event confirmed by the CEC (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is $\geq t$ for a day t relative to the date of randomization.

One-sided hypotheses are expressed in terms of the survival functions $S_{m/m,selexipag}(t)$ and $S_{m/m,placebo}(t)$.

$H_{0,m/m}$: $S_{m/m,selexipag}(t) \leq S_{m/m,placebo}(t)$ for all $t \geq 0$ versus

$H_{A,m/m}$: $S_{m/m,selexipag}(t) \geq S_{m/m,placebo}(t)$ for all $t \geq 0$ and $S_{m/m,selexipag}(t) > S_{m/m,placebo}(t)$ for some $t > 0$.

22.2 Statistical analysis

The overall one-sided significance level for the group-sequential procedure is set to 0.005, more details are provided in Section 18.1.

Kaplan-Meier estimates for the survival functions are provided, see Section 15.1.1. Censoring reasons are listed.

A table summarizing the number and percentage of each primary efficacy event type is presented (note that more than one event type is assigned if events have the same onset date).

22.2.1 Primary analysis

The primary analysis is performed on the FAS by a one-sided unstratified log-rank test in a group-sequential setting, see Section 18.2.

22.2.2 Supportive analyses

The following supportive analyses (based on the FAS if not otherwise stated) are planned:

- unstratified proportional hazards model
- log-rank test and proportional hazards model stratified by geographical region
- log-rank test and proportional hazards model stratified by PAH etiology
- log-rank test and proportional hazards model stratified by modified NYHA / WHO functional class at Baseline (classes I/II and classes III/IV)
- log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline (no/yes)
- log-rank test and proportional hazards model stratified by modified NYHA / WHO functional class at Baseline (classes I/II and classes III/IV) and concomitant PAH medication at Baseline (no/yes)

- unstratified and stratified tests/models attempting to address potential informative censoring, with the following circumstances identified as potentially informative censoring for the morbidity/mortality event:
 - morbidity/mortality event not confirmed by the CEC but study drug prematurely discontinued because of this event
 - patient lost to follow-up
- unstratified and stratified log-rank tests and proportional hazards models ignoring all data up to 16 August 2011
- unstratified and stratified log-rank tests and proportional hazards models handling morbidity/mortality events confirmed by the CEC with onset date up to 16 August 2011 as events
- competing risk analysis as described in Section 15.1.4
- subgroup analyses as specified in Sections 6.3 and 17
- unstratified log-rank test and proportional hazards model based on the PPS
- unstratified log-rank test and proportional hazards model for time to first morbidity/mortality event (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) reported by the investigator (irrespective of confirmation by the CEC).

22.2.3 Further information

For the set of all morbidity/mortality events reported by investigators (up to 7 days after last study drug intake in the AC-065A302 Treatment Period), the following information is listed and summarized in frequency tables by treatment:

- dose of PDE-5 and/or ERA concomitant medication within the interval starting 2 weeks before the onset of a morbidity/mortality event and ending with the CEC adjudication date (in case the event is based on disease progression, the dates of the 6MWD tests are listed as well)
- for the subset of morbidity/mortality events adjudicated in both CEC systems¹²:
 - agreement as confirmed event
 - agreement as non-confirmed event
 - disagreement: confirmed as event in original CEC system but not in new CEC system
 - disagreement: not confirmed as event in original CEC system but confirmed in new CEC system
- disagreement between investigator and new CEC system

¹² The original CEC system was replaced in November 2012 by a new CEC system recording more information (details are described in the CEC Charter). All events adjudicated in the old CEC system were re-adjudicated in the new CEC system.

Censoring (other than censoring introduced by the analysis cut-off date) is illustrated by Kaplan-Meier curves where “censoring” (for other reasons than reaching the analysis cut-off date) is handled as “event” and the CEC confirmed morbidity/mortality events as well as censoring introduced by the analysis cut-off date) is handled as “censored”.

23 STATISTICAL ANALYSES OF SECONDARY EFFICACY ENDPOINTS

See also Section 21 for an overview.

In case the primary statistical analysis of the primary efficacy endpoint leads to rejection of the related null hypothesis, the null hypotheses for the secondary efficacy endpoints are tested in a conditional sequential manner. The sequence is given in Section 10 (used here in Section 23 as well) and a null hypothesis is rejected if and only if the main analysis of the endpoint and all main analyses of preceding secondary efficacy endpoints result in rejection of respective null hypotheses. This procedure restricts the family-wise type-I-error rate to the overall assigned one-sided alpha of 0.005 (two-sided alpha of 0.01, respectively).

23.1 Absolute change from Baseline in 6MWD at trough at Week 26

The absolute change from Baseline in 6MWD is expected to be deviating from a normal distribution and is analyzed as described in Section 15.3.3. For patients unable to walk at Week 26 (includes patients deceased), a 0 is imputed for 6MWD at trough at Week 26; other missing values are handled as described in Section 16.5.

23.1.1 Hypotheses

Null hypothesis $H_{0,6MWD}$: “Distributions of change from Baseline in 6MWD at trough at Week 26, adjusted for 6MWD at Baseline, are identical for selexipag and placebo”

is tested against the alternative hypothesis $H_{A,6MWD}$: “Distribution of change from Baseline in 6MWD at trough at Week 26, adjusted for 6MWD at Baseline, is more favorable for selexipag as compared to placebo”.

23.1.2 Statistical analysis

In addition to a table with the usual descriptive statistics for each treatment group, the following are provided [see Sections 15.3.4 and 15.3.5]:

- point estimate and two-sided 99% CI for the location shift (selexipag minus placebo) in change from Baseline at Week 26
- point estimate (based on the Mann-Whitney statistic) for the probability to obtain a larger change to Baseline in 6MWD at trough at Week 26 for a patient treated with selexipag rather than with placebo.

Details on the 6MWD tests are listed.

23.1.2.1 Main analysis

The main analysis is performed on the FAS but excluding patients randomized to selexipag with an intake of study drug on the same day prior to the 6MWT at Week 26. A non-parametric ANCOVA as described in Section 15.3.3 is used.

23.1.2.2 Supportive analyses

The following supportive analyses are planned on the FAS but excluding patients randomized to selexipag with an intake of study drug on the same day prior to the 6MWT at Week 26:

- non-parametric ANCOVA with additional stratification for geographical region
- non-parametric ANCOVA with additional stratification for PAH etiology
- non-parametric ANCOVA with additional stratification for modified NYHA / WHO functional class at Baseline (classes I/II versus classes III/IV)
- non-parametric ANCOVA with additional stratification for concomitant PAH medication at Baseline (no/yes)
- subgroup analyses as specified in Sections 6.3 and 17.

These analyses are also performed on the entire FAS irrespective of the timing of dosing and 6MWT at Week 26.

In addition, an analysis is performed on the PPS but excluding patients randomized to selexipag with an intake of study drug on the same day prior to the 6MWT at Week 26.

23.2 Absence of worsening from Baseline in modified NYHA/WHO functional class at Week 26

Patients in functional class IV at Baseline are excluded from the analysis because, by definition, they cannot worsen. Handling of missing values is described in Section 16.6.

23.2.1 Hypotheses

Let $\pi_{sel,k,W}$ and $\pi_{pla,k,W}$, $k=1,2,3$, denote the unknown probabilities for absence of worsening from Baseline in modified NYHA/WHO functional class at Week 26 in patients with modified NYHA/WHO functional class k at Baseline for selexipag and placebo, respectively.

The null hypothesis

H_0 : $\pi_{selexipag,k,W} = \pi_{placebo,k,W}$ for all $k=1,2,3$ “in all 3 strata the probabilities for absence of worsening in modified NYHA/WHO functional class at Week 26 are the same for both treatment groups”

is tested against the two-sided alternative hypothesis

H_A : $\pi_{selexipag,j,W} \neq \pi_{placebo,j,W}$ for at least one stratum j with $1 \leq j \leq 3$ “for at least one stratum the probabilities for absence of worsening in modified NYHA/WHO functional class at Week 26 are different between selexipag and placebo”.

23.2.2 Statistical analysis

Descriptive summaries are provided by frequency tables, overall and by modified NYHA/WHO function class at Baseline.

23.2.2.1 Main analysis

The main analysis is performed on the FAS but excluding patients in functional class IV at Baseline. A Cochran-Mantel-Haenszel test stratified by modified NYHA/WHO functional class at Baseline [see Section 15.2.2] is used.

23.2.2.2 Supportive analyses

The following supportive analyses (based on the FAS but excluding patients in functional class IV at Baseline) are planned:

- if the assumption of a common odds ratio is not rejected by the Breslow-Day test [see Section 15.2.2], the effect of selexipag relative to placebo is expressed by the common odds ratio estimate and a two-sided 99% CI
- Cochran-Mantel-Haenszel test and two-sided 99% CI for common odds ratio with additional stratification for geographical region
- Cochran-Mantel-Haenszel test and two-sided 99% CI for common odds ratio with additional stratification for PAH etiology
- Cochran-Mantel-Haenszel test and two-sided 99% CI for common odds ratio with additional stratification for concomitant PAH medication at Baseline (no/yes)
- subgroup analyses as specified in Sections 6.3 and 17.

In addition, Cochran-Mantel-Haenszel test and two-sided 99% CI based on the PPS are conducted.

23.3 Borg dyspnea index at Week 26

Borg dyspnea index is not assumed to be an interval-scaled variable and is analyzed as described in Section 15.3.3 with handling of missing values as described in Section 16.5.

23.3.1 Hypotheses

Null hypothesis $H_{0,BDI}$: “Distributions of Borg dyspnea index at Week 26, adjusted for Borg dyspnea index at Baseline, are identical for selexipag and placebo”

is tested against the alternative hypothesis $H_{A,BDI}$: “Distribution of Borg dyspnea index at Week 26, adjusted for Borg dyspnea index at Baseline, is more favorable for selexipag as compared to placebo”.

23.3.2 Statistical analysis

In addition to a table with the usual descriptive statistics for each treatment group, the following are provided [see Sections 15.3.4 and 15.3.5]:

- point estimate and two-sided 99% CI for the difference of medians (selexipag minus placebo) in Borg dyspnea index at Week 26
- point estimate (based on the Mann-Whitney statistic) for the probability to obtain a lower Borg dyspnea index at Week 26 for a patient treated with selexipag rather than with placebo.

23.3.2.1 Main analysis

The main analysis is performed on the FAS using a non-parametric ANCOVA as described in Section [15.3.3](#).

23.3.2.2 Supportive analyses

The following supportive analyses (based on the FAS if not otherwise stated) are planned:

- non-parametric ANCOVA with additional stratification for geographical region
- non-parametric ANCOVA with additional stratification for PAH etiology
- non-parametric ANCOVA with additional stratification for modified NYHA / WHO functional class at Baseline (classes I/II versus classes III/IV)
- non-parametric ANCOVA with additional stratification for concomitant PAH medication at Baseline (no/yes)
- subgroup analyses as specified in Sections [6.3](#) and [17](#)
- non-parametric ANCOVA based on the PPS.

23.4 Time to death up to Study Closure

23.4.1 Hypotheses

Hypotheses are formulated in terms of survival functions $S_d(t)$, i.e., the probability that time to death (up to study closure) is $\geq t$ for a day t relative to the date of randomization.

One-sided hypotheses are expressed in terms of the survival functions $S_{d,selexipag}(t)$ and $S_{d,placebo}(t)$.

$H_{0,d}$: $S_{d,selexipag}(t) \leq S_{d,placebo}(t)$ for all $t \geq 0$ versus

$H_{A,d}$: $S_{d,selexipag}(t) \geq S_{d,placebo}(t)$ for all $t \geq 0$ and $S_{d,selexipag}(t) > S_{d,placebo}(t)$ for some $t > 0$.

23.4.2 Statistical analysis

Kaplan-Meier estimates for the survival functions are provided, see Section [15.1.1](#). Censoring reasons are listed.

23.4.2.1 Main analysis

The main analysis is performed on the FAS by a one-sided unstratified log-rank test, see Section [15.1.2.1](#).

23.4.2.2 Supportive analyses

The following supportive analyses (based on the FAS if not otherwise stated) are planned:

- unstratified proportional hazards model
- log-rank test and proportional hazards model stratified by geographical region
- log-rank test and proportional hazards model stratified by PAH etiology
- log-rank test and proportional hazards model stratified by modified NYHA / WHO functional class at Baseline (classes I/II and classes III/IV)

- log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline (no/yes)
- unstratified and stratified log-rank tests and proportional hazards models ignoring all data up to 16 August 2011
- unstratified and stratified log-rank tests and proportional hazards models handling deaths up to 16 August 2011 as events
- subgroup analyses as specified in Sections 6.3 and 17
- unstratified log-rank test and proportional hazards model based on the PPS.

23.5 Absolute change from Baseline to Week 26 in sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ score

Absolute change from Baseline in sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ score at Week 26 is not assumed to be an interval-scaled variable and is analyzed as described in Section 15.3.3 with handling of missing values as described in Section 16.5.

23.5.1 Hypotheses

Null hypothesis $H_{0,Breath}$: “Distributions of absolute change from Baseline in sub-scale ‘Breathlessness’ at Week 26, adjusted for sub-scale ‘Breathlessness’ at Baseline, are identical for selexipag and placebo”

is tested against the alternative hypothesis $H_{A,Breath}$: “Distribution of absolute change from Baseline in sub-scale ‘Breathlessness’ at Week 26, adjusted for sub-scale ‘Breathlessness’ at Baseline, is more favorable for selexipag as compared to placebo”.

23.5.2 Statistical analysis

In addition to a table with the usual descriptive statistics for each treatment group, the following are provided [see Sections 15.3.4 and 15.3.5]:

- point estimate and two-sided 99% CI for the difference of medians (selexipag minus placebo) for absolute change to Baseline in sub-scale ‘Breathlessness’ at Week 26
- point estimate (based on the Mann-Whitney statistic) for the probability to obtain a lower change to Baseline in sub-scale ‘Breathlessness’ at Week 26 for a patient treated with selexipag rather than with placebo.

23.5.2.1 Main analysis

The main analysis is performed on the QoL analysis set using a non-parametric ANCOVA as described in Section 15.3.3.

23.5.2.2 Supportive analyses

The following supportive analyses (based on the QoL analysis set) are planned:

- non-parametric ANCOVA with additional stratification for geographical region
- non-parametric ANCOVA with additional stratification for PAH etiology

- non-parametric ANCOVA with additional stratification for modified NYHA / WHO functional class at Baseline (classes I/II versus classes III/IV)
- non-parametric ANCOVA with additional stratification for concomitant PAH medication at Baseline (no/yes)
- subgroup analyses as specified in Sections 6.3 and 17.

23.6 Absolute change from Baseline to Week 26 in CAMPHOR ‘Symptoms’ score

Absolute change from Baseline in CAMPHOR ‘Symptoms’ score at Week 26 is not assumed to be an interval-scaled variable and is analyzed as described in Section 15.3.3 with handling of missing values as described in Section 16.5.

23.6.1 Hypotheses

Null hypothesis $H_{0,\text{Symp}}$: “Distributions of absolute change from Baseline in ‘Symptoms’ score at Week 26, adjusted for ‘Symptoms’ score at Baseline, are identical for selexipag and placebo”

is tested against the alternative hypothesis $H_{A,\text{Symp}}$: “Distribution of absolute change from Baseline in ‘Symptoms’ score at Week 26, adjusted for ‘Symptoms’ score at Baseline, is more favorable for selexipag as compared to placebo”.

23.6.2 Statistical analysis

Statistical analysis is performed in analogy to Section 23.5.2.

24 STATISTICAL ANALYSIS OF EXPLORATORY EFFICACY ENDPOINTS

See Section 21 for an overview.

If not otherwise indicated, significance levels are set to one-sided 0.005 (equivalent to two-sided 0.01). However, two-sided 95% CIs are provided.

24.1 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure

Hypotheses and statistical analyses are analog to the ones for the primary efficacy endpoint except for the group-sequential method.

24.2 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period

Hypotheses and statistical analyses are analog to the ones for the primary efficacy endpoint except for the group-sequential method.

24.3 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure

Hypotheses and statistical analyses are analog to the ones for the primary efficacy endpoint except for the group-sequential method.

24.4 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period

Hypotheses and statistical analyses are analog to the ones for the primary efficacy endpoint except for the group-sequential method.

24.5 Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period

Hypotheses and statistical analyses are analog to the ones for the primary efficacy endpoint except of the group-sequential method.

24.6 Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period

Hypotheses and statistical analyses are analog to the ones for the primary efficacy endpoint except of the group-sequential method.

24.7 Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study Closure

Hypotheses and statistical analyses are analog to the ones for the primary efficacy endpoint except for the group-sequential method.

24.8 Time from randomization to first CEC-confirmed morbidity/mortality event up to Study Closure

Hypotheses and statistical analyses are analog to the ones for the primary efficacy endpoint except for the group-sequential method.

24.9 Time from randomization to CEC-confirmed death due to PAH up to Study Closure

Hypotheses and statistical analyses are analog to the ones for the primary efficacy endpoint except for competing risk and group-sequential methods.

24.10 CEC-confirmed (potentially recurrent) hospitalizations due to worsening of PAH up to Study Closure

Statistical analysis is based on the Andersen-Gill model with a robust sandwich-type variance estimate, see Section 15.1.5. The treatment effect of selexipag compared to placebo is estimated by the hazard ratio and CI.

24.11 Time course of CEC-confirmed (potentially recurrent) morbidity/mortality events hospitalization due to worsening of PAH, initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH, and death up to Study Closure

It is assumed that the multi-state process $(X_t)_{t \geq 0}$ (see Section 11.11 for definition) fulfills the Markov property, i.e., transition probabilities depend only on the current time and the currently occupied state (time-inhomogeneous Markov process).

Statistical analysis follows Sections 15.1.6.2 and 15.1.6.3:

- For states $[k] \neq [m]$, the cumulative transition hazard up to time t is estimated by the Nelson-Aalen estimator.
- From these, the Aalen-Johansen estimator of the matrix of transition probabilities is derived. Two-sided point wise 95% CIs for the components of the transition probability matrix (for selected times s and t) are calculated.
- Hazard ratios for the transitions are estimated together with two-sided 95% CIs.

24.12 Other exploratory efficacy endpoints

Absolute changes from Baseline in 6MWD, in sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ and in CAMPHOR ‘Symptoms’ score at scheduled visits other than Week 26 are analyzed in analogy to the corresponding secondary endpoints. The results for the EOS visit are summarized descriptively.

The absence of worsening from Baseline in modified NYHA/WHO functional class at scheduled visits other than Week 26 is analyzed in analogy to the corresponding secondary endpoint. For each post-Baseline scheduled visit, a transition table from modified NYHA/WHO functional class at Baseline is provided. Number and percentage of patients in each functional class at Baseline and at each post-Baseline scheduled visit are displayed, as well as number and percentage of patients having an improvement/no change/worsening from Baseline at each post-Baseline scheduled visit. The results for the EOS visit are summarized descriptively.

The Borg dyspnea index at scheduled visits other than Week 26 is analyzed in analogy to the corresponding secondary endpoint. The results for the EOS visit are summarized descriptively.

Plasma NT pro-BNP levels over time are displayed using descriptive statistics by treatment group. A repeated measures mixed model [see Section [15.3.1](#)] with Baseline value as covariate may be used to analyze the effect of selexipag relative to placebo over time. The results for the EOS visit are summarized descriptively.

25 EXPLORATORY ANALYSIS OF DOSE-RESPONSE RELATIONSHIP

Interpretation of results from exploratory analyses of dose-response relationships (described below) is limited as the individual selexipag MTD in study AC-065A302 has not been randomly assigned to patients but is itself a post-Baseline outcome.

25.1 Relationship between individual MTD in study AC-065A302 and primary efficacy endpoint

Statistical analyses of the selexipag dose effect on time to first CEC-confirmed morbidity/mortality event (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) relative to placebo are performed as follows:

- unstratified proportional hazards model with individual selexipag MTD in study AC-065A302 as continuous single covariate
- unstratified proportional hazards model with individual selexipag MTD in study AC-065A302 as categorical single covariate (MTD categories: 200 to 400 µg, 600 to 1000 µg, 1200 to 1600 µg)
- unstratified proportional hazards model with individual selexipag MTD in study AC-065A302 as continuous covariate separately for patients with / without selexipag dose reductions because of “AEs typical for IP-receptor agonists”, defined by the following PTs:
 - jaw pain / temporomandibular joint syndrome / arthralgia / musculoskeletal pain / myalgia / pain in extremity
 - flushing
 - nausea / vomiting
 - diarrhoea
 - headache(both subgroups compared to all patients randomized to placebo)
- unstratified proportional hazards model with individual selexipag MTD in study AC-065A302 as continuous covariate separately for patients with / without “AEs typical for IP-receptor agonists” (both subgroups compared to all patients randomized to placebo)
- unstratified proportional hazards model with individual selexipag MTD in study AC-065A302 as categorical covariate separately for patients with / without selexipag dose reductions because of “AEs typical for IP-receptor agonists” (both subgroups compared to all patients randomized to placebo)
- unstratified proportional hazards model with individual selexipag MTD in study AC-065A302 as categorical covariate separately for patients with / without “AEs typical for IP-receptor agonists” (both subgroups compared to all patients randomized to placebo).

As an additional exploratory analysis, time to first CEC-confirmed morbidity/mortality event ignoring all data for the first 84 days after randomization is displayed by a Kaplan-Meier plot by study treatment.

25.2 Relationship between individual MTD up to Week 26 in study AC-065A302 and absolute change from Baseline in 6MWD at Week 26

Statistical analyses of the selexipag dose effect on the absolute change from Baseline in 6MWD (at trough / all) relative to placebo are performed in analogy to Section 25.1 but the proportional hazards model is replaced by the statistical analysis method for absolute change to Baseline in 6MWD at Week 26 described in Section 23.1.

26 STATISTICAL ANALYSIS OF PHARMACOECONOMIC ENDPOINTS

26.1 Annualized number of hospitalizations (for all causes) up to the EOS visit

A negative binomial model as described in Section 15.2.3 is used for the statistical analysis. The null hypothesis of no treatment effect ($\theta_{\text{treatment}}=0$) is tested by a two-sided Wald-type test at a two-sided significance level of 0.01. A two-sided 99% Wald CI is calculated for the relative reduction in mean annualized hospitalization rate for selexipag compared to placebo.

26.1.1 Main analysis

The main analysis is performed on the FAS with study treatment as the only covariate.

26.1.2 Supportive analyses

The following supportive analyses (based on the FAS if not otherwise stated) are planned:

- negative binomial model with covariate geographical region in addition to treatment
- negative binomial model with covariate PAH etiology in addition to treatment
- negative binomial model with covariate modified NYHA / WHO functional class at Baseline (classes I/II and classes III/IV) in addition to treatment
- negative binomial model with covariate concomitant PAH medication at Baseline (no/yes) in addition to treatment
- subgroup analyses as specified in Sections 6.3 and 17
- negative binomial model with treatment as the only covariate based on the PPS.

26.2 Annualized number of PAH-related hospitalizations up to the EOS visit

Statistical analysis is performed in analogy to Section 26.1.

26.3 Occurrence of recurrent hospitalizations (for all causes) up to the EOS visit

The Andersen-Gill model (with a robust sandwich-type variance estimate) as described in Section 15.1.5 is used to estimate the hazard ratio and CI.

26.3.1 Main analysis

The main analysis is performed on the FAS with an unstratified Andersen-Gill model.

26.3.2 Supportive analyses

The following supportive analyses (based on the FAS if not otherwise stated) are planned:

- Andersen-Gill model stratified by geographical region
- Andersen-Gill model stratified by PAH etiology
- Andersen-Gill model stratified by modified NYHA / WHO functional class at Baseline (classes I/II and classes III/IV)
- Andersen-Gill model stratified by concomitant PAH medication at Baseline (no/yes)
- subgroup analyses as specified in Sections 6.3 and 17

- unstratified Andersen-Gill model based on the PPS.

26.4 Annualized number of days spent in hospital for all causes up to the EOS visit

A negative binomial model as described in Section 15.2.3 is used for the statistical analysis. The null hypothesis of no treatment effect ($\theta_{\text{treatment}} = 0$) is tested by a two-sided Wald-type test at a two-sided significance level of 0.01. A two-sided 99% Wald CI is calculated for the relative reduction in mean annualized number of days spent in hospital for selexipag compared to placebo.

26.4.1 Main analysis

The main analysis is performed on the FAS with treatment as the only covariate.

26.4.2 Supportive analyses

The following supportive analyses (based on the FAS if not otherwise stated) are planned:

- negative binomial model with covariate geographical region in addition to treatment
- negative binomial model with covariate modified NYHA / WHO functional class at Baseline (classes I/II and classes III/IV) in addition to treatment
- negative binomial model with covariate concomitant PAH medication at Baseline (no/yes) in addition to treatment
- subgroup analyses as specified in Sections 6.3 and 17
- negative binomial model (with treatment as the only covariate) based on the PPS.

26.5 Annualized number of days spent in hospital for PAH-related causes up to the EOS visit

Statistical analysis is performed in analogy to Section 26.4.

27 STATISTICAL ANALYSIS OF PHARMACOKINETIC ENDPOINTS

Plasma trough concentrations of ACT-293987 (selexipag) and ACT-333679 per time point (after first study drug intake) are summarized. Descriptive statistics include the number of observations, arithmetic mean, geometric mean, minimum, median, maximum, SD, coefficient of variation (CV%), and two-sided 95% CIs of the means. The CI for the geometric mean is based on log-transformed data and presented back-transformed to the original scale.

28 STATISTICAL ANALYSIS OF SAFETY AND TOLERABILITY ENDPOINTS

For quantitative safety endpoints the descriptive statistics are the following: number of patients with the assessment, mean, median, SD, quartiles, minimum, and maximum.

28.1 Analysis of adverse events

28.1.1 Standard display of adverse events

Crude incidence summaries (see subsequent paragraph) of treatment-emergent AEs are displayed separately for

- study AC-065A302 (comparing selexipag to placebo on an inter-patient basis)
- study AC-065A303 (only selexipag)
- intra-patient comparison for patients treated with placebo in study AC-065A302 and with selexipag in study AC-065A303
- intra-patient comparison for patients treated with selexipag in both studies

The number and percentage of patients who experienced treatment-emergent AEs are tabulated by treatment, by system organ class (SOC), preferred term (PT) within each SOC and treatment. Patients with AEs coded with more than one PT are counted on each PT. Treatment-emergent AEs are also tabulated by PT (sorted by descending frequency in the selexipag group) and treatment.

Further, treatment-emergent AEs are tabulated by maximum severity and by investigator's assessment of relationship to study drug. If an AE is reported more than once within a patient, the worst category is used.

AEs leading to permanent discontinuation of study drug and SAEs are reported similarly to AEs. For patients who discontinued the study for withdrawal of consent all AEs ongoing at study discontinuation date are listed.

In addition, a table of non-serious treatment-emergent AEs (all AEs excluding SAEs) are tabulated by SOC and PT. Preferred terms are presented by descending order of frequency for AEs with frequency $\geq 5\%$. All other AE PTs with frequency below 5% are combined. This table is a request from clintrials.gov and is not to be included in the CSR.

28.1.2 Reporting and analysis of AEs of special interest

Some aspects for reporting of treatment-emergent AEs of special interest are provided already in Section 14.2.4. In addition to the crude incidences, the relative risk estimator is provided together with two-sided 95% CI.

In addition, the occurrence of (potentially recurrent) specific types of AE of special interest is analyzed within the Andersen-Gill model [see Section 15.1.5], hazards ratios (relative to placebo) with two-sided 95% CIs are provided and also displayed in a graphical form. Patients not experiencing a specific type of an AE of special interest are censored as follows:

- for patients who did not permanently discontinue GRIPHON study drug prior to the analysis cut-off date, censoring date is the analysis cut-off date
- for patients who permanently discontinued GRIPHON study drug prior to the analysis cut-off date and did not enter study AC-065A303, censoring date is the date of permanent discontinuation of GRIPHON study drug plus 7 days
- for patients who permanently discontinued GRIPHON study drug before the data cut-off date and entered study AC-065A303, censoring date is minimum[date of permanent discontinuation of GRIPHON study drug plus 7 days, date of first selexipag dose in study AC-065A303].

“AEs typical for IP-receptor agonist”, as defined in Section 25, are summarized separately for Titration Period and Maintenance Period for patients who were treated in both periods (AEs started in the Titration Period and ongoing in the Maintenance Period are counted for both periods).

28.2 Analysis of ECG data

HR, PR, PQ, QRS, QT and QTcF are summarized by descriptive statistics for the absolute values, for the changes from Baseline at each time point and to the highest/lowest (where applicable) treatment-emergent value.

Number and percentage of patients who experienced treatment-emergent ECG abnormalities coded with the same PT are summarized by treatment group.

Number and percentage of patients with QTcF prolongation [see Section 14.3.3] are summarized by gender and treatment group.

The ECG results of all patients having at least one of these QTcF prolongations are listed separately.

28.3 Analysis of laboratory test results

Treatment-emergent laboratory tests are summarized by:

- descriptive statistics for the laboratory test results at all scheduled visits (separately by factors, e.g., gender or age category, if associated with different normal ranges for a laboratory test)
- descriptive statistics for the highest/lowest (where applicable) post-Baseline laboratory test result (separately by factors, e.g., gender or age category, if associated with different normal ranges for a laboratory test)
- descriptive statistics for absolute change from Baseline at all scheduled visits
- descriptive statistics for absolute change from Baseline to highest/lowest (where applicable) post-Baseline laboratory test result

Treatment-emergent (marked/alert) laboratory abnormalities [see Table 7] are summarized separately for both directions, e.g., a patient with treatment-emergent HH and LL for the same laboratory test (at different visits) is counted for each direction in summary tables.

Number and percentage of patients with treatment-emergent elevated liver function tests are tabulated for the categories as defined in Section 14.4.5.

Frequencies of shift from Baseline to the worst treatment-emergent value are provided based on the definition of (marked) laboratory test abnormalities. For each direction, if applicable, the worst category is taken for the analysis.

28.3.1 Analysis of drug-induced serious hepatotoxicity (eDISH)

A graphical representation of total bilirubin versus ALT is produced to identify possible cases of Hy's Law. The graph displays the peak of total bilirubin times $\times$ ULN against the peak ALT $\times$ ULN, on a $\log_{10}$ scale for all patients having assessments $> 0.0625 \times$ ULN for both peaks [Watkins 2011]. Two reference lines are plotted identifying the $2 \times$ ULN for total bilirubin and $3 \times$ ULN for ALT.

Normal patients are on the left lower quadrant, possible Hy's Law cases appear on the right upper quadrant. The latter patients are listed in addition.

28.4 Analysis of vital signs and body weight

Vital signs and body weight are summarized by descriptive statistics for the absolute values, for absolute changes from Baseline at each scheduled visit and to the highest/lowest (where applicable) on treatment value.

28.5 Analysis of study drug exposure

Study drug exposure is summarized by descriptive statistics for each treatment group including:

- exposure intervals: 1 day to 8 weeks, 57 days to 16 weeks, 112 days to 26 weeks, 182 days to 52 weeks, 364 days to 78 weeks, and at every interval of 26 weeks thereafter, showing number and percentage of patients in the safety analysis set
- cumulative exposure intervals: at least 8 weeks, at least 16 weeks, at least 26 weeks, at least 52 weeks, at least 78 weeks, and at every interval of 26 weeks thereafter, showing number and percentage of patients in the safety analysis set
- inverse cumulative distribution function
- MTDs (as defined for studies AC-065A302 and AC-065A303 in Section 7) are summarized by number of patients and percentage.

28.6 Analysis of premature permanent discontinuation of study drug

Primary reason for premature discontinuation of study drug is tabulated by treatment group and dose of study drug.

For both treatment groups, demographic and Baseline characteristics are tabulated for patients with or without premature permanent discontinuation of study drug.

28.7 Analysis of medications and PAH specific medication

For each treatment group, previous medications, medications concomitant at Baseline and medication started during treatment period are summarized by number and percentage of patients having any medication, having a medication in each ATC class, and having each individual medication (preferred term).

In the total number of treatments the preferred term / medication linked to more than one class within the same patient is counted only once. Thus total number of treatments in the main total may not equal the sum of the subtotals by class.

For each preferred term the class/es are allocated using the 3 digits of the ATC code.

28.8 Ophthalmologic sub-study

Baseline findings and post-Baseline findings and variables are summarized descriptively by study treatment.

For the absolute change from Baseline in retinal arterial tortuosity to each visit up to EOS, two-sided 95% CIs for the difference of selexipag and placebo means (assuming normal distribution) are calculated.

29 DEFINITIONS

29.1 Formulas

Month = 30 days

Weight (kg) = weight (lbs)*0.4536

Height (cm) = height (inch)*2.54

Body Mass Index BMI = weight(kg) / (height(m))²

29.2 Dates

29.2.1 Randomization date in study AC-065A302

The randomization date in study AC-065A302 is taken from the IWRS/IVRS database (ICON) as the date of randomization with VisitCode="V1".

29.2.2 Study drug start date and study drug end date in study AC-065A302

Study drug start date in study AC-065A302 is taken from the "Start Date" of the first interval (sorted by chronological order) in the Study Drug Log CRF.

Study drug end date in study AC-065A302 is taken from the "End Date" of the last interval (sorted by chronological order of all records not completely empty) in the Study Drug Log CRF (with missing at the end of the ordering). If the study drug end date is missing, study drug is considered as ongoing at the analysis cut-off date.

29.2.3 Study drug start date and study drug end date in study AC-065A303

Study drug start date in study AC-065A303 is taken from the "Start Date" of the first interval (sorted by chronological order) in the Study Drug Log CRF.

Study drug end date in study AC-065A303 is taken from the "End Date" of the last interval (sorted by chronological order) in the Study Drug Log CRF (with missing at the end of the ordering). If the study drug end date is missing, study drug is considered as ongoing at the analysis cut-off date.

29.2.4 Date of last contact

The date of last contact is the last date the patient was known to be alive based on CRF data (irrespective of study), i.e., the maximum of [visit dates, sample dates, AE onset dates, morbidity events, date of last contact from the Survival Follow-Up CRF page].

29.3 Study Days

Study Day in study AC-065A302

AC-065A302 Study Day refers to the number of days elapsed since the day of study drug start in AC-065A302 plus 1 (i.e., AC-065A302 Study Day 1 is the day of study drug start in study AC-065A302). For dates prior to start of study drug in study AC-065A302, Study Day is the negative number of days elapsed between the date under consideration and the

day of study drug start in study AC-065A302. Therefore, the Study Day is always different from 0.

Study Day in study AC-065A303

AC-065A303 Study Day refers to the number of days elapsed since the day of study drug start in AC-065A303 plus 1 (i.e., AC-065A303 Study Day 1 is the day of study drug start in study AC-065A303). For dates prior to start of study drug in study AC-065A303, Study Day is the negative number of days elapsed between the date under consideration and the day of study drug start in study AC-065A303. Therefore, the Study Day is always different from 0.

Study Day in combined studies AC-065A302 and AC-065A303

For the combined studies AC-065A302 and AC-065A303, Overall Study Day refers to the number of days elapsed since the day of study drug start in AC-065A302 plus 1 (i.e., Overall Study Day 1 is the day of study drug start in study AC-065A302). For dates prior to start of study drug in study AC-065A302, Overall Study Day is the negative number of days elapsed between the date under consideration and the day of study drug start in study AC-065A302. Therefore, the Overall Study Day is always different from 0.

29.4 Time windows

In order to summarize data descriptively over time in an at least approximate order, all recorded relevant assessments (for both studies AC-065A302 and AC-065A303, if applicable) are assigned to the most appropriate “visit window”. These visit windows are based on respective Study Day [see Section 29.3] as described in the tables below¹³.

Should more than one assessment fall within the same time window, then the closest value to the nominal planned time point is assigned to the respective visit window. In case of values that are equidistant to the planned time point, the worst of these values is used in case of continuous data, the maximum of these values in case of ordered categorical data.

¹³ Values not retained in summaries over time are kept in the datasets and used as appropriate.

Table 9 Visit windows for study AC-065A302

Visit window	AC-065A302 Study Day (nominal value)	Lower limit for AC-065A302 Study Day	Upper limit for AC-065A302 Study Day
Baseline	1	not applicable	1
Week 4	28	2	42
Week 8	56	43	84
Week 16	112	85	147
Week 26	182	148	271
Month 12	360	272	450
Month 18	540	451	630
Month 24	720	631	810
Month 30	900	811	990
Month 36	1080	991	1170
Month 42	1260	1171	1350
Month 48	1440	1351	1530
Month 54	1620	1531	1710
Month 60	1800	1711	1890

Table 10 Visit windows for study AC-065A303

Visit window	AC-065A303 Study Day (nominal value)	Lower limit for AC-065A303 Study Day	Upper limit for AC-065A303 Study Day
Day 1	1	1	1
Week 4	28	2	42
Week 8	56	43	84
Week 16	112	85	147
Week 26	182	148	271
Month 12	360	272	450
Month 18	540	451	630
Month 24	720	631	810
Month 30	900	811	990
Month 36	1080	991	1170
Month 42	1260	1171	1350
Month 48	1440	1351	1530
Month 54	1620	1531	1710
Month 60	1800	1711	1890

Table 11 Visit windows for combined studies AC-065A302 and AC-065A303

Visit window	Overall Study Day (nominal value)	Lower limit for Overall Study Day	Upper limit for Overall Study Day
Baseline	1	not applicable	1
Week 4	28	2	42
Week 8	56	43	84
Week 16	112	85	147
Week 26	182	148	271
Month 12	360	272	450
Month 18	540	451	630
Month 24	720	631	810
Month 30	900	811	990
Month 36	1080	991	1170
Month 42	1260	1171	1350
Month 48	1440	1351	1530
Month 54	1620	1531	1710
Month 60	1800	1711	1890

29.5 Baseline values

Except where otherwise specified, the Baseline value for a given assessment is the last assessment performed before or on the randomization date.

30 MODIFICATIONS FROM STUDY PROTOCOL TO SAP

As usual, Statistical Analysis Plans are more detailed than relevant sections of the Study Protocols; such additions and refinements are therefore not mentioned in this section. Instead, only true deviations from statements in the study protocol (last amended version) to the SAP are listed (in the sequence of SAP sections) together with a brief rationale.

Section 5: An additional condition for all analysis sets was added to reflect that only patients with signed informed consent for study AC-065A302 will be included. Although no patients without a signed informed consent have been identified so far, this potential major protocol violation has been added now to avoid later amendment of the SAP.

Section 5.5: A “QoL analysis set” has been added as the CAMPHOR questionnaire has not been available in a suitable language for all patients. This implied changes in subsequent sections, e.g., Sections 5.6, 23.5 and 23.6.

Section 6.3: Because of a sub-optimally designed CRF the categories for race (Caucasian, Asian, Black, other) are partly mixed up with ethnicity (Hispanic). Therefore, the related subgroups in the SAP are defined: “race/ethnicity: Caucasian/Hispanic versus Asian versus Black versus Hispanic versus other”.

Section 10.1: The definition of 6MWT “at trough” has been changed from “12 hours post dose” (in the study protocol) to “date of last selexipag administration prior to the 6MWT is before the date of the 6MWT” (in the SAP). Rationale: the CRF does not contain information on the timing of the last study drug dose prior to the 6MWT.

Section 13: The definition of trough plasma sample has been changed from “before the morning dose” (in the study protocol) to “before the morning dose, with the last study drug administration one day prior to the PK sampling” in the SAP. Rationale: interruption of study drug administration prior to PK sampling needs to be taken into account.

Section 18.1.2: Table 3 of the study protocol contains a typo: a 0 is missing in the criterion for p-value for the final analysis. The value 0.04991 has been corrected by 0.004991 in Table 8 of the SAP.

Section 24: For exploratory efficacy endpoints, the study protocol stated that two-sided 99% confidence intervals will be provided. This has been changed in the SAP to two-sided 95% confidence intervals as it is felt this is more appropriate for exploratory endpoints even for submissions with one single pivotal study.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (yyyy-MM-dd HH:mm)
Peter Jakobs	Clinical Approval	2013-04-16 09:15 GMT+0200



Statistical Analysis Plan (SAP)

Purpose of Analysis:	Clinical Study Report including <i>post-hoc</i> analyses
Investigational Drug:	Selexipag
Protocol Number:	AC-065A302 / GRIPHON AC-065A303 / GRIPHON OL
Document Number:	D-14.302
Document Status / Version Number	Final 6.0
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AC-065A302 AND AC-065A303: STATISTICAL ANALYSIS PLAN FOR INTERIM ANALYSIS AND CLINICAL STUDY REPORT INCLUDING *POST-HOC* ANALYSES

MULTICENTER CLINICAL INVESTIGATIONS TO EVALUATE EFFICACY AND SAFETY OF SELEXIPAG IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

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Version 1.0 has been approved in the document system iTrack in 2013.

Version 2.0

Version 2.0 has been approved in the document system iTrack on 26 April 2013. Main objective for this new version was the recommendation by an external reviewer (Thomas Fleming) to add a supportive statistical analysis for morbidity/mortality-related efficacy endpoints. This analysis is viewed as an important alternative to the censoring of morbidity/mortality events with a CEC-confirmed onset date up to 16 August 2011. Sections 21, 22.2.2, 23.4.2.2 are affected.

In addition, some clarifications in Sections 14.2.4.5, 14.2.4.9, 19, 22.2.2, 23.1.2.1, 28.3, 28.5 and 29.4 have been introduced.

Version 3.0

Version 3.0 was approved in the document system iTrack on 27 February 2014.

Key changes to version 2.0:

- the secondary efficacy endpoint “Borg dyspnea index at Week 26” has been changed into an exploratory efficacy endpoint
- the exploratory efficacy endpoint “Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period” has been changed into a secondary efficacy endpoint. In the conditional sequential testing procedure for the secondary efficacy endpoints this upgraded secondary efficacy endpoint has taken the position of the previous “Borg dyspnea index at Week 26” (which has been downgraded to an exploratory endpoint).

These two changes represent modifications to the amended protocol of study AC-065A302. Regulatory interactions following the macitentan filing made it evident that the composite of PAH-death and hospitalization (as reflected in the efficacy endpoint “Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period”) bears a high level of relevance for regulatory agencies based on the association with disease-specific survival and morbidity. The Borg dyspnea index has not been linked to any other outcome parameter and therefore is perceived as bearing little clinical relevance.

Other changes in the SAP version 3.0 are corrections, clarifications, some additional analyses as well as some removed analyses. In detail:

- Additional analyses based on availability of new data (blinded expert review of baseline PAH characteristics, which was introduced with the protocol version 7 of AC-065A302, and collection of laboratory data for study AC-065A303 which was introduced with the AC-065A303 protocol version 4). Sections 6.2, 16, 17.2.2, 18.1.2.3, 14.4 and 23.3 are affected.
- Additional summary of demographics and baseline characteristics by PAH etiology and by NYHA/WHO functional class at Baseline to allow a better characterization of these subgroups and, in addition, demographics for patients included in the ophthalmologic sub-study as requested by the Ophthalmology Safety Board (meeting held on 24 October 2013).
- Additional analysis set defined for patients included ophthalmologic sub-study.
- Additional category for age at Screening to align with the SAP for the Summary of Clinical Safety.
- Introduction of medical history of special interest in Section 6.3 and 16 to support the analysis of AEs of special interest.
- Change in the summary of baseline RHC data by time before randomization from 3 months to 6 months before randomization.
- Subgroup “PAH diagnosis within 6 months prior to randomization” removed
- Update of the definition of subgroup race: “Caucasian/Hispanic” constitutes one category and “Hispanic” is not a separate category, as Hispanic is considered an ethnicity within the race “Caucasian”.
- Change in wording: “maximum tolerated dose” replaced by “individual maintenance dose” in Section 7.
- Additional summary of major protocol deviations and summary of reasons for screening failure in Section 15 to fulfill ICH E3.
- Additional listings to complete the analysis of patients disposition Section 15.
- Additional summary of reasons for discontinuation of study drug by time since randomization (during up-titration versus after up-titration) in Section 23.6.
- Additional definition of premature discontinuation from study drug in Section 7.1 in order to differentiate mandatory discontinuations from study drug per protocol from others.
- Additional Kaplan-Meier analysis for the time to premature discontinuation [Section 23.6].
- Additional sensitivity analyses in Section 17.2.2 for the primary endpoint: ignoring CEC-confirmed “disease progression” if second 6MWT was not performed; handling

signs of disease worsening as events for patients who prematurely discontinued study drug.

- Additional summary of morbidity/mortality events that needed CEC consensus [Section 17.2.3].
- Additional analysis of repeated measures for 6MWT, Borg dyspnea index and CAMPHOR exploratory endpoints in Section 19.10.
- Additional competing risk analysis based on Gray's test.
- Update of the definition of the Per-protocol analysis set in Section 5.2. Protocol violation (PV) codes are removed as they may change with a new release of the PV code list document, a reference to the PV code list document is added instead. In addition, the criterion for relevant dose increase of the same drug for an existing PAH therapy is removed as this criterion is not a PV for patients with CWE reported.
- Correction of the definition of the CAMPHOR 'Symptoms' score as the scores are from 1 to 25.
- In order to focus on main efficacy analyses the following changes (mostly removals of planned analyses) are made:
 - General revision of Section 19 for analyses of exploratory efficacy endpoints.
 - Removal of all sensitivity analyses for the pharmacoeconomic endpoints.
 - Removal of the exploratory efficacy endpoint "Time course of CEC-confirmed (potentially recurrent) morbidity/mortality events hospitalization due to worsening of PAH, initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH, and death up to Study Closure". The rationale is explained in Section 29.
 - Removal of the exploratory efficacy endpoint "CEC-confirmed (potentially recurrent) hospitalizations due to worsening of PAH up to Study Closure" and the pharmacoeconomic endpoint "Occurrence of recurrent hospitalization (all cause and PAH related) up to EOS visit". The rationale is explained in Section 29.
 - Removal of the additional Kaplan-Meier analysis for dose-response ignoring all data for the first 84 days after randomization, initially defined in Section 20.1. This analysis is considered to have limited relevance as it would take into account only a selected set of patients.
- Removal of East software version number Section 28.2 (version number will be documented in the CSR).
- Update of the definition of the PAH-specific medication in Section 8 with new medications recently approved for PAH and with a PDE5-I used for PAH off-label use (Udenafil). PAH-non-specific medications are also defined. In addition, a summary of concomitant PAH-specific medication at Baseline is added by geographical region [Section 23.7].

- Additional analysis of AEs leading to dose reduction in Section 14.2.3 and Section 23.1.4 in order to complete the analysis of titration of the study drug.
- Additional analysis of mean arterial pressure in Section 14.5.1 in order to complete the analysis of vital signs.
- Additional summary of AEs of special interest eye disorder/retinal disorder by age groups and separately for patients included in the ophthalmologic sub-study as requested by the Ophthalmology Safety Board (meeting held on 24 October 2013).
- Additional listing of SAEs occurring outside of the treatment-emergent period as mentioned in the protocol.
- Additional listing of patients randomized but not treated as these patients are not included in the Safety analysis set but may have experienced SAEs.
- Additional summary of AEs of special interest that led to discontinuation, were serious, or had a fatal outcome.
- Update of the definition of prostacyclin-like associated AEs in Section 14.2.6 including “dizziness” as prostacyclin-like associated AEs. This was omitted in the previous version.
- Update and clarification of the definition of confounding concomitant medication planned for AEs of special interest in Section 14.2.5. The definition of confounding concomitant medication is updated in order to take into account combinations of drugs and relevant routes of administration. Additional confounding factors are introduced for the “hypotension” AE of special interest.
- Update of the definition of the AE of special interest “Liver disorders” in Section 14.2.5.6 in order to align with macitentan analyses.
- In order to focus on main safety analyses, the following changes have been made:
 - Combine “Retinal disorder” with “Eye disorder” AE of special interest and “Gastrointestinal haemorrhage” with “Haemorrhage” AE of special interest.
 - Removal of the specific definition of “Gastrointestinal disorders” AE of special interest and “Thyroid disorders” AE of special interest.
 - Removal of summary of laboratory test results by concomitant treatment with ERA.
- Additional definition of AEs suggestive of PAH worsening to allow additional sensitivity analysis of the primary endpoint.
- Update of the censoring rules for analyses of AEs of special interest as the rules were set up for the interim analysis in Section 23.1.2.1.
- Update of the definition of abnormalities in liver function tests.
- Additional local laboratory data from the Argus database included for analyses of laboratory test results in Section 14.4.

- Removal of the definition of protein total marked laboratory abnormality as protein total is not measured in AC-065A302.
- General revision of the definition of treatment-emergent low blood pressure in Section 14.5.2.

In addition, some clarifications in Sections 2, 3, 6.4, 9, 10, 12, 14, 25.3.2, 26.1, 17.2, 18, 19, 22, 23 and 24 (including corresponding subsections) have been introduced and some text has been moved to other sections in order to better separate definitions from analyses.

Version 4.0

Version 4.0 was approved in the document system iTrack on 03 June 2014.

Key changes to version 3.0:

- In the analysis of the secondary endpoint “absolute change from Baseline to Week 26 in 6MWD”, 6MWTs not performed at trough are included. The analysis restricted to the 6MWTs performed at trough becomes a supportive analysis. The rationale is explained in Section 29.
- Missing efficacy data (other than time-to-event data) are not handled with multiple imputation but with single imputation as detailed in Section 10 for the respective endpoints. Rationale: advice received from FDA after pre-NDA meeting.
- A number of planned analyses (primarily for exploratory efficacy endpoints) have been removed as they currently were not meant to be of relevance for the Clinical Study Report or will be described in detail in the Summary of Clinical Safety.
- Restricting the usage of local laboratory data from the Argus database as described in Section 14.4.

Other changes in the SAP version 4.0 are corrections and clarifications. In detail:

- Explicit data cut-off dates for the final analysis have become known and are inserted in Sections 3.2, 5.2 and 14.1.
- Definitions of weighted-average of selexipag dose and IMD are clarified in Section 7.2.
- Definition of baseline for endpoints related to CAMPHOR questionnaire is added in Section 10.5.
- The route ‘intra-arterial’ is added to the list of routes of administration to be considered for the confounding medications in Section 14.2.5.
- In Section 18, the conditional sequential testing procedure for the secondary efficacy endpoints has been renamed to "conditional hierarchical" in order to better differentiate this procedure from the group-sequential procedure for the primary efficacy endpoint.

- Clarification in Section 23.2 that the preferred ‘no code needed’ is not considered as an ECG abnormality.
- Clarification in Section 23.1.1 that preferred term “DISEASE PROGRESSION” is not displayed in summary tables.
- Correction of the SI unit for erythrocytes in Section 14.4.
- Censoring rules for sensitivity analysis of the primary endpoint on the PPS is added in Section 17.2.
- Definition of enrolment in study AC-065A303 is added in Section 24.
- Handling of incomplete CEC onset date is added in Section 24.
- Section 25.4 with specifications for boxplots is added.
- Clarification added in various sections: CEC-confirmed morbidity/mortality events adjudicated in the PTOP CEC system and reported as “no” by the investigator are excluded in the analysis which includes PTOP MM events. This convention has become necessary because of an unexpected possibility for the CEC members in the PTOP CEC system.

Version 5.0

Version 5.0 was approved in the document system iTrack on 12 June 2014.

Key changes to version 4.0:

- During a blinded review of SDTM datasets generated after database lock and before unblinding of study AC-065A302, the following observations have been made:
 - o for two patients visit dates in SDTM are later than the cut-off date for study AC-065A302 (27 April 2014)
 - o these visit dates originate from laboratory sample dates stored in ARGUS
 - o upon further investigation it became obvious that the inclusion of such visit dates (originating from laboratory sample dates stored in ARGUS) affected the censoring dates for patients without a CEC-confirmed morbidity/mortality event, in particular for secondary and exploratory time-to-event efficacy endpoints “up to Study Closure”.

In order to assure that the statistical analysis of time-to-event endpoints (in particular the derivation of censoring dates) is not impacted by the inclusion of visit dates originating from ARGUS, the definition of the “date of last contact” in Section 24.2.4 is updated.

- A refinement of the specifications for the display of Kaplan-Meier plots has been added in Section 25.1.1.

Version 6.0

Key changes to version 5.0:

In contrast to the previously approved SAP versions 1.0 to 5.0, this version was generated after unblinding of GRIPHON. The majority of changes highlighted in this version reflect topics discussed at a meeting with the FDA held on 11 July 2014 to present the study's top-line results.

Key changes / additions to version 5.0:

- Medical history or AEs denoting anemia or hemoglobin decrease are defined in Section 6.3 and Section 14.2.8. The definitions are provided by Actelion's Global Drug Safety department and are based on preferred terms presented in CSR Table TAESF2_S. These AEs are summarized overall and the influence of potential confounding factors is explored. Rationale: these analyses were requested by Actelion's Global Drug Safety department in order to further explore these specific AEs.
- Significant protocol deviations were defined in Section 6.5 and summarized in order to select relevant protocol deviations with most significant impact on evaluation of efficacy or safety.
- IMD in study AC-065A302 is defined for placebo equivalent in Section 7.2.2. Rationale: to assess the execution of study drug titration in both treatment arms.
- Following an agreement with the FDA (meeting held on 11 July 2014), it was decided to exclude events with an onset date up to 16 August 2011 only for the main analysis of the primary endpoint and to include events with an onset date up to 16 August 2011 in all sensitivity and subgroup analyses of the primary endpoint as well as in all secondary and exploratory time-to-event endpoints analyses. Changes are reflected in Sections 9, 10, 11, 17, 18, 19 and 20.
- For all the endpoints analyzed up to Study Closure, the definition of the censoring rules in the protocol included the EOS visit date as one of the potential censoring dates. In some specific cases, this rule resulted in premature censoring of patients who should have been censored later i.e., at their date of last contact. In the post-hoc SAP, the rules are updated and all patients are censored at their date of last contact if applicable. Changes are reflected in Sections 10.4, 11.1, 11.3, 11.6, 11.7, and 11.8.
- In order to better characterize the patient flow in study AC-065A302 (including PTOp) and study AC-065A03, the vital status at Study Closure is further described in Section 15.1.
- Summary of patients with data excluded in the per-protocol analysis of the primary endpoint and secondary endpoint change from baseline to Week 26 in 6MWD are added in Section 15.1 in order to better characterize the per-protocol analysis set.
- The reason for treatment discontinuation prior to Study Closure in study AC-065A302 is summarized to complete the analysis of premature treatment discontinuation.

- The demographics and baseline characteristics are summarized for the patients treated in AC-065A303 in order to better characterize the patient population for study AC-065A303.
- The primary endpoint is further analyzed adjusting for covariates in Section 17.2.2. Rationale: to assess whether any baseline covariate has an impact on the treatment effect.
- The type of first CEC-confirmed event is further summarized displaying all components with same onset date. In addition, all morbidity/mortality event components with onset date up to 7 days after last study drug intake in the AC-065A302 Treatment Period are summarized in the order of occurrence [Section 17.2.3]. Rationale: to understand the sequence of events in detail.
- The listing of dose of PDE5-I and/or ERA concomitant medications described in Section 17.2.3 of the SAP versions 1.0 to 5.0 is removed. Rationale: the date when the CEC adjudicated the cases was not available in the SDTM data prior to unblinding.
- The primary endpoint and secondary endpoint ‘time to death up to Study Closure’ are analyzed in the patients with typical PAH according to the blinded expert review [Section 17.2.2 and Section 18.4]. Rationale: to restrict the analysis to a more homogenous population.
- The secondary endpoint ‘time to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening (up to 7 days after last study drug intake in the AC-065A302 Treatment Period)’ is analyzed by subgroup and displayed in a forest plot. Rationale: to explore the heterogeneity of the treatment effect.
- The exploratory endpoint ‘time to CEC-confirmed death due to PAH up 7 days after last study drug intake’ is analyzed in the patients with typical or consistent PAH according to the blinded expert review [Section 19.5]. Rationale: to restrict the analysis to a more homogenous population.
- The annualized number of days spent in hospital for all causes / for PAH reasons up to EOS visit is analyzed in the non-parametric way in Section 21.3 and Section 21.4. Rationale: the negative binomial model did not fit the data.
- Treatment-emergent AEs are tabulated by IMD categories [Section 23.1.1] in order to assess a potential dose relationship between IMD and AE.
- Treatment-emergent AEs “Hemorrhage” are presented by maximum severity to complete the summary of AE “Hemorrhage”.
- The separate influence of potential confounding medications is explored for AEs of special interest “Hypotension” and “Hemorrhage” in Section 23.1.2.3 and Section 23.1.2.4. Rationale: these analyses were requested by Actelion’s Global Drug Safety department in order to further explore these specific AEs.

- Patients with low marked/alert laboratory abnormalities in leukocytes and hemoglobin are listed separately [Section 23.3]. Rationale: these analyses were requested by Actelion's Global Drug Safety department in order to further explore these specific AEs.
- The statistical methods described in Sections 25.1.4.1, 25.1.4.2 and 25.1.3 (competing risks analysis) of the CSR SAP versions 1.0 to 5.0 are removed in the *post-hoc* CSR SAP. Rationale: these analyses are planned for the Summary of Clinical Efficacy SAP.
- The SAS code described in Section 25.3.2 is updated to allow the non-parametric analysis of the pharmaco-economic endpoints.
- A table of treatment-emergent SAEs with fatal outcome was added to Section 23.

Other changes in the SAP version 5.0 are corrections and clarifications. In detail:

- Section 7.3.2 clarifies that this section defines only selexipag IMD, as patients enrolled in study AC-065A303 are all treated with selexipag.
- Section 8.1 clarifies the following: selexipag administered in AC-065A303 and reported in AC-065A302/PTOP has been coded as "Investigational drug". Therefore patients having taken selexipag during AC-065A303 are described as receiving "Investigational drug" in tables summarizing concomitant medications not for PAH.
- ATC codes with 7 levels are not available in the SDTM. Therefore the definition of oxygen is refined in Section 8.2 using the preferred term.
- One patient randomized but not treated experienced an event 1 day after randomization. It has been clarified in Section 9, Section 10 and Section 11 that this patient is counted as having an event.
- Clarifications on the date of death are added to Section 11.1, Section 11.3, Section 11.6, Section 11.7 and Section 11.8. Rationale: CEC had to confirm the date of death only for death in the AC-065A302 Treatment Period or in PTOP. For other cases of death the date of death is derived from the investigator CRF.
- Blood urea nitrogen is added in Section 14.4.2 and Table 8 in order to be consistent with Table 7.
- Presence of retinal arterial tortuosity at Baseline is added in Section 14.6 in order to complete the summary of change from baseline in severity of retinal arterial tortuosity to all visits up to EOS in the Ophthalmologic sub-study.
- Clarifications are added in Section 15.1 regarding the summary of protocol deviations in study AC-065A303. Rationale: some protocol deviations in study AC-065A303 had not yet been manually assigned as confirmed or not confirmed at the time of data dump on 12 June 2014.

- Clarification added in Section [17.2.2](#) regarding the display of the summary of the type of event in the supportive analysis ignoring “disease progression” event component when the second 6MWT was not done.
- In order to facilitate the review of the relationship between IMD and primary endpoint, the four IMD categories are displayed in a single graph [Section [20.1](#)].
- It has been clarified that for study AC-065A303 AEs leading to discontinuation are presented overall and by treatment received in AC-065A302 in Section [23.1](#).
- Analyses of treatment exposure, premature discontinuation of study drug and IMD have been moved from Section [23](#) to Section [15](#) to align with the structure of the CSR.
- The rules for missing end date of study drug in Section [24.2.2](#) and Section [24.2.3](#) have been clarified. More details can be found in the document ‘Programming Standards and Conventions’.
- It has been clarified in Section [17.2.3](#) that information about events needing consensus between the two adjudication systems was only listed but not summarized.
- In section [25.1.1](#), the termination of the horizontal axis of the KM curves has been clarified.
- The list of outputs to be included in the CSR has been added as [Appendix A](#).

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-Minute walk distance
6MWT	6-Minute walk test
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
b.i.d.	<i>bis in die</i> / twice daily
BMI	Body mass index
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CEC	Critical Event Committee
CWE	Clinical Worsening Event
CI	Confidence interval
CO	Cardiac output
CRF	Case Report Form
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
dPAP	Diastolic pulmonary arterial pressure
ECG	Electrocardiogram
EMA	European Medicines Agency
EOS	End of Study
EOTE	End-of-Treatment-Extension
ERA	Endothelin receptor antagonist
FAS	Full analysis set
FC	Functional class
FDA	Food and Drug Administration
HR	Hazard ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMD	Individual maintenance dose
i.v.	Intravenous
IWRS/IVRS	Interactive Web / Voice Response System

KM	Kaplan-Meier
LVEDP	Left ventricular end diastolic pressure
MAP	Mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
MTD	Maximum tolerated dose
NT pro-BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OAS	Ophthalmologic analysis set
o.d.	Once daily
OL	Open-label
PAH	Pulmonary arterial hypertension
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
PDE-5	Phosphodiesterase 5
PDE5-I	PDE-5 inhibitor
PK	Pharmacokinetic
PPS	Per-protocol set
PT	Preferred Term
PTOCV	Post-Treatment Observation Closure Visit
PTOP	Post-Treatment Observation Period
PV	Protocol violation
PVR	Pulmonary vascular resistance
Q1	First Quartile
Q3	Third Quartile
QoL	Quality of Life
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RCI	Repeated confidence interval
RHC	Right heart catheterization
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation

SDG	Standardized Drug Groupings
SDTM	Study Data Tabulation Model
SFU	Safety Follow-up
SI	Standard International
SMQ	Standard MedDRA Query
SOC	System Organ Class
sPAP	Systolic pulmonary arterial pressure
SVO ₂	Mixed venous oxygen saturation
T3	Triiodothyronine
T4	Thyroxine
TB	Total bilirubin
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes statistical analysis methods planned for

- the efficacy and safety interim analysis of studies AC-065A302 and AC-065A303; performed by the Statistical Analysis Center and provided to the independent Data Monitoring Committee (DMC), see more details in Section [3.1](#).
- the final analysis of study AC-065A302 and study AC-065A303 up to the analysis cut-off date; performed by Actelion Biostatistics for the Clinical Study Report, see more details in Section [3.2](#).

The analysis of data from the Treatment-Extension Period of study AC-065A302 [see Section [2.1](#)] will be covered by a separate SAP.

2 STUDY DESIGN AND FLOW

2.1 Study design AC-065A302

Study AC-065A302 is designed as a multicenter, randomized, double-blind, parallel group, placebo-controlled, group-sequential Phase 3 study to compare efficacy, safety, tolerability of selexipag (administered in the range of 200 to 1600 mcg twice daily [b.i.d.]) versus placebo. The randomization scheme is stratified by site, using permuted blocks, -an allocation ratio of 1:1 and executed by an interactive web / voice response system (IWRS/IVRS).

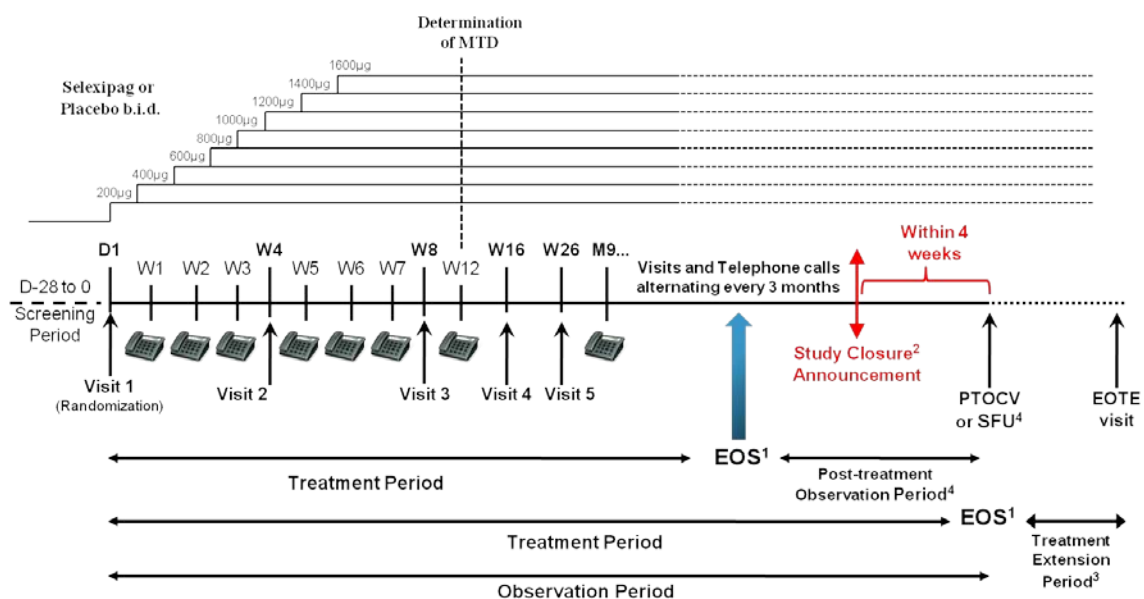
The study has the following periods:

- **Screening Period** starting with the patient signing the informed consent form and ending with the randomization, for eligible patients.
- **Treatment Period** starting with the Baseline Visit (Day 1) and ending with the End Of Study (EOS) Visit
 - Due to the fact that patients are to take their first dose of study medication (200 mcg or matching placebo) on the evening of the Baseline Visit, this day is called Day 1. Patients are then up-titrated following a gradually progressive dose escalation scheme with weekly increments of 200 mcg b.i.d. until reaching the individual maintenance dose (IMD) in the range of 200 to 1600 mcg b.i.d. Dose reduction may occur at any time if clinically indicated.
 - Study closure is announced by the sponsor either following the recommendation of the DMC or when approximately 331 first morbidity/mortality events (with onset date as per the Critical Event Committee [CEC] later than 16 August 2011 and up to 7 days after last study drug intake) have been confirmed by the CEC. In order to eliminate any concern that the study protocol amendment 5 (increase in required number of morbidity/mortality events and sample size) could be considered informed, events were observed up to 16 August 2011 in the primary endpoint analysis [more details are given in Section 9].
 - All patients still on study drug at study closure must have an EOS Visit within 4 weeks. Patients who have prematurely discontinued the study drug in AC-065A302 may enter the AC-065A302 Post-Treatment Observation Period, see below. However, patients who declined to enter the AC-065A302 Post-Treatment Observation Period may be contacted (if they had not withdrawn consent) at the time of Study Closure to record their vital status.
- **Post-Treatment Safety Follow-Up Period for serious adverse events (SAEs):** SAEs must be reported up to 30 days after last study drug intake or until administration of the first dose of selexipag in study AC-065A303, whichever comes first.
- **Post-Treatment Observation Period (introduced with Global protocol amendment 6):** starting with the EOS Visit (for patients with premature discontinuation of study drug in AC-065A302) and ending with the Post-Treatment

Observation Closure Visit (PTOCV) within 4 weeks following announcement of Study Closure by the sponsor. Patients with premature discontinuation of study drug in AC-065A302 may enter the AC-065A302 Post-Treatment Observation Period irrespective of whether they enter study AC-065A303.

- **Treatment-Extension Period:** starting with the EOS Visit following Study Closure and ending with the End-Of-Treatment-Extension (EOTE) Visit following unblinding of the database by the sponsor. Once the unblinding of the database is announced by the sponsor, the patients must have the EOTE Visit shortly thereafter (within 14 days). This period will be covered by a separate SAP.

Figure 1 Design of study AC-065A302



- 1 EOS Visit for an individual patient may occur before Study Closure or within 4 weeks after announcement of Study Closure. Patients who discontinue study drug before announcement of Study Closure must have an EOS Visit and a Post-treatment Safety Follow-Up (SFU) phone call.
- 2 Study Closure will be announced either after interim analysis or when the target number of CEC-confirmed morbidity/mortality events has been reached.
- 3 In case study AC-065A303 is approved by the national Health Authority, patients who are on study drug in AC-065A302 at Study Closure and who wish to enter study AC-065A303 must enter the Treatment-Extension Period of study AC-065A302.
- 4 Patients who prematurely discontinued study drug in AC-065A302 before Study Closure may enter the Post-Treatment Observation Period of AC-065A302, irrespective of whether they enter study AC-065A303 or not. When Study Closure is announced by the sponsor, a PTOCV is scheduled within 4 weeks. Patients not consenting to participate in the AC-065A302 Post-Treatment Observation Period may be contacted at the time of Study Closure to record their vital status.

Table 1 Visit and assessment schedule in study AC-065A302

	Screening	Visit 1	Tel. ^a W1	Tel. ^a W2	Tel. ^a W3	Visit 2	Tel. ^a W5	Tel. ^a W6	Tel. ^a W7	Visit 3	Tel. ^a W12	Visit 4	Visit 5 & onwards	Tel. ^a M9 & every 6 M ± 7d	Morbidity Mortality Event ^b	EOS Visit ^k	Safety Follow-up ^a 30 days after drug discontin. ^o	EOTE visit ^m
	≤ 28 days before Day 1	BL D 1 Randomization	Day 8 ± 3 d	Day 15 ± 3 d	Day 22 ± 3 d	Week 4 ± 3 d	Week 5 ± 3 d	Week 6 ± 3 d	Week 7 ± 3 d	Week 8 ± 3 d	Week 12 ± 3 d	Week 16 ± 3 d	W26 (M6) & every 6M ± 7 days					
Written informed consent	X ^t																	
Inclusion/exclusion crit. (incl. hemodynamics)	X	Re-confirm																
Med. history incl. PAH	X	X																
Concomitant medications	X	X				X				X		X	X	X	X	X		X
Mod. NYHA/WHO FC	X	X				X				X		X	X		X	X		
Physical examination	X	X				X				X		X	X		X	X		
Weight and height ^h	X	X				X				X		X	X		X	X		
Vital signs	X	X				X				X		X	X		X	X		
12-lead ECG		X				X				X		X	X ^p		X	X		
6-minute walk test	X ^c	X								X		X	X		X	X		
Borg dyspnea score	X ^c	X								X		X	X		X	X		
CAMPBOR (subset)		X										X	X ^r			X		
Pregnancy test (if appl.) ⁱ	X	X				X				X	X	X	X			X		X
Laboratory test ^d	X	X				X				X		X	X		X	X		
Plasma NT pro-BNP		X				X				X		X	X			X		
PK sampling		X				X				X		X ⁿ	X ^e			X		
Ophthalmol (subset)		X ^q											X ^r			X ^s		
Study drug dispensing		X				X				X		X	X					
First dose of study drug		X ^{pm}																
Dose titration			X	X	X	X	X	X	X		X ^g							
Drug accountability						X				X		X	X			X		X
(Serious) adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital status																X ^l		
Addendum to written ICF																X ^u		

a: Tel. = Scheduled telephone call. **b:** In case of suspected clinical worsening. **c:** Conducted ≤ 14 days before Day 1. **d:** Laboratory test (hematology and blood chemistry). **e:** On Visit 5 (Week 26, Month 6) & Visit 6 (Month 12) only. **f:** On Visit 5 (Week 26, Month 6), Visit 6 (Month 12) and Visit 8 (Month 24) only. **g:** Confirmation of MTD. **h:** Height measured only at screening. **i:** Serum pregnancy test to be performed at screening and urine pregnancy tests monthly until 1 month after study drug discontinuation. **k:** In case of premature discontinuation of study drug and for all patients on study drug at Study Closure. **l:** Survival follow-up phone call at Study Closure for patients with premature EOS not entering the Post-Treatment Observation Period. **m:** The End of Treatment Extension visit must be performed only for patients still on study drug at Study Closure and who wish to enter study AC-065A303 (if approved by the national Health Authority in the country). **n:** Two PK samplings will be taken at this visit, one pre-dose and one post-dose. **o:** For patients who will enter study AC-065A303, SAEs must be followed-up until the first dose of ACT-293987 in study AC-065A303. **p:** At Visit 6 (Month 12), two additional ECGs will be performed 2 and 4 hours after study drug intake. **q:** Performed at Baseline/Randomization Visit (Visit 1) (or within the screening period [28 days before Day1]) **r:** Only at Visit 6 (Month 12). **s:** Performed at EOS Visit or within 2 weeks before or after the scheduled EOS Visit. (* 6 months corresponds to 26 weeks). **t:** Confirm that treatment-naïve patients cannot tolerate or have no access to PAH-specific therapy and that NYHA FC IV patients cannot be treated with i.v. prostanoid. Throughout the course of the study, it is recommended to regularly discuss with the patient whether new PAH therapy is becoming available. **u:** applies to patients who will enter the Post-Treatment Observation Period after approval of amendment 6 while on study drug.

Table 2 Visit and assessment schedule in the AC-065A302 Post-Treatment Observation Period

	Site visits for patients in the AC-065A302 Post-Treatment Observation Period	Phone calls for patients in the AC-065A302 Post-Treatment Observation Period	Unscheduled visit in case of PAH worsening	Post-Treatment Observation Closure Visit (within 4 weeks after Study Closure announcement)
	<u>Site visit</u> ² : 6 months after EOS visit and every 6 months thereafter	<u>Phone call</u> : 3 months after EOS Visit/first site visit ³ and every 6 months thereafter		
Addendum to Written Informed Consent Form	X if not already signed at EOS			
Concomitant medications for PAH ¹ (incl. O ₂ therapy)	X	X	X	X
Mod. NYHA/WHO functional class	X		X	X
Hospitalization for PAH worsening since last visit		X		
Morbidity/mortality event details (excluding “disease progression”) ⁴	X		X	X
Vital status	X	X		X

¹ Concomitant medications for PAH include ERA, PDE5-I, prostanoid and chronic O₂ therapy (change in dose will not be collected)

² For patients who had their EOS visit prior to approval of amendment 6, the first site visit of the Post-Treatment Observation Period may be scheduled more than 6 months after EOS visit. In such case, a retrospective data collection covering the entire period since EOS visit will be done.

³ For patients who had their EOS visit prior to approval of amendment 6, the first phone call will be three months after the first site visit

⁴ Morbidity/mortality event form records clinical information needed for the adjudication of the event (e.g. hospitalization for PAH worsening, PAH worsening resulting in need of lung transplantation/atrial septostomy, symptoms of PAH worsening, ...).

2.2 Study design AC-065A303

The study is designed as an open-label, uncontrolled, multicenter study to assess long-term safety and tolerability in:

- patients experiencing a CEC-confirmed morbidity event during study AC-065A302, and
- patients who have completed study AC-065A302 as scheduled, i.e., without premature end of study drug. (These patients may transition to study AC-065A303 only after results are available for study AC-065A302.)

Patients entering study AC-065A303 following a CEC-confirmed morbidity event during study AC-065A302 are transferred without knowledge of their previous study drug allocation (selexipag or placebo) to preserve the integrity of study AC-065A302. These patients start with a selexipag dose of 200 mcg b.i.d. with subsequent up-titration in weekly increments of 200 mcg b.i.d. until reaching the IMD in the range of 200 to 1600 mcg b.i.d. Dose reduction may occur at any time if clinically indicated.

Future potential transition of patients to AC-065A303 immediately after their AC-065A302 End-of-Treatment-Extension visit will be done with knowledge of the patients' previous study drug allocations (selexipag or placebo). Therefore:

- patients who have received selexipag in study AC-065A302 continue with the same selexipag dose as they ended in study AC-065A302. Dose reduction may occur at any time if clinically indicated.
- patients who have received placebo in study AC-065A302 start with a selexipag dose of 200 mcg b.i.d. with subsequent up-titration in weekly increments of 200 mcg b.i.d. until reaching the IMD in the range of 200 to 1600 mcg b.i.d. Dose reduction may occur at any time if clinically indicated.

The transition of patients from study AC-065A302 to study AC-065A303 is recorded by the IWRS/IVRS.

Table 3 Visit and assessment schedule in study AC-065A303 for patients starting selexipag with up-titration

	Visit ² 1	TITRATION PERIOD ¹										MAINTENANCE PERIOD			Safety follow up ⁴ 30 days after EOS
		Tel. ⁴ W1	Tel ⁴ W2	Tel ⁴ W3	Visit 2	Tel ⁴ W5	Tel ⁴ W6	Tel ⁴ W7	Visit 3	Tel ⁴ W12	Visit 4	Visit 5	Tel ⁴	EOS Visit	
	Day 1	Day 8 ± 3 days	Day 15 ± 3 days	Day 22 ± 3 days	Week 4 ± 3 days	Week 5 ± 3 days	Week 6 ± 3 days	Week 7 ± 3 days	Week 8 ± 3 day	Week 12 ± 3 days	Week 16 ± 3 days	Month 6* and every 6 months ± 7 days	Month 9 and every 6 months ± 7 days		
Written informed consent ⁷	X														
Concomitant medications	X				X				X		X	X		X	
Vital signs	X				X				X		X	X		X	
Body weight	X				X				X		X	X		X	
Laboratory tests ⁵	X				X				X		X	X		X	
Physical examination ⁶	X				X				X		X	X		X	
Pregnancy test ³	X				X				X	X	X	X	X	X	X
Dispensing of study drug	X				X				X		X	X			
Drug accountability					X				X		X	X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

¹ Only for patients who were on placebo or patients who experienced an adjudicated morbidity event during AC-065A302; ² Visit 1 should correspond to the last visit in the double-blind study or, if not possible, must be at the latest within 2 weeks (14 days). When Visit 1 is performed the same day as the last visit of the double-blind study, assessments that are common to both studies are not to be repeated. Results are to be reported on CRF pages of both studies; ³ Monthly urine pregnancy test for women of childbearing potential until 1 month after study drug discontinuation; ⁴ Scheduled telephone call; ⁵ Hematology and blood chemistry tests to be performed at Visit 1 only if the last assessment in AC-065A302 was performed more than 4 weeks ago, and then at every visit until EOS. ⁶ Physical examination results will not be collected in the CRF. ⁷ Throughout the course of the study, it is recommended to regularly discuss with the patient whether new PAH therapy is becoming available. * 6 months correspond to 26 weeks.

Table 4 Visit and assessment schedule in study AC-065A303 for patients starting selexipag without up-titration

	Visit ¹ 1	TITRATION PERIOD ²	MAINTENANCE PERIOD				EOS Visit	Safety follow up ⁴
		NA	Tel ⁴ W12	Visit 5	Tel ⁴			
	Day 1	NA	Week 12 ± 3 days	Month 6* and every 6 months ± 7 days	Month 9 and every 6 months ± 7 days			30 days after EOS
Written informed consent ⁷	X	NA						
Concomitant medications	X	NA		X		X		
Vital signs	X	NA		X		X		
Body weight	X	NA		X		X		
Laboratory tests ⁵	X	NA		X		X		
Physical examination ⁶	X	NA		X		X		
Pregnancy test (if appl.) ³	X	NA	X	X	X	X		X
Dispensing of study drug	X	NA		X				
Drug accountability		NA		X		X		
Adverse events	X	NA	X	X	X	X		
Serious adverse events	X	NA	X	X	X	X		X

¹ For patients on study drug until unblinding of AC-065A302, Visit 1 should correspond to the last visit in the double-blind study AC-065A302 or, if not possible, must be at latest within 2 weeks (14 days); ² Not applicable, patient will switch directly from Visit 1 to Week 12 phone call and Visit 5; ³ Monthly urine pregnancy test for women of childbearing potential until 1 month after study drug discontinuation; ⁴ Scheduled telephone call. ⁵ Hematology and blood chemistry tests to be performed at Visit 1 only if the last assessment in AC-065A302 was performed more than 4 weeks ago, and then at every visit until EOS. ⁶ Physical examination results will not be collected in the CRF. ⁷ Throughout the course of the study, it is recommended to regularly discuss with the patient whether new PAH therapy is becoming available.

* 6 months correspond to 26 weeks.

CRF = Case Report Form; EOS = End of Study; NA = Not applicable.

3 INTERIM AND FINAL ANALYSIS

3.1 Interim analysis

The interim efficacy and safety analysis is conducted by a Statistical Analysis Center (Frontier Science) not otherwise involved in the study and interim results are reviewed by an independent DMC. A DMC Charter is in place.

The interim analysis includes efficacy, safety and tolerability data from study AC-065A302 as well as safety data from patients in study AC-065A303.

Cut-off dates for the interim analysis

- 22 January 2013 for safety data
- 22 January 2013 for efficacy data other than those related to morbidity/mortality events
- 25 March 2013 for confirmation of morbidity/mortality events by the CEC.

The interim analysis includes efficacy data only from the Treatment Period of study AC-065A302. Efficacy data from the AC-065A302 Post-Treatment Observation Period is not available due to the timing of AC-065A302 Protocol Amendment 6 (dated 23 January 2013) and the timing of the interim analysis.

The detailed selection of endpoints and statistical methods for the interim analysis (as agreed between the DMC and Actelion; however, the DMC may request additional analyses from the Statistical Analysis Center) are provided as outlined below:

- Sections 15, 16 and 17 (including competing risk analysis).
- Sections 18.1 and 18.2.
- Sections 19.2 and 19.4.
- Efficacy analyses only for the Full analysis set (FAS), not for the Per-protocol set (PPS).
- Safety analyses same as for regular DMC meetings described in the DMC SAP (based on Safety Analysis Set but with study treatments as randomized and not as treated).

3.2 Final analysis

The final analysis covers data from study AC-065A302 including all data from the AC-065A302 Post-Treatment Observation Period (PTOP) but excluding data from the Treatment-Extension Period. In addition, the final analysis includes all safety data up to an analysis cut-off date (defined as last patient's last visit in the Treatment Period / PTOF of study AC-065A302) from patients who participate in study AC-065A303.

Cut-off dates for the final analysis

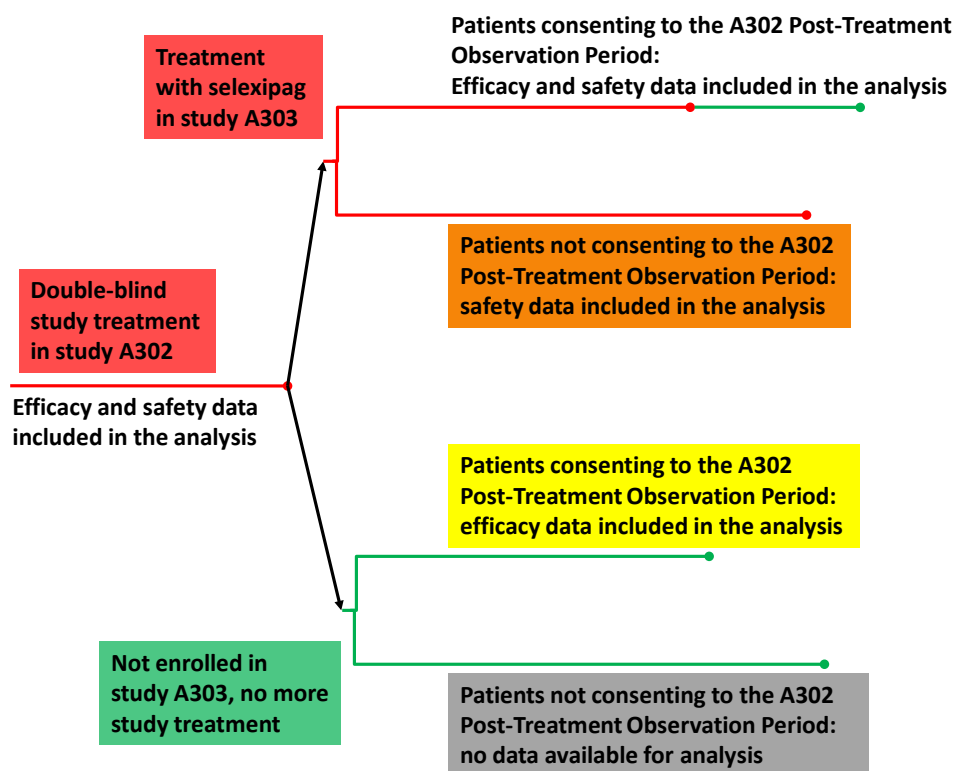
- For study AC-065A302: all data (excluding Treatment-Extension Period) up to maximum (date of last PTOCV, date of last EOS visit in AC-065A302, date of last

dose of study medication in AC-065A302 Treatment Period + 7 days) which is 27 April 2014 (included).

- For study AC-065A303: all data up to 10 March 2014 (included).

Figure 2 Inclusion of data for the final analysis

(recording survival status at time of AC-065A302 Study Closure is not included in the figure for simplicity, red lines indicate study treatment, green lines indicate no study treatment)



Data sources to generate Study Data Tabulation Model (SDTM) datasets are the following:

- IWRS/IVRS data (provided by ICON for AC-065A302 and AC-065A303)
- Case Report Form (CRF) data (including coding where applicable) (for AC-065A302 and AC-065A303) and CAMPHOR questionnaire data (for AC-065A302 only).
- Protocol violation (PV) / protocol deviation data (provided by the PV system and defined in the "PV code list" document for AC-065A302 and AC-065A303). Note: The terms 'protocol deviation' and 'protocol violation' are interchangeable.
- CEC data including PTOC CEC data for AC-065A302 only.

- Blinded expert review of pulmonary arterial hypertension (PAH) characteristics at Baseline for AC-065A302 only.
- Central laboratory data provided by Quest for AC-065A302 and Eurofins for AC-065A303.
- Central ECG data provided by Cardiabase for AC-065A302 only
- Pharmacokinetic (PK) data provided by Swiss BioQuant AG for AC-065A302 only.
- Ophthalmologic data provided by Moorfields Eye Hospital Reading Center for AC-065A302 sub-study.
- Argus database for AC-065A302 and AC-065A303.

4 STUDY OBJECTIVES

4.1 Primary objective (study AC-065A302)

The primary objective is to determine whether selexipag has a favorable effect (relative to placebo) on time to first morbidity/mortality event in patients with PAH.

4.2 Secondary objectives

Secondary objectives are:

- to evaluate the effects of selexipag (relative to placebo) on exercise capacity and other secondary and exploratory efficacy endpoints in patients with PAH (objective for study AC-065A302).
- to evaluate the safety and tolerability of selexipag in patients with PAH (objective for study AC-065A302 and study AC-065A303).

5 ANALYSIS SETS

Patients are only included in any of the analysis sets described below if signed informed consent for study AC-065A302 has been documented.

5.1 Full analysis set

The FAS includes all randomized patients in study AC-065A302.

All main statistical analyses of all efficacy endpoints are based on the FAS. In order to adhere to the intention-to-treat principle as much as possible:

- patients are evaluated according to the study drug they have been randomized to (which may be different from the study drug they have received)
- all available efficacy data is included.

5.2 Per-protocol set

The PPS comprises data from all patients included in the FAS who

- were at least 18 years old at screening (based on CRF data)
- belonged to one of the subgroups of the Updated Clinical Classification for PAH Group 1 from Dana Point, mentioned in AC-065A302 inclusion criterion #3 at screening (based on PV code list document)
- received at least one dose of study drug in study AC-065A302 (based on PV code list document)
- did not interrupt intake of study drug (according to drug log CRF) for a total of at least 50% of the time between first and last study drug intake in AC-065A302 (based on CRF data)
- have not been off-treatment for at least 4 weeks at any point between first and last dosing of study drug in study in AC-065A302 (based on CRF data)
- had a valid 6-minute walk test (6MWT) at Visit 1, with “valid” defined as
 - o 6MWT performed prior to first intake of study drug (based on PV code list document)
 - o 6MWT not interrupted for reason not related to PAH (based on CRF data)

and up to (and including) the date when any of the following events (defined at patient level as the PPS cut-off date; it is not applicable for patients without any of the following events) occurred:

- administration of phosphodiesterase 5 (PDE-5) inhibitor or endothelin receptor agonist (ERA) or prostacyclin or prostacyclin analogs for more than 7 days after randomization without a CEC-confirmed morbidity/mortality event or prior to the onset date of a CEC-confirmed morbidity/mortality event (a switch within a drug class is not considered for exclusion) (based on PV code list document)
- intake of study drug in AC-065A302 other than which they were randomized to (based on PV code list document)

- individual unblinding of study drug to the investigator.

Patients are evaluated according to the study drug they have been randomized to.

The statistical analyses of the primary and secondary efficacy endpoints based on the PPS supplement those based on the FAS and assess the robustness of treatment effects.

5.3 Safety analysis set

The Safety analysis set includes all randomized patients who received at least one dose of study drug in study AC-065A302. All statistical safety analyses are based on the Safety analysis set.

Patients are evaluated according to the study drug they have received (which may be different from the study drug to which they have been randomized).

Safety analyses of study AC-065A302 only are presented on two treatment groups, defined as follows:

- If a patient has taken at least one dose of selexipag in study AC-065A302, then she/he is assigned to the AC-065A302 selexipag treatment group.
- If a patient has taken only placebo in study AC-065A302, then she/he is assigned to the AC-065A302 placebo treatment group.

Safety analyses of study AC-065A303 only are presented on the selexipag treatment group defined as follows:

- If a patient has taken at least one dose of selexipag in study AC-065A303, then she/he is assigned to the AC-065A303 selexipag treatment group.

Safety analyses of combined studies AC-065A302 and AC-065A303 (i.e., intra-patients comparison) are presented on four treatment groups, defined as follows:

- If a patient has taken at least one dose of selexipag in study AC-065A302 and no dose of selexipag in study AC-065A303, then she/he is assigned to the AC-065A302 selexipag treatment group.
- If a patient has taken only placebo in study AC-065A302 and no dose of selexipag in study AC-065A303, then she/he is assigned to the AC-065A302 placebo treatment group.
- If a patient has taken at least one dose of selexipag in each of the studies AC-065A302 and AC-065A303, then she/he is assigned to the selexipag/selexipag treatment group.
- If a patient has taken only placebo in study AC-065A302 and at least one dose of selexipag in study AC-065A303, then she/he is assigned to the placebo/selexipag treatment group.

Unless otherwise stated (e.g., for SAEs), the Safety analysis set comprises all available safety data of AC-065A302 up to analysis cut-off date for AC-065A302 (defined in

Section 3.2 and which is 27 Apr 2014) and all safety data of AC-065A303 up to 10 March 2014 (analysis cut-off date for AC-065A303).

5.4 PK analysis set

The PK analysis set includes all patients in the FAS who received at least one dose of the study drug in AC-065A302 and had at least one PK sample collected after initiation of study drug in AC-065A302.

5.5 QoL analysis set

The Quality of Life (QoL) analysis set includes all patients in the FAS for whom a suitable language of the CAMPHOR questionnaire for study AC-065A302 has been available at his/her site.

5.6 Ophthalmologic sub-study analysis set

The Ophthalmologic sub-study analysis set (OAS) includes all patients in the Safety analysis set who participate in the ophthalmologic sub-study.

5.7 Use of statistical analysis sets

Table 5 provides an overview of the use of the different analysis sets for the final analysis.

Table 5 Overview of the different analysis sets and their usage

	Full analysis set	Per-protocol set	QoL analysis set	Safety analysis set	PK analysis set	Ophthalmologic analysis set
Protocol deviations	✓					
Demographics	✓					✓
Baseline disease characteristics	✓					
Previous and concomitant therapies	✓					✓
Treatment exposure	✓			✓		✓
Primary and secondary efficacy endpoints (except CAMPHOR related efficacy endpoints)	✓	✓				
Exploratory efficacy endpoints (except CAMPHOR related efficacy endpoints)	✓					
CAMPHOR-related efficacy endpoints			✓			
Pharmacoeconomic endpoints	✓					
Safety endpoints				✓		
Listings	✓					
PK trough					✓	
Ophthalmologic sub-study endpoints						✓

6 PATIENT CHARACTERISTICS

6.1 Demographics

Demographics of the patients are sex, race, country, geographical region, age as a continuous variable as well as categorized into < 65 years, 65–74 years and ≥ 75 years, weight (kg), height (cm), and body mass index (BMI), all at AC-065A302 Screening. BMI is categorized as <25, 25–30, >30 kg/m².

Geographical regions are defined as follows (numbers are the first two digits of the center number):

Asia includes any country with the center number starting with 14 (China), 29 (Singapore), 45 (Taiwan), 65 (India), 66 (Malaysia), 71 (South Korea), or 72 (Thailand)

Eastern Europe includes any country with the center number starting with 16 (Czech Republic), 26 (Poland), 27 (Slovakia), 38 (Serbia), 39 (Hungary), 49 (Turkey), 61 (Belarus), 69 (Romania), 70 (Russia), or 73 (Ukraine)

Latin America includes any country with the center number starting with 60 (Argentina), 62 (Chile), 63 (Colombia), 67 (Mexico), or 68 (Peru)

North America includes any country with the center number starting with 13 (Canada) or 31 (USA)

Western Europe + Australia includes any country with the center number starting with 10 (Australia), 11 (Austria), 12 (Belgium), 17 (Denmark), 19 (France), 20 (Germany), 23 (Italy), 32 (Spain), 33 (Sweden), 34 (Switzerland), 35 (Great Britain), 40 (Israel), 41 (Netherlands), 50 (Ireland), or 64 (Greece).

6.2 Baseline disease characteristics

Baseline value for a given assessment is defined as the last assessment performed before or on the randomization date.

Baseline disease characteristics are:

- time from PAH diagnosis confirmed by right heart catheterization (RHC) to randomization
- RHC data (separately for patients with RHC within 6 months before randomization and for patients with RHC more than 6 months before randomization): systolic pulmonary arterial pressure (sPAP), diastolic pulmonary arterial pressure (dPAP), mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), mean right atrial pressure (mRAP), pulmonary capillary wedge pressure (PCWP), left ventricular end diastolic pressure (LVEDP), cardiac index, cardiac output (CO) and mixed venous oxygen saturation (SVO₂).
- etiology of PAH
- modified NYHA/WHO functional class at Baseline

- systolic blood pressure, diastolic blood pressure, heart rate at Baseline
- 6-minute walk distance (6MWD) at Baseline
- Borg dyspnea index at Baseline
- Outcome of the blinded expert review of PAH characteristics at Baseline is defined by the following three categories (as defined in the Charter of Expert medical review of blinded Baseline data):
 - o Typical PAH
 - o Atypical PAH (outcome is further categorized by the reviewers into Dana Point Classification 2, 3, 4, 5 or other)
 - o Consistent PAH.

6.3 Medical history of special interest

The following categories for medical history (ongoing or not) of special interest are defined based on MedDRA version 16:

- Eye disorder: any Preferred Term (PT) belonging to System Organ Class (SOC) “Eye disorder” or to the Standard MedDRA Query (SMQ) “Retinal disorders” (including both narrow and broad PTs).
- Hemorrhage: any PT belonging to at least of the following SMQ
 - o SMQ Haemorrhage (excluding laboratory terms)
 - o SMQ Gastrointestinal haemorrhage
- Thrombocytopenia: any PT belonging to at least one of the following SMQs:
 - o SMQ Haematopoietic thrombocytopenia (including both narrow and broad PTs)
 - o SMQ Haematopoietic cytopenias affecting more than one type of blood cell (narrow PTs only)
 - o or PT containing the string “Thrombocytop”.
- Hypotension: any PT listed below
 - o Blood pressure ambulatory decreased
 - o Blood pressure decreased
 - o Blood pressure diastolic decreased
 - o Blood pressure orthostatic decreased
 - o Blood pressure systolic decreased
 - o Diastolic hypotension
 - o Hypotension
 - o Mean arterial pressure decreased
 - o Orthostatic hypotension
 - o Procedural hypotension

- Bone disorders: any PT belonging to at least one of the following SMQs:
 - o SMQ Osteoporosis/osteopenia (including both narrow and broad PTs)
 - o SMQ Osteonecrosis (including both narrow and broad PTs)
 - o or with PTs containing the string “fracture”
- Liver disorders: any PT belonging to at least one of the following SMQs:
 - o SMQ “Hepatic disorder”, but excluding PTs listed in sub-SMQ “Liver-related coagulation and bleeding disturbances”
 - o SMQ “Biliary disorders”.
- Medical history denoting anemia or hemoglobin decrease: any of the following PTs:
 - ANAEMIA
 - IRON DEFICIENCY ANAEMIA
 - PANCYTOPENIA
 - BICYTOPENIA
 - HAEMOLYTIC ANAEMIA
 - NORMOCHROMIC NORMOCYTIC ANAEMIA
 - AUTOIMMUNE PANCYTOPENIA
 - BONE MARROW FAILURE
 - HYPOCHROMIC ANAEMIA
 - ANAEMIA MEGALOBLASTIC
 - MICROCYTIC ANAEMIA
 - PERNICIOUS ANAEMIA
 - HAEMOGLOBIN DECREASED
 - HAEMATOCRIT DECREASED
 - ANAEMIA MACROCYTIC

6.4 Definition of subgroups

The following subgroups, classifying patients according to relevant AC-065A302 demographic characteristics and disease characteristics at Baseline, are considered for the evaluation of selected efficacy and/or safety endpoints:

- concomitant specific PAH therapy groups at Baseline [see Section 8.1]:
 - o no PAH-specific medication
 - o ERA monotherapy
 - o PDE-5 inhibitor (PDE5-I) monotherapy
 - o combination of both ERA and PDE5-I
- NYHA/WHO functional class at Baseline:
 - o I/II
 - o III/IV

- sex:
 - male
 - female
- race/ethnicity:
 - Caucasian/Hispanic¹
 - Asian
 - Black
 - other
- age at screening:
 - < 65 years
 - ≥ 65 years
- PAH etiology at Baseline:
 - idiopathic, heritable, drug or toxin induced, associated with HIV infection
 - associated with connective tissue disease
 - associated with congenital heart disease with corrected systemic-to-pulmonary shunts
- geographical regions [see Section 6.1]:
 - Asia
 - Eastern Europe
 - Latin America
 - North America
 - Western Europe + Australia.

6.5 Definition of significant protocol deviations

The following protocol deviations are considered significant protocol deviations in order to have a restricted summary of patients with protocol deviations with most significant impact:

Inclusion/exclusion criteria:

- PAH belonging to the Dana Point Group 1 subgroups excluded per protocol (PV code 112)
- Subject has congenital heart disease with simple systemic to pulmonary shunt not repaired since at least 1 year (PV code 155)
- PAH belonging to the Dana Point classification Groups 2–5 (PV code 113)

¹ In the CRF collection of race included option “Hispanic” (in addition to option “Caucasian”) although Hispanic is actually an ethnicity within race “Caucasian”.

- Study entry RHC parameter criteria not met (PV code 111)
- Screening 6MWT not done (PV code 132)
- The walk distance at screening is not in the range of the protocol (PV code 136)
- Acute or chronic impairment (other than dyspnea) limiting the ability to comply with study requirements, in particular with 6MWT (e.g., angina pectoris, claudication, musculoskeletal disorder, need for walking aids) (PV code 120)
- Moderate or severe obstructive lung disease (PV code 114)
- Moderate or severe restrictive lung disease (PV code 115)
- Patient is < 18 years old or > 75 years old – PV confirmed (PV 1031)

Major significant GCP:

- Informed consent process not followed – Informed consent process not followed (PV code 5011)
- Patient randomized before Baseline Visit 1 (PV code 516)
- Informed consent process not followed for Post-treatment Observation Period (PTOP) – No signed ICF by patient/patients' next of kin (or no IRB, EC approval to waive ICF addendum 3) prior to starting study-mandated procedures and/or collecting any PTOP information (PV code 5111).

IMP dispensation:

Administration of wrong study medication bottle(s) and treatment from the other group received at any visit (defined by at least one of the following PV codes: 2011, 29341, 29351, 29361, 29371, 29381, 29391, 29401, 29411, 29421, 29431, 29441, 29451).

7 EXPOSURE TO STUDY DRUG

Duration of study treatment is defined for study AC-065A302 (selexipag and placebo) in Section 7.2 and for study AC-065A303 (selexipag) in Section 7.3.

7.1 Reason for discontinuation of study drug

The following rules are applied for the interim analysis to identify patients who discontinued study drug (separately for studies AC-065A302 and AC-065A303):

- EOS visit date present and preferred term for “Reason for End Date” of the last chronological interval in the study drug CRF different from “END OF DOUBLE-BLIND TREATMENT” or “UP-TITRATION”
- EOS visit date not present and preferred term for “Reason for End Date” equal to “DEATH” or “LOST TO FOLLOW UP” or “WITHDRAWAL OF CONSENT”.

For the final analysis it is assumed that for study AC-065A302 all patients are discontinued from study treatment at the end of the AC-065A302 Treatment Period. For study AC-065A303 patients who prematurely discontinued study drug are those with study completion page completed.

The reason for discontinuation of study drug is collected in the last record (chronological order by start date) of the study drug CRF pages.

Patients are considered as prematurely discontinued from study drug in study AC-065A302 if:

- reason for discontinuation is not “END OF TREATMENT PERIOD”
- and
- patient did not have a CEC-confirmed M/M event with onset date prior to or on end date of study drug.

7.2 Duration of study treatment in AC-065A302

Duration of study treatment in study AC-065A302 is defined as date of last intake of study drug minus date of first intake of study drug plus 1.

If the date of last study drug intake is missing, the analysis cut-off date of AC-065A302 (27 Apr 2014) is used – unless the patient has the EOS visit date or died prior to the analysis cut-off date of AC-065A302. In this case, minimum(EOS visit date, date of death) is used.

7.2.1 Study drug Titration Period and Maintenance Periods in study AC-065A302

The AC-065A302 study drug Titration Period starts at date of first intake of study drug and ends at AC-065A302 Study Day 87 (or earlier, if selexipag is discontinued before). Study Day 87 has been chosen according to the study protocol-specified maximum duration of the Titration Period including a 3 days’ tolerance. The AC-065A302 study

drug Maintenance Period starts at AC-065A302 Study Day 88 and ends at the date of last intake of study drug in study AC-065A302.

Study drug dose at the end of the AC-065A302 Titration Period is defined as the dose taken by the patient at AC-065A302 Study Day 87 (0 for patients with study drug discontinuation prior to AC-065A302 Study Day 87).

For each patient, the following study drug doses b.i.d. are defined:

- maximum and weighted-average selexipag dose in the AC-065A302 Titration Period
- maximum and weighted-average selexipag dose in the AC-065A302 Maintenance Period (for patients who entered this period)
- maximum and weighted-average selexipag dose in the entire AC-065A302 Treatment Period.

Weighting is done on the amount of time exposed to b.i.d. selexipag dose according to the drug log CRF. It is assumed that study drug is taken for the first time in the evening and this once daily (o.d.) dose is included in the weighted-average. When patients change dose during a day, it is assumed the previous dose is taken in the morning and the changed dose is taken in the evening of the same day. CRF entries like “3.5 tablets b.i.d.” are interpreted as 3 tablets (i.e., 600 mcg) in the morning and 4 tablets (i.e., 800 mcg) in the evening. All of these dosings are included in the calculation of weighted-average. Other non-b.i.d. dosings are not included (neither in the numerator nor denominator).

7.2.2 Individual maintenance dose of study drug in study AC-065A302

Note: The placebo equivalent IMD is not set to 0 but is defined in the following section similarly to selexipag IMD in order to assess the execution of study drug titration in both treatment arms.

For a patient with last study drug intake after AC-065A302 Study Day 87, her/his AC-065A302 IMD is defined as the selexipag or placebo equivalent dose b.i.d. to which she/he was reported to have taken for the longest duration in the maintenance period in study AC-065A302. If the longest duration corresponds to more than one b.i.d. dose (same number of days exposed with each b.i.d. dose) the IMD is the highest of these doses.

For a patient with last study drug intake before AC-065A302 Study Day 88, her/his AC-065A302 IMD is defined as the highest selexipag or placebo equivalent dose b.i.d. that did not lead to study drug discontinuation or down-titration in study AC-065A302.

For patients treated with a dosing regimen other than b.i.d., the IMD is set to “other”; the same holds for patients randomized but never treated.

For patients treated with selexipag or placebo equivalent 200 mcg b.i.d. only:

- if the dose 200 mcg b.i.d. did not lead to study drug discontinuation (reason for study drug end date is ‘end of treatment period’), then IMD is set to 200 mcg

- if the dose 200 mcg b.i.d. led to study drug discontinuation (reason for study drug end date is not 'end of treatment period'), then IMD is set to 0 mcg.

7.3 Duration of selexipag treatment in study AC-065A303

Duration of selexipag treatment in study AC-065A303 is defined as date of last intake of selexipag (up to the analysis cut-off date for AC-065A303, 10 Mar 2014) in study AC-065A303 minus date of first intake of selexipag in study AC-065A303 plus 1.

7.3.1 Selexipag Titration Period and Maintenance Period in study AC-065A303

The AC-065A303 selexipag Titration Period starts at date of first intake of selexipag in study AC-065A303 and ends at AC-065A303 Study Day 87 (or earlier, if selexipag is discontinued before). The AC-065A303 selexipag Maintenance Period starts at AC-065A303 Study Day 88 and ends at the date of last intake of selexipag in study AC-065A303.

Selexipag dose at the end of the AC-065A303 Titration Period is defined as the selexipag dose taken by the patient at AC-065A303 Study Day 87 (0 for patients with study drug discontinuation prior to AC-065A303 Study Day 87).

For each patient, the following selexipag doses b.i.d. are defined:

- maximum and weighted-average selexipag dose in the AC-065A303 Titration Period
- maximum and weighted-average selexipag dose in the AC-065A303 Maintenance Period (for patients who entered this period)
- maximum and weighted-average selexipag dose in the entire AC-065A303 Treatment Period.

Weighting is done on the amount of time exposed to b.i.d. selexipag dose according to the drug log CRF. It is assumed that study drug is taken for the first time in the evening and this o.d. dose is included in the weighted-average. When patients are up-titrated on the same day of their last previous dose intake, it is assumed the previous dose is taken o.d. on that day and the up-titrated dose is taken o.d. on that same day. These o.d. dosings are included in the calculation of weighted-average. Other non b.i.d. dosings are not included (neither in the numerator nor denominator).

7.3.2 Individual maintenance dose in study AC-065A303

For a patient with last study drug intake after AC-065A303 Study Day 87, her/his AC-065A303 IMD is defined as the selexipag dose b.i.d. to which she/he was exposed for the longest duration in study AC-065A303. If the longest duration corresponds to more than one b.i.d. dose (same number of days exposed with each b.i.d. dose) the IMD is the highest of these doses.

For a patient with last study drug intake before AC-065A303 Study Day 88, her/his AC-065A303 IMD is defined as highest b.i.d. dose that did not lead to study drug discontinuation or down-titration in study AC-065A303.

For patients treated with selexipag with but with a dosing regimen other than b.i.d., the IMD is set to “other”; the same holds for patients enrolled but never treated.

For patients treated with selexipag 200 mcg b.i.d. only:

- if the dose 200 mcg b.i.d. did not lead to study drug discontinuation (study completion page is not completed), then IMD is set to 200 mcg
- if the dose 200 mcg b.i.d. led to study drug discontinuation (study completion page is completed), then IMD is set to 0 mcg.

8 PREVIOUS AND CONCOMITANT MEDICATIONS

8.1 PAH-specific medication

This includes any of the following PAH-specific medication (except study treatment): “Ambrisentan”, “Bosentan”, “Sitaxentan”, “Macitentan”, “Sildenafil”, “Tadalafil”, “Vardenafil”, “Udenafil”, “Riociguat”, “Iloprost”, “Epoprostenol”, “Treprostinil”, “Beraprost”. The following subgroups of patients are defined (separately for studies AC-065A302 and AC-065A303):

- Treatment with ERAs monotherapy – identified by the following preferred terms (“Ambrisentan” OR “Bosentan” OR “Sitaxentan” OR “Macitentan”) AND NOT (“Sildenafil” OR “Tadalafil” OR “Vardenafil” OR “Udenafil”) AND NOT “Riociguat”.
- Treatment with PDE5-Is monotherapy – identified by the following preferred terms (“Sildenafil” OR “Tadalafil” OR “Vardenafil” OR “Udenafil”) AND NOT (“Ambrisentan” OR “Bosentan” OR “Sitaxentan” OR “Macitentan”) AND NOT “Riociguat”.
- Treatment with combination of both ERAs and PDE5-Is – identified by the following preferred terms (“Ambrisentan” OR “Bosentan” OR “Sitaxentan” OR “Macitentan”) AND (“Sildenafil” OR “Tadalafil” OR “Vardenafil” OR “Udenafil”) AND NOT “Riociguat”.
- Treatment with prostacyclin/analogs (irrespective of treatment with ERAs or PDE5-Is or “Riociguat”) – identified by the following preferred terms “Iloprost” OR “Epoprostenol” OR “Treprostinil” OR “Beraprost” (it is expected to be rare as prostacyclin/analogs are not allowed to be co-administered according to the study protocol).
- Treatment with soluble guanylate cyclase stimulator (irrespective of ERAs or PDE5-Is or prostacyclin/analogs) – identified by the preferred term “Riociguat”.
- No treatments as defined in the bullet points above.

Note: Selexipag administered in AC-065A303 and reported in AC-065A302/PTOP has been coded as “Investigational drug”. Therefore patients having taken selexipag during AC-065A303 are described as receiving “Investigational drug” in tables summarizing concomitant medications not for PAH.

Previous PAH-specific medication

Previous PAH-specific medication is any PAH-specific medication/therapy with end date prior to the AC-065A302 study drug start date.

PAH-specific medication concomitant at Baseline

PAH-specific medication concomitant at Baseline is defined as any PAH-specific medication/therapy with start date prior to the AC-065A302 study drug start date and end date after or on the AC-065A302 study drug start date.

Concomitant new PAH-specific medication

Concomitant PAH-specific medication is defined as any PAH-specific medication/therapy with start date on or after the AC-065A302 study drug start date and on or before the study drug discontinuation date in study AC-065A303 (or AC-065A302 for patients who have not entered study AC-065A303).

Subsequent PAH-specific medication

Subsequent PAH-specific medication is defined as any PAH-specific medication/therapy with start date after the study drug discontinuation date in study AC-065A303 (or AC-065A302 for patients who have not entered study AC-065A303) part of PTOP.

8.2 PAH-non-specific medication

This includes any medication with preferred term belonging to any of the ATC code: Diuretics (ATC code C03), calcium-channel blocker (ATC code C08), oxygen (ATC code V03AN0 and PT “Oxygen”) or Glycosides (ATC code C01A).

Previous PAH-non-specific medication

Previous PAH-non-specific medication is any PAH-non-specific medication/therapy with end date prior to the AC-065A302 study drug start date.

PAH-non-specific medication concomitant at Baseline

PAH-non-specific medication concomitant at Baseline is defined as any PAH-non-specific medication/therapy with start date prior to the AC-065A302 study drug start date and end date after or on the AC-065A302 study drug start date.

Concomitant new PAH-non-specific medication

Concomitant PAH-non-specific medication is defined as any PAH-non-specific medication/therapy with start date on or after the AC-065A302 study drug start date and on or before the study drug discontinuation date in study AC-065A303 (or AC-065A302 for patients who have not entered study AC-065A303).

8.3 Medication not for PAH

This includes any medication reported that is not PAH-specific or PAH-non-specific as defined in Section [8.1](#) or Section [8.2](#).

Previous medication not for PAH

A previous medication not for PAH is defined as any medication not for PAH with end date prior to the AC-065A302 study drug start date.

Medication not for PAH concomitant at Baseline

Medication not for PAH concomitant at Baseline is defined as any medication not for PAH with start date before the AC-065A302 study drug start date and end date after or on the AC-065A302 study drug start date.

Concomitant new medication not for PAH

Concomitant medication not for PAH is defined as any medication not for PAH with start date on or after the AC-065A302 study drug start date and on or before the study drug discontinuation date in study AC-065A303 (or AC-065A302 for patients who have not entered study AC-065A303).

9 PRIMARY ENDPOINT DEFINITION

For the primary efficacy endpoint, the following morbidity/mortality events occurring up to 7 days after last study drug intake in the AC-065A302 Treatment Period and confirmed by the CEC are considered:

- death (all-cause mortality)
- hospitalization for worsening of PAH based on criteria defined in the study protocol
- worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy
- initiation of parenteral (subcutaneous or intravenous) prostanoid therapy or chronic oxygen therapy due to worsening of PAH
- disease progression (patients in modified NYHA/WHO functional class II or III at Baseline) confirmed by a decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) and worsening of NYHA/WHO functional class
- disease progression (patients in modified NYHA/WHO functional class III or IV at Baseline) confirmed by a decrease in 6MWD from Baseline ($\geq 15\%$, confirmed by 2 tests on different days within 2 weeks) and need for additional PAH-specific therapy.

The last two bullet points imply: for patients in modified NYHA/WHO functional class I at Baseline visit (Visit 1), the component disease progression is disregarded for the primary endpoint (even if disease progression would be confirmed by CEC).

Date of the first CEC-confirmed morbidity/mortality event (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is defined as the first event onset date provided by the CEC.

Time to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as date of the first CEC-confirmed morbidity/mortality event (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) minus date of randomization plus 1.

Note: Patient 7003-22769 was randomized on 15 March 2011 to placebo but was never treated. The patient experienced a CEC-confirmed event “Disease progression” on 16 March 2011. This event is accounted for in all analyses beyond the primary analysis of the primary endpoint.

Censoring rules

For a patient without a CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in the AC-065A302 Treatment Period, time to first CEC-confirmed morbidity/mortality event (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is defined as

- for randomized patients with at least one intake of study drug and not consented for the AC-065A302 Post-Treatment Observation Period: $\text{minimum}(\text{date of last study drug intake in the AC-065A302 Treatment Period plus 7, EOS visit date, date of last contact, analysis cut-off date of AC-065A302 [27 Apr 2014]})$ minus date of randomization plus 1
- for randomized patients with at least one intake of study drug and consented for the AC-065A302 Post-Treatment Observation Period: $\text{minimum}(\text{date of last study drug intake in the AC-065A302 Treatment Period plus 7, date of last contact, 27 Apr 2014})$ minus date of randomization plus 1
- for randomized patients without any intake of study drug: $\text{minimum}(\text{maximum}[\text{EOS visit date, randomization date}], \text{date of last contact, 27 Apr 2014})$ minus date of randomization plus 1.

These constitute right-censored observations.

CEC-confirmed morbidity/mortality events with onset date (as per CEC) up to 16 August 2011 are considered as censored at event onset date in the primary statistical analysis. In the event that a patient with a CEC-confirmed morbidity/mortality event with onset date up to 16 August 2011 has a subsequent CEC-confirmed morbidity/mortality event with onset date after 16 August 2011, then the first event is disregarded and the second event counts as the event in the statistical analysis.

Following an agreement with the FDA (meeting held on 11 July 2014), it was decided to exclude events with an onset date up to 16 August 2011 only for the main analysis of the primary endpoint and to include events with an onset date up to 16 August 2011 in all sensitivity and subgroup analyses of the primary endpoint as well as in all secondary and exploratory time-to-event endpoints analyses. Therefore in the supportive analyses (including sub-group analyses) of the primary efficacy endpoint, CEC-confirmed morbidity/mortality events with onset date (as per CEC) up to 16 August 2011 are considered as events. In the supportive analysis of morbidity/mortality events as reported by the investigator (irrespective of CEC-confirmation), morbidity/mortality events with onset date (as per investigator) up to 16 August 2011 are considered as events.

10 SECONDARY ENDPOINTS DEFINITIONS

10.1 Absolute change from Baseline to Week 26 in 6MWD measured at trough

The absolute change from Baseline to Week 26 in 6MWD measured at trough level of study drug is defined as the difference between Week 26 value and Baseline value. The Week 26 value is the one identified for the Week 26 window as defined in Section 24.4, including all available 6MWT values. If the date of the 6MWT at Clinical Worsening Event (CWE) Visit is missing, the date of the NYHA/WHO functional class or blood pressure assessments is used.

A 6MWT at Week 26 is defined as “at trough” if the date of last selexipag administration prior to the 6MWT at Week 26 is the day before the date of the 6MWT at Week 26 or on the same date but if there is at least 12 hours between the last selexipag intake and the 6MWT (defined for selexipag patients with relevant PV code). If the 6MWT at Week 26 corresponds to a 6MWT performed at CWE visit, the 6MWT is considered by default at trough.

For the main analysis, all available 6MWT data at Week 26 are used irrespective of whether the test was performed at trough or not.

For patients without any 6MWD available at Week 26, the following main imputation algorithm is applied:

- Rule 1: For patients unable to walk at Week 26 (includes
 - patients who died before study Day 271 without any visit performed in the Week 26 time window
 - patients for whom Week 26 visit corresponds to a CWE visit and were unable to walk for PAH reason, i.e., reason is ‘Dyspnea/Fatigue’ or reason is coded as ‘Related to Pulmonary Arterial Hypertension’),
a 0 is imputed for 6MWD at Week 26. Note: For patients unable to walk for PAH reasons at scheduled visits, 0 m is entered in the CRF.
- Rule 2 (if rule 1 does not apply): the second lowest observed 6MWD value at Week 26 (irrespective of at trough level) in the same analysis set (FAS or FAS excluding selexipag patients with 6MWT at Week 26 not performed at trough, or PPS excluding selexipag patients with 6MWT at Week 26 not performed at trough), irrespective of study treatment group, is imputed.

The following sensitivity imputation algorithms are defined for patients without any 6MWD at Week 26 available:

- Sensitivity imputation algorithm A: applying only rule 1 defined above. Rule 2 is not applied and the remaining missing values are not imputed.
- Sensitivity imputation algorithm B: applying rule 1 defined above. Rule 2 is replaced by the following rule: the 25th percentile of the observed 6MWD values at Week 26 in the FAS, irrespective of study treatment group, is imputed.

- Sensitivity imputation algorithm C: applying rule 1 defined above. Rule 2 is replaced by the following rule: the patient's last available 6MWD prior to Week 26 (may be the baseline 6MWD) is imputed.

10.2 Absence of worsening from Baseline to Week 26 in modified NYHA/WHO functional class

Worsening is defined as any increase in functional class level as compared to modified NYHA/WHO functional class at Baseline.

For patients with missing modified NYHA/WHO functional class at Week 26, the modified NYHA/WHO functional class is considered as having worsened from Baseline at Week 26 in the main analysis.

As a sensitivity approach, missing modified NYHA/WHO functional class values at Week 26 are not imputed, hence the absence of worsening is set to missing.

10.3 Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period

The following two CEC-confirmed morbidity/mortality events are considered:

- hospitalization for worsening of PAH based on predefined criteria
- death due to PAH.

Date of the first CEC-confirmed hospitalization due to PAH worsening or death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as the onset date provided by the CEC.

Time to first CEC-confirmed hospitalization due to PAH worsening or death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is defined as the date of the first CEC-confirmed hospitalization due to PAH worsening or death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed hospitalization due to PAH worsening or death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period), time to first CEC-confirmed hospitalization due to PAH worsening or death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is defined as

- for patients with at least one administration of study drug and who died (but not due to PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period: date of death.
- for patients with at least one administration of study drug and who did not consent to the AC-065A302 Post-Treatment Observation Period: minimum(date of last study

drug intake in the AC-065A302 Treatment Period plus 7, EOS visit date, date of last contact, analysis cut-off date of AC-065A302 [27 Apr 2014]) minus date of randomization plus 1.

- for patients with at least one administration of study drug and who consented to the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, date of last contact, 27 Apr 2014) minus date of randomization plus 1.
- for randomized patients without any administration of study drug: minimum(maximum[EOS visit date, randomization date], date of last contact, 27 Apr 2014) minus date of randomization plus 1.

These constitute (potentially informative) right-censored observations.

10.4 Time from randomization to death up to Study Closure

Time from randomization to death up to Study Closure [as defined in Section 24.2.5] is defined as date of death minus date of randomization plus 1.

Censoring rules

For patients not known to be deceased, time from randomization to death is defined as minimum(date of last contact, analysis cut-off date of AC-065A302 [27 Apr 2014]) minus date of randomization plus 1

These constitute right-censored observations.

10.5 Cambridge Pulmonary Hypertension Outcome Review (CAMPBOR)

The details on the CAMPBOR questionnaire administration, score/subscale calculations and rules for missing items are described in the CAMPBOR Guidelines for Users, [Galen Research 2004].

CAMPBOR questionnaire was administered only in centers selected by availability of validated questionnaire in local language.

Baseline is defined as the last assessment performed before or on date of randomization.

10.5.1 Absolute change from Baseline to Week 26 in sub-scale ‘Breathlessness’ of CAMPBOR ‘Symptoms’

For patients in the QoL analysis set, the sub-scale ‘Breathlessness’ of CAMPBOR ‘Symptoms’ is defined as the sum of the ‘Breathlessness’ items 11 to 18. It will range from 0 (good) to 8 (poor).

Absolute change from Baseline to Week 26 in sub-scale ‘Breathlessness’ of CAMPBOR ‘Symptoms’ is defined as the difference between the Week 26 value and the Baseline value.

For patients with sub-scale ‘Breathlessness’ of CAMPBOR ‘Symptoms’ score available at baseline but without any sub-scale ‘Breathlessness’ of CAMPBOR ‘Symptoms’ score available at Week 26, the following imputation algorithm is applied:

- Rule 1: For patients who died before study Day 271 without any visit performed in the Week 26 time window, a score of 8 (worst possible score) is imputed.
- Rule 2 (if rule 1 does not apply): For patients who discontinued study drug before study Day 271 without any visit performed in the Week 26 time window:
 - if patient's last available modified NYHA/WHO functional class is I or II: the 88th percentile of the observed sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score values at Week 26 in patients with modified NYHA/WHO functional class I or II at Week 26 (irrespective of study treatment group) is imputed.
 - if patient's last available modified NYHA/WHO functional class is III or IV: the 88th percentile of the observed sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score values at Week 26 in patients with modified NYHA/WHO functional class III or IV at Week 26 (irrespective of study treatment group) is imputed.
- Rule 3 (if rule 1 and rule 2 do not apply): patient's last available sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score prior to Week 26 is imputed.

10.5.2 Absolute change from Baseline to Week 26 in CAMPHOR 'Symptoms' score

For patients in the QoL analysis set, the CAMPHOR 'Symptoms' score is defined as the sum of the 'Symptoms' items 1 to 25. It will range from 0 (good) to 25 (poor).

Absolute change from Baseline to Week 26 in CAMPHOR 'Symptoms' score is defined as the difference between the Week 26 value and the Baseline value.

For patients with CAMPHOR 'Symptoms' score available at baseline but without any CAMPHOR 'Symptoms' score available at Week 26, the following imputation algorithm is applied:

- Rule 1: For patients who died before study Day 271 without any visit performed in the Week 26 time window, a score of 25 (worst possible score) is imputed.
- Rule 2 (if rule 1 does not apply): For patients who discontinued study drug before study Day 271 without any visit performed in the Week 26 time window:
 - if patient's last available modified NYHA/WHO functional class is I or II: the 88th percentile of the observed CAMPHOR 'Symptoms' score values at Week 26 in patients with modified NYHA/WHO functional class I or II at Week 26 (irrespective of study treatment group) is imputed.
 - if patient's last available modified NYHA/WHO functional class is III or IV: the 88th percentile of the observed CAMPHOR 'Symptoms' score values at Week 26 in patients with modified NYHA/WHO functional class III or IV at Week 26 (irrespective of study treatment group) is imputed.
- Rule 3 (if rule 1 and rule 2 do not apply): patient's last available CAMPHOR 'Symptoms' score prior to Week 26 is imputed.

11 EXPLORATORY ENDPOINTS DEFINITIONS

Table 6 Overview of exploratory efficacy endpoints

Exploratory efficacy endpoints related to morbidity/mortality	
11.1	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure
11.2	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period
11.3	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure
11.4	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period
11.5	Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period
11.6	Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study Closure
11.7	Time from randomization to first CEC-confirmed morbidity/mortality event up to Study Closure
11.8	Time from randomization to CEC-confirmed death due to PAH up to Study Closure
Exploratory efficacy endpoints related to 6MWD	
11.9	Absolute changes in 6MWD at trough from Baseline to all scheduled visits other than Week 26
11.9	Absolute change in 6MWD at trough from Baseline to EOS
Exploratory efficacy endpoints related to modified NYHA/WHO functional class	
11.10	Absence of worsening from Baseline at scheduled visits other than Week 26
11.10	Absence of worsening from Baseline to EOS
Exploratory efficacy endpoints related to Borg dyspnea index	
11.11	Borg dyspnea index at scheduled visits
11.11	Borg dyspnea index at EOS

Exploratory efficacy endpoints related to plasma NT pro-brain natriuretic peptide	
11.12	Absolute change in plasma NT pro-BNP from Baseline at scheduled visits
11.12	Absolute change in plasma NT pro-BNP from Baseline to EOS
Exploratory efficacy endpoints related to CAMPHOR	
11.13	Absolute changes in CAMPHOR sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ from Baseline at scheduled visits other than Week 26
11.13	Absolute changes in CAMPHOR ‘Symptoms’ score from Baseline at scheduled visits other than Week 26
11.13	Absolute change in CAMPHOR sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ from Baseline to EOS
11.13	Absolute change in CAMPHOR ‘Symptoms’ score from Baseline to EOS

Note: Following an agreement with the FDA (meeting held on 11 July 2014), it was decided to exclude events with an onset date up to 16 August 2011 only for the main analysis of the primary endpoint and to include events with an onset date up to 16 August 2011 in all sensitivity and subgroup analyses of the primary endpoint as well as in all secondary and exploratory time-to-event endpoints analyses. Therefore in all the analyses of the exploratory efficacy endpoints CEC-confirmed morbidity/mortality events with onset date (as per CEC) up to 16 August 2011 are considered as events and deaths with date of death up to 16 August 2011 are considered as deaths.

11.1 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure

The following four CEC-confirmed morbidity/mortality events are considered:

- death (all-cause mortality)
- hospitalization for worsening of PAH based on predefined criteria
- worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy
- initiation of parenteral (subcutaneous or intravenous) prostanoid therapy or chronic oxygen therapy due to worsening of PAH.

Morbidity/mortality events in the PTOP CEC system and reported as “no” by the investigator are excluded in the analysis. This convention has become necessary because of an unexpected possibility for the CEC members in the PTOP CEC system.

Date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure [as defined in Section 24.2.5] is defined as the onset date provided by the CEC (or the investigator, if the date is not provided by the CEC).

Time to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure is defined as the date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression”) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed morbidity/mortality event (other than “disease progression”), time to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure is defined as minimum(date of last contact, analysis cut-off date of AC-065A302 [27 Apr 2014]) minus date of randomization plus 1

These constitute right-censored observations.

11.2 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period

The same four CEC-confirmed morbidity/mortality events as mentioned in Section [11.1](#) are considered.

Date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as the onset date provided by the CEC.

Time to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as the date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression”) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed morbidity/mortality event (other than “disease progression”), time to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as

- for randomized patients with at least one intake of study drug and not consented for the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, EOS visit date, date of last contact, analysis cut-off date of AC-065A302 [27 Apr 2014]) minus date of randomization plus 1
- for randomized patients with at least one intake of study drug and consented for the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, date of last contact, 27 Apr 2014) minus date of randomization plus 1
- for all randomized patients without any intake of study drug: minimum(maximum[EOS visit date, randomization date], date of last contact, 27 Apr 2014) minus date of randomization plus 1.

These constitute right-censored observations.

11.3 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure

The following three CEC-confirmed morbidity/mortality events are considered:

- death (all-cause mortality)
- hospitalization for worsening of PAH based on predefined criteria
- worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy.

Morbidity/mortality events in the PTOP CEC system and reported as “no” by the investigator are excluded in the analysis. This convention has become necessary because of an unexpected possibility for the CEC members in the PTOP CEC system..

Date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure is defined as the onset date provided by the CEC (or the investigator, if the date is not provided by the CEC).

Time to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure is defined as the date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) minus date of randomization plus 1.

Censoring rules

- For patients without a CEC-confirmed morbidity/mortality event (other than “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH), time to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure is defined as minimum(date of last contact, analysis cut-off date of AC-065A302 [27 Apr 2014]) minus date of randomization plus 1

These constitute right-censored observations.

11.4 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period

The same three CEC-confirmed morbidity/mortality events as mentioned in Section 11.3 are considered.

Date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as the onset date provided by the CEC.

Time to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as the date of the first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed morbidity/mortality event (other than “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH), time to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as

- for randomized patients with at least one intake of study drug and not consented for the AC-065A302 Post-Treatment Observation Period: $\text{minimum}(\text{date of last study drug intake in the AC-065A302 Treatment Period plus 7, EOS visit date, date of last contact, analysis cut-off date of AC-065A302 [27 Apr 2014]})$ minus date of randomization plus 1
- for randomized patients with at least one intake of study drug and consented for the AC-065A302 Post-Treatment Observation Period: $\text{minimum}(\text{date of last study drug intake in the AC-065A302 Treatment Period plus 7, date of last contact, 27 Apr 2014})$ minus date of randomization plus 1
- for all randomized patients without any intake of study drug: $\text{minimum}(\text{maximum}[\text{EOS visit date, randomization date}], \text{date of last contact, 27 Apr 2014})$ minus date of randomization plus 1.

These constitute right-censored observations.

11.5 Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period

Date of CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as the date of death provided by the CEC.

Time to CEC-confirmed death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is defined as the date of death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period), time to death due to PAH (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is defined as

- for patients with at least one administration of study drug and who died (not due to PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period: date of death
- for patients with at least one administration of study drug and who did not consent to the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, EOS visit date, date of last contact, analysis cut-off date of AC-065A302 [27 Apr 2014]) minus date of randomization plus 1
- for patients with at least one administration of study drug and who consented to the AC-065A302 Post-Treatment Observation Period: minimum(date of last study drug intake in the AC-065A302 Treatment Period plus 7, date of last contact, 27 Apr 2014) minus date of randomization plus 1
- for randomized patients without any administration of study drug: minimum(maximum[EOS visit date, randomization date], date of last contact, 27 Apr 2014) minus date of randomization plus 1.

These constitute (potentially informative) right-censored observations.

11.6 Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study Closure

The following two CEC-confirmed morbidity/mortality events are considered:

- hospitalization for worsening of PAH based on predefined criteria
- death due to PAH.

Morbidity/mortality events in the PTOP CEC system and reported as “no” by the investigator are excluded in the analysis. This convention has become necessary because of an unexpected possibility for the CEC members in the PTOP CEC system.

Date of the first CEC-confirmed hospitalization due to PAH worsening or death due to PAH up to Study Closure is defined as the onset date provided by the CEC (or the investigator, if the date is not provided by the CEC).

Time to first CEC-confirmed hospitalization due to PAH worsening or death due to PAH (up to Study Closure) is defined as the date of the first CEC-confirmed hospitalization due to PAH worsening or death due to PAH (up to Study Closure) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed hospitalization due to PAH worsening or death due to PAH, time to first CEC-confirmed hospitalization due to PAH worsening or death due to PAH up to Study Closure is defined as

- date of death for patients deceased (not due to PAH) up to Study Closure and for all other patients defined as
- minimum(date of last contact, analysis cut-off date of AC-065A302 [27 Apr 2014]) minus date of randomization plus 1

These constitute right-censored observations.

11.7 Time from randomization to first CEC-confirmed morbidity/mortality event up to Study Closure

The components of this endpoint are the same as for the primary efficacy endpoint described in Section 9.

Morbidity/mortality events in the PTOP CEC system and reported as “no” by the investigator are excluded in the analysis. This convention has become necessary because of an unexpected possibility for the CEC members in the PTOP CEC system.

Date of the first CEC-confirmed morbidity/mortality event up to Study Closure is defined as the onset date provided by the CEC (or the investigator, if the date is not provided by the CEC).

Time to first CEC-confirmed morbidity/mortality event up to Study Closure is defined as the date of the first CEC-confirmed morbidity/mortality event minus date of randomization plus 1.

Note: Patient 7003-22769 was randomized on 15 March 2011 to placebo but was never treated. The patient experienced an CEC-confirmed event “Disease progression” on 16 March 2011. This event is accounted for in all analyses of this exploratory endpoint.

Censoring rules

For patients without a CEC-confirmed morbidity/mortality event, time to first CEC-confirmed morbidity/mortality event up to Study Closure is defined as

minimum(date of last contact, analysis cut-off date of AC-065A302 [27 Apr 2014]) minus date of randomization plus 1

These constitute right-censored observations.

11.8 Time from randomization to CEC-confirmed death due to PAH up to Study Closure

Date of CEC-confirmed death due to PAH up to Study Closure is defined as the date of death due to PAH provided by the CEC (or the investigator, if the date is not provided by the CEC).

Time to CEC-confirmed death due to PAH up to Study Closure is defined as the date of death due to PAH (up to Study Closure) minus date of randomization plus 1.

Censoring rules

For patients without a CEC-confirmed death due to PAH, time to CEC-confirmed death due to PAH up to Study Closure is defined as

- date of death for patients deceased (not due to PAH) up to Study Closure and for all other patients defined as
- minimum(date of last contact, analysis cut-off date of AC-065A302 [27 Apr 2014]) minus date of randomization plus 1

These constitute right-censored observations.

11.9 Exploratory endpoints related to 6MWD

Absolute changes from Baseline to all scheduled visits other than Week 26 in 6MWD measured at trough The definition of absolute change from Baseline to all scheduled visits other than Week 26 is analogous to the absolute change from Baseline to Week 26 described in Section 10.1. All available 6MWD values at a scheduled visit other than Week 26 are used irrespective of whether the test was performed at trough or not. For patients without any 6MWD values available at a scheduled visit other than Week 26, no imputation is applied.

Absolute change in 6MWD from Baseline to EOS at trough

The absolute change from Baseline to EOS in 6MWD measured at trough level of study drug is defined as the difference between EOS value and Baseline value.. All available 6MWD values at EOS are used irrespective of whether the test was performed at trough or not. For patients without any 6MWD values available at EOS, no imputation is applied.

11.10 Exploratory endpoints related to modified NYHA/WHO functional class

Absence of worsening from Baseline at scheduled visits other than Week 26

The definition is analogous to the absence of worsening from Baseline at Week 26 described in Section 10.2. For patients with missing modified NYHA/WHO functional class at a scheduled visit other than Week 26, no imputation is applied.

Absence of worsening from Baseline to EOS

For patients alive at EOS, the definition is analogous to the absence of worsening from Baseline at Week 26 described in Section 10.2. For patients with missing modified NYHA/WHO functional class at EOS visit, no imputation is applied.

11.11 Exploratory endpoints related to Borg dyspnea index

No imputation is applied for missing Borg dyspnea index values.

Borg dyspnea index at scheduled visits

The Borg dyspnea index at scheduled visits is directly taken from the CRF.

Borg dyspnea index at EOS

For patients alive at EOS, the Borg dyspnea index at EOS is directly taken from the CRF.

11.12 Exploratory endpoints related to plasma NT pro-BNP

No imputation is applied for missing plasma N-terminal pro-brain natriuretic peptide (NT pro-BNP) values.

Absolute change in plasma NT pro-BNP from Baseline at scheduled visits

The absolute change from Baseline in plasma NT pro-BNP is defined as the differences between the values at scheduled visits and the Baseline value.

Absolute change in plasma NT pro-BNP from Baseline to EOS

For patients alive at EOS, the absolute change from Baseline to EOS in plasma NT pro-BNP is defined as the difference between the value at EOS and the Baseline value.

11.13 Exploratory endpoints related to CAMPHOR

Absolute changes in CAMPHOR sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ from Baseline at scheduled visits other than Week 26

The definition is analogous to the absolute change from Baseline to Week 26 described in Section 10.5.1. For patients without any sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ score available at a scheduled visit other than Week 26, no imputation is applied.

Absolute changes in CAMPHOR ‘Symptoms’ score from Baseline at scheduled visits other than Week 26

The definition is analogous to the absolute change from Baseline to Week 26 described in Section 10.5.2. For patients without any CAMPHOR ‘Symptoms’ score available at a scheduled visit other than Week 26, no imputation is applied.

Absolute change in CAMPHOR sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ from Baseline to EOS

For patients alive at EOS, the definition is analogous to the absolute change from Baseline to Week 26 described in Section [10.5.1](#). For patients without any sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ score available at EOS visit, no imputation is applied.

Absolute change in CAMPHOR ‘Symptoms’ score from Baseline to EOS

For patients alive at EOS, the definition is analogous to the absolute change from Baseline to Week 26 described in Section [10.5.2](#). For patients without any CAMPHOR ‘Symptoms’ score available at EOS visit, no imputation is applied.

12 PHARMACO-ECONOMIC ENDPOINTS DEFINITIONS

All-cause hospitalizations are taken from the adverse event (AE) CRF page in which hospital admission dates are documented.

PAH-related hospitalizations are defined as hospitalizations associated with AEs coded by the following MedDRA (version 16) Preferred Terms: “acute right ventricular failure”, “right ventricular failure”, “cardiac failure”, “pulmonary arterial hypertension”, “pulmonary hypertension”, “cardiac failure chronic”, “cor pulmonale acute”, “cardiac failure congestive”, “right ventricular dysfunction”, “syncope”, “loss of consciousness”, “dyspnoea”, “dyspnoea at rest”, “hypoxia”, “pulmonary oedema”, “oedema peripheral”, “atrial fibrillation”, “atrial flutter”, “cardio-respiratory arrest”, “cardiopulmonary failure”.

12.1 Annualized number of all-cause and PAH-related hospitalizations up to the EOS visit

The number of hospitalizations initiated after randomization up to the EOS visit is annualized by multiplying with 365.25 days divided by (EOS visit date minus randomization date + 1). If there is no EOS visit available for a patient, the date of last contact is used.

12.2 Annualized number of days spent in hospital up to the EOS visit

For each hospitalization, the number of days in hospital is calculated as discharge date minus admission date plus 1. For each patient, the number of days spent in hospital is the sum of the number of days in hospital for all his/her hospitalizations up to the EOS visit. If there is no EOS visit available for a patient, the date of last contact is used.

The number of days spent in hospital for all causes is annualized by multiplying with 365.25 days divided by (EOS visit date minus randomization date + 1).

12.3 Annualized number of days spent in hospital for PAH-related causes up to the EOS visit

For each hospitalization for PAH-related causes, the number of days in hospital is calculated as discharge date minus admission date plus 1. For each patient, the number of days spent in hospital for PAH-related causes is the sum of the number of days in hospital for all his/her hospitalizations for PAH-related causes up to the EOS visit. If there is no EOS visit available for a patient, the date of last contact is used.

The number of days spent in hospital for PAH-related causes is annualized by multiplying with 365.25 days divided by (EOS visit date minus randomization date + 1).

13 PHARMACODYNAMIC AND PHARMACOKINETIC ENDPOINTS DEFINITIONS

Trough plasma concentrations of ACT-293987 (selexipag) and ACT-333679 are measured at Baseline Visit, Week 4, Week 8, Week 16, Week 26 (Month 6), Week 52 (Month 12), and EOS.

The PK endpoints are trough plasma concentrations of ACT-293987 (selexipag) and ACT-333679 after start of study drug. For this purpose, “trough” is defined as the plasma sample taken before the morning dose, with the last study drug administration one day prior to the PK sampling. If the date of last study drug administration prior to PK sampling is more than one calendar day before or on the same calendar day as the actual PK sampling the measurement is excluded from the statistical analysis.

The population PK analysis of all plasma concentrations (trough concentrations and concentrations of post-dose samples at Visit 4) and the population pharmacokinetic/pharmacodynamic analysis are described in a separate document.

14 SAFETY AND TOLERABILITY ENDPOINTS DEFINITIONS

Both interim and final analyses are based on MedDRA version 16, and SOC/PT/SMQ definitions are taken from there.

For the analysis of safety endpoints in study AC-065A302, Baseline is defined as the last assessment prior to or on start date of study drug intake in study AC-065A302. If more than one assessment is performed on the start date of study drug intake, then the mean of these assessments is defined as Baseline value (however, if an assessment on the start date of study drug intake is recorded under the “Screening Visit” label, it is not considered for calculation of the mean).

For analysis of safety endpoints in study AC-065A303, Baseline is defined as the last assessment prior to or on start date of study drug in study AC-065A302 for patients in the AC-065A302 selexipag treatment group and as the last assessment prior to or on start date of study drug in study AC-065A303 for patients in the AC-065A302 placebo treatment group.

14.1 Definition of treatment-emergent events/data

For safety data (e.g., AEs, laboratory abnormalities, laboratory test results, ECG abnormalities, etc.) included in the Safety analysis set the term “treatment-emergent” is defined in the final analysis of both AC-065A302 and AC-065A303 as follows:

- for patients who did not enter study AC-065A303 prior to 11 March 2014: all safety data that are new or worsening compared to Baseline with
 - event (onset) date after first dose of study drug in AC-065A302 AND
 - event (onset) date not later than 7 days after last study drug intake in AC-065A302 Treatment Period
- for patients who entered study AC-065A303 prior to 11 March 2014: all safety data that are new or worsening compared to Baseline with
 - event (onset) after first dose of study drug in AC-065A302 AND
 - event (onset) not later than minimum[date of last study drug intake in AC-065A303 + 3 days, 10 March 2014].
- for an analysis summarizing treatment-emergent safety events/data for study AC-065A302: all safety data included in the Safety analysis set with
 - event (onset) after first dose of study drug in AC-065A302, AND
 - event (onset) not later than minimum(date of last study drug intake in AC-065A302 Treatment Period + 7 days, date of first study drug intake in AC-065A303 [only available for patients enrolled in AC-065A303]).
- for an analysis summarizing treatment-emergent safety events/data for study AC-065A303: all safety data with
 - event (onset) after first dose of study drug in AC-065A303, AND

- o event (onset) not later than minimum(date of last study drug intake in AC-065A303 + 3 days, 10 March 2014).

As patients are to take their first dose of study medication on the evening of the Baseline Visit, safety assessments (i.e., ECG, laboratory test, vital signs and ophthalmologic assessments) performed on start date of study drug intake are considered as performed prior to first intake of study drug and therefore are not considered as belonging to the treatment-emergent period. However AEs with onset date on start date of study drug are considered as treatment-emergent.

14.2 Adverse events

14.2.1 Treatment-emergent adverse events

Treatment-emergent AEs are events documented on the AE CRF page that fulfill the definition in Section 14.1.

14.2.2 AEs leading to discontinuation of study drug

AEs leading to the discontinuation of study drug are those for which the AE CRF tick box 'Permanently discontinued' of 'Action taken with study drug' has been marked.

14.2.3 AEs leading to dose reduction

AEs leading to dose reduction of study drug are those for which the AE CRF tick box 'Dose reduced' of 'Action taken with study drug' has been marked.

14.2.4 Treatment-emergent SAEs

A treatment-emergent SAE is any treatment-emergent AE for which the AE CRF tick box 'Yes' of the 'Serious' question has been marked.

14.2.5 Treatment-emergent AEs of special interest

In subsequent lists of confounding medications, only the following routes of administration (Actelion coded terms) are considered: received as one of the following route of administration: intradermal, intramuscular, intrathecal, intravenous, nasal, oral, parenteral, rectal, respiratory (inhalation), subcutaneous, transdermal, vaginal, intrauterine, intra-arterial.

14.2.5.1 Eye disorders

Treatment-emergent AEs of special interest "Eye disorders" are defined as treatment-emergent AEs with PTs belonging to at least one of the following SOC/SMQ:

- SOC "Eye disorder"
- SMQ "Retinal disorders" (including both narrow and broad PTs).

A specific ophthalmology sub-study has been set up; its endpoint and analysis are described in Sections 14.6 and 23.6.

14.2.5.2 Hemorrhage

Treatment-emergent AEs of special interest “Hemorrhage” are defined as treatment-emergent AEs with PTs listed in at least one of the following SMQs:

- SMQ Haemorrhage (excluding laboratory terms)
- SMQ Gastrointestinal haemorrhage

Potentially confounding medications (concomitant at Baseline or newly concomitant) or medical history events are defined as:

- “Antithrombotic agents” (as defined by the Standardized Drug Groupings (SDG) developed by UPPSALA Monitoring Center)
- “Non-steroidal anti-inflammatory drugs (NSAIDs)” (as defined by the SDG)
- “Corticosteroids” (as defined by the SDG)
- medical history “Haemorrhage”.
- PAH associated with connective tissue disease.

14.2.5.3 Hypotension

Treatment-emergent AEs of special interest “Hypotension” are defined as treatment-emergent AEs with PTs listed below:

- Blood pressure ambulatory decreased
- Blood pressure decreased
- Blood pressure diastolic decreased
- Blood pressure orthostatic decreased
- Blood pressure systolic decreased
- Diastolic hypotension
- Hypotension
- Mean arterial pressure decreased
- Orthostatic hypotension
- Procedural hypotension

Potentially confounding new concomitant/concomitant treatments or medical history events at Baseline are defined as:

- PDE5-Is, ERAs, Riociguat [as defined in Section 8.1]
- “Anti-hypertensives” or “Diuretics” (as defined by the SDG)
- medical history “Hypotension”
- low blood pressure at Baseline defined as:
 - o Systolic blood pressure (SBP) < 90 mmHg or
 - o Diastolic blood pressure (DBP) < 50 mmHg.

14.2.6 Prostacyclin-like associated AEs

“Prostacyclin-like associated AEs” are defined by the following PTs:

- pain in jaw / temporomandibular joint syndrome / arthralgia / musculoskeletal pain / myalgia / pain in extremity
- flushing
- nausea / vomiting
- diarrhoea
- headache
- dizziness.

14.2.7 AEs suggestive of PAH worsening

AEs suggestive of PAH worsening are defined by the following PTs:

ATRIAL FIBRILLATION

ATRIAL FLUTTER

ATRIAL NATRIURETIC PEPTIDE ABNORMAL

ATRIAL NATRIURETIC PEPTIDE INCREASED

ACUTE RIGHT VENTRICULAR FAILURE

CARDIAC FAILURE

CARDIAC INDEX DECREASED

CARDIOGENIC SHOCK

CARDIOPULMONARY FAILURE

CHRONIC RIGHT VENTRICULAR FAILURE

COR PULMONALE

COR PULMONALE ACUTE

OEDEMA PERIPHERAL

JUGULAR VEIN DISTENSION

LUNG TRANSPLANT

PULMONARY ARTERIAL HYPERTENSION

PULMONARY ARTERIAL PRESSURE ABNORMAL

PULMONARY ARTERIAL PRESSURE INCREASED

PULMONARY OEDEMA

PULMONARY HYPERTENSION

PULMONARY HYPERTENSIVE CRISIS

RIGHT ATRIAL DILATATION

RIGHT ATRIAL PRESSURE INCREASED

RIGHT VENTRICULAR DYSFUNCTION

RIGHT VENTRICULAR FAILURE

SYNCOPE

VASCULAR RESISTANCE PULMONARY INCREASED

14.2.8 AEs denoting anemia or hemoglobin decrease

AEs denoting anemia or hemoglobin decrease are defined by the following PTs:

ANAEMIA
IRON DEFICIENCY ANAEMIA
PANCYTOPENIA
HAEMORRHAGIC ANAEMIA
MICROCYTIC ANAEMIA
NORMOCHROMIC NORMOCYTIC ANAEMIA
HYPOCHROMIC ANAEMIA
HAEMOGLOBIN DECREASED
HAEMATOCRIT DECREASED
MYELODYSPLASTIC SYNDROME

Potentially confounding medications (concomitant at Baseline or newly concomitant) are defined as:

- ERAs [as defined in Section 8.1]
- “Antithrombotic agents” (as defined by the SDG)

14.3 Electrocardiogram in study AC-065A302

ECG results of study AC-065A302 are reported by a central reader (Cardibase).

14.3.1 Treatment-emergent qualitative ECG abnormalities

Findings / original terms (tick boxes and free text) reported by CRO Cardibase are coded using the Actelion ECG dictionary and the latest study-specific Coding Assignment version.

14.3.2 Absolute changes from Baseline in ECGs data

The change from Baseline in ECG data (heart rate and the intervals PR, QRS, QT and QTcF) is defined for each visit in study AC-065A302.

14.3.3 QTcF categories

For QTcF, the following (non-mutually exclusive) categories are used according to [ICH 2005]:

- $QTcF \leq 450$ ms
- $QTcF > 450$ ms
- $QTcF > 480$ ms
- $QTcF > 500$ ms
- QTcF increase from Baseline ≤ 30 ms
- QTcF increase from Baseline > 30 ms
- QTcF increase from Baseline > 60 ms

In addition, the following categories are used:

- QTcF $\leq$ 450 ms or QTcF increase from Baseline $\leq$ 30 ms
- QTcF $>$ 450 ms and QTcF increase from Baseline $>$ 30 ms
- QTcF $>$ 450 ms and QTcF increase from Baseline $>$ 60 ms

14.4 Laboratory test results

Laboratory tests results of study AC-065A302 are obtained by a central laboratory (Quest) and provided to Actelion in Standard International (SI) units together with Quest's laboratory test normal ranges in the same units.

Laboratory test results of study AC-065A303 are obtained by a central laboratory (Eurofins) and provided to Actelion in SI units together with Eurofins' laboratory test normal ranges in the same units. The data transfer from Eurofins contains laboratory test results performed by the central lab Eurofins and by the local laboratories for test results performed prior to the approval of AC-065A303 protocol global amendment 3.

In the event that the SI units label provided by Quest and the SI units label provided by Eurofins differ, then the SI units label provided by Quest is used for data reporting as given in [Table 7](#) below.

For bone alkaline phosphatase, the reference range for female patients from Quest depends on menopausal status (i.e., pre-menopausal: 2.9–14.5 $\mu\text{g/L}$, post-menopausal: 3.8–22.6 $\mu\text{g/L}$). As menopausal status is not collected in the study these reference ranges are not transferred to Actelion. For the purpose of the analysis of bone alkaline phosphatase test results, the reference range of bone alkaline phosphatase for female patients is defined as 2.9–22.6 $\mu\text{g/L}$.

In addition, laboratory test results (from local laboratories) as part of SAE reporting and stored in Actelion's Global Drug Safety database Argus are converted to SI units (as per [Table 7](#) below) and made available in the SDTM datasets. However, inclusion of these laboratory test results for statistical reporting and analysis in the Clinical Study Report is currently not planned – but may be considered for selected laboratory tests at a later stage.

Table 7 SI units for reporting of laboratory test results

Laboratory test group	Laboratory test	SI unit for reporting
Hematology	hemoglobin	g/L
	hematocrit	l
	erythrocytes	Tl/LGI/L
	leukocytes, platelets	GI/L
	absolute neutrophils, total	

Laboratory test group	Laboratory test	SI unit for reporting
	lymphocytes, monocytes, eosinophils, basophils relative neutrophils, total lymphocytes, monocytes, eosinophils, basophils	% (of leukocytes)
Chemistry	alanine aminotransferase (ALT) aspartate aminotransferase (AST) alkaline phosphatase (ALP) total bilirubin (TB) direct bilirubin serum creatinine estimated creatinine clearance urea blood urea nitrogen glucose sodium (Na) potassium (K) albumin	U/L U/L U/L mcmol/L mcmol/L mcmol/L mL/min/1.73 m ² mmol/L mmol/L mmol/L mmol/L mmol/L g/L
thyroid markers	free triiodothyronine (T3) free thyroxine (T4) thyroid stimulating hormone (TSH)	pmol/L pmol/L MU/L
bone turnover markers	bone alkaline phosphatase carboxy-terminal telopeptide	mcg/L ng/L

For all laboratory summaries, values below or above the limit of detection (e.g. '< 3' for alanine aminotransferase [ALT]) are substituted with the limit of detection (e.g. '< 3' is substituted by '3'). The values are listed including the < or > sign.

14.4.1 Absolute change from Baseline in hematology test results

Hematology tests are hemoglobin, hematocrit, platelet count, leukocyte count and erythrocyte count from the central laboratory. The absolute change from Baseline is defined for each scheduled assessment.

In addition, for AC-065A303 study the following hematology tests are collected: neutrophils, total lymphocytes, monocytes, eosinophils and basophils, each for the percent and absolute counts. These test results are only listed.

14.4.2 Absolute change from Baseline in chemistry test results

Chemistry tests are ALT, aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, direct bilirubin, serum creatinine, estimated creatinine clearance, urea, blood urea nitrogen, glucose (irrespective of fasting status), sodium, potassium and albumin. The absolute change from Baseline is defined for each scheduled assessment.

14.4.3 Absolute change from Baseline in thyroid markers in study AC-065A302

Thyroid markers are free triiodothyronine (T3), free thyroxine (T4) and thyroid stimulating hormone (TSH) for patients randomized under study AC-065A302 protocol Amendment 3 or higher. The absolute change from Baseline is defined for each scheduled assessment.

14.4.4 Absolute change from Baseline in bone turnover markers in study AC-065A302

Bone turnover markers include bone alkaline phosphatase and carboxy-terminal telopeptide. The absolute change from Baseline is defined for each scheduled assessment.

14.4.5 Treatment-emergent laboratory abnormalities

A laboratory test abnormality is defined as any value outside the normal range as provided by the central laboratory. The direction of the abnormality (below or above the normal range) is indicated using 'H' and 'L', if applicable.

A marked (alert) laboratory test abnormality is defined as any value that fulfills the applicable condition listed in [Table 8](#) below for LL / HH (or LLL / HHH, respectively).

Table 8 Definition of marked laboratory abnormalities

Parameter	LL Marked	LLL Alert	HH Marked	HHH Alert
Hemoglobin (g/L)	< 100	< 80	> maximum (ULN, Baseline) + 20	> maximum (ULN, Baseline) + 40
Hematocrit (l)	< 0.28 for females; < 0.32 for males	< 0.20	> 0.55 for females; > 0.6 for males	> 0.65
Platelet count (GI/L)	< 75	< 50	> 600	> 999
WBC count (GI/L)	< 3.0	< 2.0	> 20.0	> 100.0
AST (U/L)	NA	NA	> 3 ULN	> 5 ULN
ALT (U/L)	NA	NA	> 3 ULN	> 5 ULN
Total bilirubin (μmol/L)	NA	NA	> 2 ULN	> 5 ULN
Alkaline Phosphatase (U/L)	NA	NA	> 2.5 ULN	> 5 ULN

Parameter	LL Marked	LLL Alert	HH Marked	HHH Alert
Creatinine (μmol/L)	NA	NA	> 1.5 ULN or 1.5 BL	> 3 ULN or 3 BL
Urea (mmol/L)	NA	NA	> 2.5 ULN	> 5 ULN
Blood urea nitrogen (mmol/L)	NA	NA	> 2.5 ULN	> 5 ULN
Albumin (g/L)	< 30	< 20	NA	NA
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0
Sodium (mmol/L)	NA	< 130	> 150	> 155

ULN refers to the upper limit of the central laboratory normal range. Definition of marked and alert laboratory abnormalities are based on Actelion document OTH-000005.

14.5 Vital signs and body weight

14.5.1 Absolute change from Baseline in vital signs

Vital signs include blood pressure (systolic, diastolic and mean arterial pressure [MAP]) and heart rate. MAP is defined in Section 24.1.

The absolute change from Baseline is defined for patient's lowest and highest treatment-emergent value and for each scheduled assessment.

14.5.2 Treatment-emergent low blood pressure

The following abnormalities for SBP and DBP are defined as:

- SBP < 90 mmHg
- DBP < 50 mmHg
- decrease of ≥ 40 mmHg in SBP relative to Baseline.
- decrease of ≥ 20 mmHg in DBP relative to Baseline
- all 4 conditions.

14.5.3 Absolute change from Baseline in body weight

The absolute change from Baseline is evaluated for patient's lowest and highest treatment-emergent value and for each scheduled assessment.

14.6 Ophthalmologic sub-study

Presence of retinal arterial tortuosity at Baseline as well as change from Baseline in severity of retinal arterial tortuosity to all visits up to EOS in AC-065A302 are assessed in a qualitative manner; and ophthalmic findings and changes compared to baseline findings are provided. Quantitative assessments are also performed by the ophthalmic evaluation but are not considered in this SAP and Clinical Study Report.

15 STATISTICAL ANALYSIS OF PATIENT DISPOSITION AND EXPOSURE TO STUDY TREATMENT

15.1 Statistical analysis of patient disposition

The numbers of subjects included in each analysis set [described in Section 5] are presented. Reasons for excluding patients from analysis sets are summarized by frequency tables and listed. Number of patients with data excluded in the per-protocol analysis of the primary endpoint and secondary endpoint change from baseline to Week 26 in 6MWD are presented.

All confirmed protocol deviations are summarized by treatment group and by country. Protocol deviations which are not confirmed to be protocol violations (by manual assignment) are not displayed in the summaries but are listed. Protocol deviations from the ongoing study AC-065A303 not yet manually assigned as confirmed or not confirmed at the time of data dump on 12 June 2014 are displayed and flagged as such in tables and listings.

Three further categories (defined in the PV code list document) are displayed in the summary: deviations at study entry, deviations during the study conduct (i.e. after randomization) and deviations after end of study treatment. Major protocol deviations are summarized separately. In addition, significant protocol deviations are summarized separately for study AC-065A302 (grouped by category inclusion/exclusion criteria, major significant GCP, IMP dispensation as defined in Section 6.5). Protocol deviations are listed together with PV comments from the PV system.

Patients with treatment unblinded prior to database lock are listed together with reasons for unblinding (by investigator via IVRS or by sponsor because of SUSAR) and patient's outcome (with/without confirmed morbidity/mortality event).

Screening failures, together with the reason for screening failure, are listed and summarized (information stored in IWRS data).

Patients who are deceased or with vital status unknown at the time of study closure are listed. In the listing, patients who withdrew consent or who were lost to follow up during the treatment period (i.e., 'Lost to follow up' is the reason for study drug discontinuation) are identified.

Patient disposition by country and center is summarized.

Further, the vital status at Study Closure (Alive, Deceased or Unknown) is summarized on the FAS for the following categories:

- Patients with a primary endpoint event: the vital status is displayed separately for patients who entered PTOP (i.e., consented to PTOP) and study AC-065A303, for patients who entered PTOP but not study AC-065A303, for patients who did not enter PTOP but entered study AC-065A303, and for patients who did not enter either PTOP or study AC-065A303. For patients entering PTOP the vital status is

presented for patients with/without at least one morbidity/mortality event in PTOP. Patients who died up to 7 days after last study drug intake in AC-065A302 and did not enter PTOP or study AC-065A303 are displayed separately.

- Patients with early treatment discontinuation: patients censored because of discontinuation prior to Study Closure with no morbidity/mortality event in the AC-065A302 Treatment Period are further classified as above.
- Patients with study completion without morbidity/mortality event in the AC-065A302 Treatment Period

15.2 Statistical analysis of exposure to study treatment

15.2.1 Analysis of study treatment duration

Duration of study treatment is summarized by study treatment as follows for the Safety analysis set:

- intervals: 1 day to 56 days (8 weeks), 57 days to 112 days (16 weeks), 113 days to 182 days (26 weeks), 183 days to 364 days (52 weeks), 365 days to 546 days (78 weeks), and at every interval of 182 days (26 weeks) thereafter, showing number and percentage of patients.
- cumulative intervals: at least 8 weeks, at least 16 weeks, at least 26 weeks, at least 52 weeks, at least 78 weeks, and at every interval of 26 weeks thereafter, showing number and percentage of patients.
- inverse cumulative distribution function for duration of study treatment (i.e., time to discontinuation of study treatment).

15.2.2 Analysis of (premature) discontinuation of study drug

All summaries are provided on the Safety analysis set.

Reason for premature discontinuation of study drug [see Section 7.1] is tabulated by study treatment group and separately by dose of study drug (at time of discontinuation) and by time since randomization (< 12 weeks after randomization versus ≥ 12 weeks after randomization). In addition, reason for treatment discontinuation prior to Study Closure in study AC-065A302 is summarized. Reasons coded with multiple preferred terms are concatenated in summary tables.

Kaplan-Meier estimates for the time to premature discontinuation of study drug in AC-065A302 are presented as described in Section 25.1.1. Patients who did not discontinue prematurely are censored at date of last study drug intake in AC-065A302.

15.2.3 Analysis of individual maintenance dose

IMDs of selexipag (as defined for studies AC-065A302 and AC-065A303 in Section 7.2.2 and Section 7.3.2) are summarized by number of patients and percentages on the Safety analysis set. In addition, IMDs of selexipag and placebo equivalent in study

AC-065A302 [as defined in Section [7.2.2](#) and Section [7.3.2](#)] are summarized by number of patients and percentages on the FAS.

16 STATISTICAL ANALYSIS OF DEMOGRAPHIC AND BASELINE DISEASE CHARACTERISTICS

Demographic characteristics and baseline disease characteristics (including 6MWD and right heart catheterization data) are summarized by treatment group and separately by NYHA/WHO functional class at Baseline for the FAS and in addition for the subset of the patients included in the SAF and treated in AC-065A303. Demographics are presented also for patients included in the OAS.

The outcome of the blinded expert medical review of PAH baseline characteristics is listed and summarized by treatment group.

Previous and concomitant diseases at Baseline are summarized by presenting, for each treatment group, the number and percentage of patients having a disease in each SOC, and having each individual disease (preferred term) for FAS and OAS. Medical history of special interest is summarized by treatment group.

17 STATISTICAL ANALYSES OF THE PRIMARY EFFICACY ENDPOINT

See also Section 31 for an overview.

17.1 Hypotheses

Hypotheses are formulated in terms of “survival” functions $S_{m/m}(t)$, i.e., the probability that time to first morbidity/mortality event confirmed by the CEC (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is $\geq t$ for a day t relative to the date of randomization.

One-sided hypotheses are expressed in terms of the survival functions $S_{m/m,selexipag}(t)$ and $S_{m/m,placebo}(t)$.

$H_{0,m/m}$: $S_{m/m,selexipag}(t) \leq S_{m/m,placebo}(t)$ for all $t \geq 0$ versus

$H_{A,m/m}$: $S_{m/m,selexipag}(t) \geq S_{m/m,placebo}(t)$ for all $t \geq 0$ and $S_{m/m,selexipag}(t) > S_{m/m,placebo}(t)$ for some $t > 0$.

17.2 Statistical analysis

The overall one-sided significance level for the group-sequential procedure is set to 0.005, more details are provided in Section 28.1.

Kaplan-Meier estimates for the survival functions are provided, see Section 25.1.1. Censoring reasons are listed.

Number and percentage of each primary efficacy event type are presented. If more than one event type have the same onset date for a patient, then the more severe one (according to the definition in Section 9) is displayed.

17.2.1 Primary analysis

The primary analysis is performed on the FAS by a one-sided unstratified log-rank test in a group-sequential setting.

17.2.2 Supportive analyses

Note: in this section, except where otherwise stated, the events confirmed by the CEC with onset date up to 16 August 2011 are considered as events.

The following supportive analyses (based on the FAS if not otherwise stated) are planned:

- unstratified proportional hazards model handling CEC-confirmed morbidity/mortality events with onset date (as per CEC) up to 16 August 2011 as excluded/censored, see above for the main analysis).
- unstratified log-rank test and proportional hazards model.
- Number and percentage of each primary efficacy event type are presented. If more than one event type have the same onset date for a patient, then the more severe one

(according to the definition in Section 9) is displayed. Note: this is done *post-hoc* in order to complement the supportive analysis of the primary endpoint.

- log-rank test and proportional hazards model stratified by geographical region (Asia, Eastern Europe, Latin America, North America, Western Europe + Australia).
- log-rank test and proportional hazards model stratified by PAH etiology ((idiopathic, heritable, drug or toxin induced, associated with HIV infection), associated with connective tissue disease, associated with congenital heart disease with corrected systemic-to-pulmonary shunts).
- log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline (classes I/II and classes III/IV).
- log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline (no/yes).
- log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline (classes I/II and classes III/IV) and concomitant PAH medication at Baseline (no/yes).
- proportional hazards model adjusted for modified NYHA/WHO functional class at Baseline (classes I/II and classes III/IV), concomitant PAH medication at Baseline (no and yes), geographic regions [as defined in Section 6.4], PAH etiology [as defined in Section 6.4], sex, race/ethnicity Caucasian/Hispanic (Yes and No), age categories [as defined in Section 6.4] – see Section 25.1.3.3 for methodology.
- unstratified and stratified tests/models attempting to address potential informative censoring, with the following circumstances identified as potentially informative censoring for the morbidity/mortality event:
 - morbidity/mortality event not confirmed by the CEC but study drug discontinued within 21 days after onset date of the respective morbidity/mortality event; in case of a CEC-confirmed morbidity/mortality event within 21 days after onset of the unconfirmed event, the event confirmed by the CEC is taken as event for the analysis.
 - patient lost to follow-up in the treatment period (event date is the date of last visit).
- unstratified and stratified log-rank tests and proportional hazards models for the originally planned number (202) of first CEC-confirmed morbidity/mortality events up to 7 days after last study drug intake in the AC-065A302 Treatment Period observed in the originally planned number (first 670) randomized patients. Cut-off date (and censoring date, where applicable) is the onset date of the 202nd CEC-confirmed morbidity/mortality event in the first 670 randomized patients.
- competing risk analysis as described in Section 25.1.4.
- subgroup analyses as specified in Section 6.4 and Section 27.

- analysis restricted to patients with typical or consistent PAH according to the blinded expert review.
- analysis restricted to patients with typical PAH according to the blinded expert review.
- unstratified log-rank test and proportional hazards model based on the PPS. Time to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in the AC-065A302 Treatment Period is defined as date of the first CEC-confirmed morbidity/mortality event up to minimum(7 days after last study drug intake in the AC-065A302 Treatment Period, per-protocol cut-off date) minus date of randomization plus 1. The same censoring rules as described in Section 9 are used replacing “date of last contact” by “minimum(date of last contact, per-protocol cut-off date)” in the censoring rules.
- unstratified log-rank test and proportional hazards model for time to first morbidity/mortality event (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) reported by the investigator (irrespective of confirmation by the CEC) and using the onset date as reported by the investigator. Censoring rules for patients without a morbidity/mortality event (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) are censored in the same sense as outlined for the primary efficacy endpoint in Section 9.
- unstratified log-rank tests and proportional hazards models ignoring CEC-confirmed “disease progression” event component when the second 6MWT was not performed. The number of “disease progression” event components ignored in the supportive analysis is displayed.
- descriptive comparison of data before and after the interim analysis.
- the following analysis is performed in order to assess the impact on the trial results of patients who discontinued treatment without experiencing a CEC-confirmed morbidity/mortality event (i.e., prematurely discontinued). For these patients, the presence of signs of disease worsening is identified. Signs of disease worsening are identified for patients meeting any of the following criteria:
 - last available NYHA/WHO functional class (up to last study drug intake in the AC-065A302 Treatment Period) is greater than Baseline, or
 - last available 6MWD (up to last study drug intake in the AC-065A302 Treatment Period) is < 15% of the Baseline value with no evidence of cause not related to PAH worsening, or
 - PAH-specific medication started within 4 weeks prior to and up to last study drug intake in the AC-065A302 Treatment Period, or
 - an AE suggestive of PAH worsening [as defined in Section 14.2.7] ongoing at last study drug intake in the AC-065A302 Treatment Period.

Patients who prematurely discontinued study drug with signs of disease worsening are considered as having an event on the day of last study drug intake. Patients who

prematurely discontinued study drug without signs of disease worsening are censored at date of last study drug intake. Patient who did not prematurely discontinue study drug are treated as in the primary analysis of the primary endpoint. One-sided unstratified log-rank test and proportional hazards models are performed.

17.2.3 Further information

For the set of all morbidity/mortality events reported by investigators (up to 7 days after last study drug intake in the AC-065A302 Treatment Period), the following information is listed and summarized (unless otherwise specified) in frequency tables by study treatment:

- for the subset of morbidity/mortality events adjudicated in both CEC systems (The original CEC system was replaced in November 2012 by a new CEC system recording more information; details are described in the CEC Charter. All events adjudicated in the old CEC system were re-adjudicated in the new CEC system.):
 - agreement as confirmed event
 - agreement as non-confirmed event
 - disagreement: confirmed as event in original CEC system but not in new CEC system
 - disagreement: not confirmed as event in original CEC system but confirmed in new CEC system
 - needed consensus (information only listed)
- disagreement between investigator and new CEC system

Censoring (other than censoring introduced by the Study Closure) is illustrated by Kaplan-Meier curves where

- original “censoring” for reasons other than Study Closure (i.e. reason for study drug end date is not “End of treatment period”) is displayed as “event” (with event date set to the censoring date in the primary analysis)
- CEC-confirmed morbidity/mortality events as well as censoring for Study Closure (i.e. reason for study drug end date is “End of treatment period”) are handled as “censored” (with censoring date set to the event date in the primary analysis).

In order to understand the sequence of events in detail, the following analyses are performed.

CEC-confirmed morbidity/mortality events up to 7 days after last study drug intake in the AC-065A302 Treatment Period

All observed combinations of CEC-confirmed morbidity/mortality event types up to 7 days after last study drug intake in the AC-065A302 Treatment Period are summarized in a frequency table by treatment group in the FAS.

Morbidity/mortality components are concatenated in the order of occurrence. If more than one component has the same onset date for a patient, then the less severe one [according to the definition in Section 9] is displayed first².

Possible combinations of components of morbidity/mortality events up to 7 days after last study drug intake in the AC-065A302 Treatment Period include (list not exhaustive):

- Death
- Hospitalization
- Hospitalization / Death
- Disease progression
- Disease progression / Death
- Disease progression / Hospitalization for PAH worsening
- Disease progression / Hospitalization for PAH worsening / Death
- Disease progression / Hospitalization for PAH worsening / Death
- Disease progression / Parenteral prostanoid therapy or chronic oxygen therapy
- Disease progression / Parenteral prostanoid therapy or chronic oxygen therapy / Hospitalization for PAH worsening / Death

This frequency table is generated by:

- excluding CEC-confirmed morbidity/mortality events with onset date (as per CEC) up to 16 August 2011.
- including CEC-confirmed morbidity/mortality events with onset date up to 16 August 2011 as events.

Type of first CEC-confirmed morbidity/mortality events up to 7 days after last study drug intake in the AC-065A302 Treatment Period

Event type of first CEC-confirmed morbidity/mortality events up to 7 days after last study drug intake in the AC-065A302 Treatment Period is summarized in a frequency table by treatment group in the FAS. If more than one event type has the same onset date for a patient, then the most severe is displayed as first event [according to the definition in Section 9] and the potential concomitant event types are displayed below. For example, if a patient had as first CEC-confirmed events CEC-confirmed hospitalization for worsening of PAH and on the same day death, the patient is summarized in the table

² For example, if a patient had CEC-confirmed disease progression and later CEC-confirmed hospitalization for worsening of PAH and death on the same day (all with onset date up to 7 days after last study drug intake in the AC-065A302 Treatment Period) and no other CEC-confirmed morbidity/mortality events up to 7 days after last study drug intake in the AC-065A302 Treatment Period, then the patient is summarized in the table under 'Disease progression / Hospitalization for PAH worsening / Death'.

under 'Death' (as in table TCEC_F) and further categorized as 'Hospitalization for PAH worsening / Death' beneath the 'Death' category.

The summary is produced twice:

- excluding CEC-confirmed morbidity/mortality events with onset date (as per CEC) up to 16 August 2011.
- including CEC-confirmed morbidity/mortality events with onset date up to 16 August 2011 as events.

18 STATISTICAL ANALYSES OF SECONDARY EFFICACY ENDPOINTS

See also Section 31 for an overview.

If the primary statistical analysis of the primary efficacy endpoint leads to rejection of the related null hypothesis, the null hypotheses for the secondary efficacy endpoints are tested in a conditional hierarchical manner. The hierarchy is given in Section 10 (used here in Section 18 as well) and a null hypothesis is rejected if and only if the main analysis of the endpoint and all main analyses of preceding secondary efficacy endpoints result in rejection of respective null hypotheses. This procedure restricts the family-wise type-I-error rate to the overall assigned one-sided alpha of 0.005 (two-sided alpha of 0.01, respectively).

18.1 Absolute change from Baseline in 6MWD at trough at Week 26

The absolute change from Baseline in 6MWD is expected to be deviating from a normal distribution and is analyzed as described in Section 25.3.

18.1.1 Hypotheses

The null hypothesis

$H_{0,6MWD}$: “Distributions of change from Baseline in 6MWD at trough at Week 26, adjusted for 6MWD at Baseline, are identical for selexipag and placebo”

is tested against the alternative hypothesis

$H_{A,6MWD}$: “Distribution of change from Baseline in 6MWD at trough at Week 26, adjusted for 6MWD at Baseline, is more favorable for selexipag as compared to placebo”.

18.1.2 Statistical analysis

The proportion of patients with supplemental oxygen given at Baseline or Week 26 is presented.

In addition to a table with the usual descriptive statistics for each treatment group, the following statistics [see Sections 25.3.2 and 25.3.3] are provided:

- point estimate and two-sided 99% confidence interval (CI) for the location shift (selexipag minus placebo) in change from Baseline at Week 26
- point estimate (based on the Mann-Whitney statistic) for the probability to obtain a larger change to Baseline in 6MWD at trough at Week 26 for a patient treated with selexipag rather than with placebo.

These statistics are provided:

- on the FAS using the main imputation algorithm as well as the sensitivity imputation algorithms A, B and C for missing values as described in Section 10.1

- on the FAS excluding selexipag patients with 6MWT not performed at trough at Week 26 and using the main imputation algorithm for missing values as described in Section 10.1
- on the PPS excluding selexipag patients with 6MWT not performed at trough at Week 26 and using the main imputation algorithm for missing values as described in Section 10.1.

Details on the 6MWT are listed.

18.1.2.1 Main analysis

The main analysis is performed on the FAS. A non-parametric analysis of covariance (ANCOVA) as described in Section 25.3.1 is used with the main imputation algorithm for missing values as described in Section 10.1.

18.1.2.2 Sensitivity analyses

Sensitivity analyses (non-parametric ANCOVA as described in Section 25.3.1) are performed:

- on the FAS using the sensitivity imputation algorithms A, B and C for missing values as described in Section 10.1
- on the FAS excluding selexipag patients with 6MWT not performed at trough at Week 26 and using the main imputation algorithm for missing values as described in Section 10.1
- on the PPS excluding selexipag patients with 6MWT not performed at trough at Week 26 and using the main imputation algorithm for missing values as described in Section 10.1.

18.1.2.3 Supportive analyses

The following supportive analyses are planned on the FAS using the main imputation algorithm for missing values as described in Section 10.1:

- non-parametric ANCOVA with additional stratification for geographical region (Asia, Eastern Europe, Latin America, North America, Western Europe + Australia)
- non-parametric ANCOVA with additional stratification for PAH etiology [(idiopathic, heritable, drug or toxin induced, associated with HIV infection), associated with connective tissue disease, associated with congenital heart disease with corrected systemic-to-pulmonary shunts]
- non-parametric ANCOVA with additional stratification for modified NYHA/WHO functional class at Baseline (classes I/II versus classes III/IV)
- non-parametric ANCOVA with additional stratification for concomitant PAH medication at Baseline (no/yes)
- subgroup analyses as specified in Sections 6.4 and 27.

- analysis restricted to patients with typical or consistent PAH according to the blinded expert review.

18.2 Absence of worsening from Baseline in modified NYHA/WHO functional class at Week 26

Patients in functional class IV at Baseline are excluded from the analysis because, by definition, they cannot worsen.

Handling of missing values is described in Section 10.2.

18.2.1 Hypotheses

Let $\pi_{sel,k,W}$ and $\pi_{pla,k,W}$, $k=1,2,3$, denote the unknown probabilities for absence of worsening from Baseline in modified NYHA/WHO functional class at Week 26 in patients with modified NYHA/WHO functional class k at Baseline for selexipag and placebo, respectively.

The null hypothesis

H_0 : $\pi_{selexipag,k,W} = \pi_{placebo,k,W}$ for all $k=1,2,3$ “in all 3 strata the probabilities for absence of worsening in modified NYHA/WHO functional class at Week 26 are the same for both treatment groups”

is tested against the two-sided alternative hypothesis

H_A : $\pi_{selexipag,j,W} \neq \pi_{placebo,j,W}$ for at least one stratum j with $1 \leq j \leq 3$ “for at least one stratum the probabilities for absence of worsening in modified NYHA/WHO functional class at Week 26 are different between selexipag and placebo”.

18.2.2 Statistical analysis

Descriptive summaries are provided using the main and sensitivity imputation algorithm described in Section 10.2 by frequency tables, overall and by modified NYHA/WHO function class at Baseline.

18.2.2.1 Main analysis

The main analysis is performed on the FAS but excluding patients in functional class IV at Baseline. A Cochran-Mantel-Haenszel test stratified by modified NYHA/WHO functional class at Baseline [see Section 25.2.2] is used with the main imputation algorithm for missing values as described in Section 10.2.

18.2.2.2 Sensitivity analyses

In a sensitivity analysis, missing modified NYHA/WHO functional class values at Week 26 are not imputed.

In addition, Cochran-Mantel-Haenszel test and two-sided 99% CI for common odds ratio based on the PPS are conducted using the main imputation algorithm for missing modified NYHA/WHO functional class values at Week 26.

18.2.2.3 Supportive analyses

The following supportive analyses (based on the FAS but excluding patients in functional class IV at Baseline) are planned using the main imputation algorithm for missing modified NYHA/WHO functional class values at Week 26 [see Section 10.2]:

- if the assumption of a common odds ratio is not rejected by the Breslow-Day test [see Section 25.2.2], the effect of selexipag relative to placebo is expressed by the common odds ratio estimate and a two-sided 99% CI
- Cochran-Mantel-Haenszel test and two-sided 99% CI for common odds ratio with additional stratification for geographical region (Asia, Eastern Europe, Latin America, North America, Western Europe + Australia)
- Cochran-Mantel-Haenszel test and two-sided 99% CI for common odds ratio with additional stratification for PAH etiology ([idiopathic, heritable, drug or toxin induced, associated with HIV infection], associated with connective tissue disease, associated with congenital heart disease with corrected systemic-to-pulmonary shunts)
- Cochran-Mantel-Haenszel test and two-sided 99% CI for common odds ratio with additional stratification for concomitant PAH medication at Baseline (no/yes)

18.3 Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period

18.3.1 Hypotheses

Hypotheses are formulated in terms of survival functions $S_d(t)$, i.e., the probability that time to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) is $\geq t$ for a day t relative to the date of randomization.

One-sided hypotheses are expressed in terms of the survival functions $S_{d,\text{selexipag}}(t)$ and $S_{d,\text{placebo}}(t)$.

$H_{0,d}$: $S_{d,\text{selexipag}}(t) \leq S_{d,\text{placebo}}(t)$ for all $t \geq 0$ versus

$H_{A,d}$: $S_{d,\text{selexipag}}(t) \geq S_{d,\text{placebo}}(t)$ for all $t \geq 0$ and $S_{d,\text{selexipag}}(t) > S_{d,\text{placebo}}(t)$ for some $t > 0$.

18.3.2 Statistical analysis

Kaplan-Meier estimates for the survival functions are provided [see Section 25.1.1]. Censoring reasons are listed.

18.3.2.1 Main analysis

The main analysis is performed on the FAS by a one-sided unstratified log-rank test [see Section 25.1.2.1].

18.3.2.2 Supportive analyses

The following supportive analyses (based on the FAS if not otherwise stated) are planned:

- unstratified proportional hazards model
- log-rank test and proportional hazards model stratified by geographical region (Asia, Eastern Europe, Latin America, North America, Western Europe + Australia)
- log-rank test and proportional hazards model stratified by PAH etiology ([idiopathic, heritable, drug or toxin induced, associated with HIV infection], associated with connective tissue disease, associated with congenital heart disease with corrected systemic-to-pulmonary shunts)
- log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline (classes I/II and III/IV)
- log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline (no, yes)
- subgroup analysis (forest plot only as detailed in Section 27)
- unstratified log-rank test and proportional hazards model restricted to patients with typical or consistent PAH as per blinded expert review
- log-rank test and proportional hazards model based on the PPS.

18.4 Time to death up to Study Closure

18.4.1 Hypotheses

Hypotheses are formulated in terms of survival functions $S_d(t)$, i.e., the probability that time to death (up to study closure) is $\geq t$ for a day t relative to the date of randomization.

One-sided hypotheses are expressed in terms of the survival functions $S_{d,selexipag}(t)$ and $S_{d,placebo}(t)$.

$H_{0,d}$: $S_{d,selexipag}(t) \leq S_{d,placebo}(t)$ for all $t \geq 0$ versus

$H_{A,d}$: $S_{d,selexipag}(t) \geq S_{d,placebo}(t)$ for all $t \geq 0$ and $S_{d,selexipag}(t) > S_{d,placebo}(t)$ for some $t > 0$.

18.4.2 Statistical analysis

Kaplan-Meier estimates for the survival functions are provided [see Section 25.1.1]. Censoring reasons are listed.

18.4.2.1 Main analysis

The main analysis is performed on the FAS by a one-sided unstratified log-rank test [see Section 25.1.2.1].

18.4.2.2 Supportive analyses

The following supportive analyses (based on the FAS if not otherwise stated) are planned:

- unstratified proportional hazards model
- log-rank test and proportional hazards model stratified by geographical region (Asia, Eastern Europe, Latin America, North America, Western Europe + Australia)

- log-rank test and proportional hazards model stratified by PAH etiology ([idiopathic, heritable, drug or toxin induced, associated with HIV infection], associated with connective tissue disease, associated with congenital heart disease with corrected systemic-to-pulmonary shunts)
- log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline (classes I/II and classes III/IV)
- log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline (no/yes)
- analysis restricted to patients with typical or consistent PAH according to the blinded expert review
- analysis restricted to patients with typical PAH according to the blinded expert review.

18.5 Absolute change from Baseline to Week 26 in sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ score

Absolute change from Baseline in sub-scale ‘Breathlessness’ of CAMPHOR ‘Symptoms’ score at Week 26 is not assumed to be an interval-scaled variable and is analyzed as described in Section 25.3 with handling of missing values as described in Section 10.5.1. All analyses are based on the QoL analysis set.

18.5.1 Hypotheses

The null hypothesis

$H_{0,Breath}$: “Distributions of absolute change from Baseline in sub-scale ‘Breathlessness’ at Week 26, adjusted for sub-scale ‘Breathlessness’ at Baseline, are identical for selexipag and placebo”

is tested against the alternative hypothesis

$H_{A,Breath}$: “Distribution of absolute change from Baseline in sub-scale ‘Breathlessness’ at Week 26, adjusted for sub-scale ‘Breathlessness’ at Baseline, is more favorable for selexipag as compared to placebo”.

18.5.2 Statistical analysis

In addition to a table with the usual descriptive statistics for each treatment group, the following statistics are provided [see Sections 25.3.2 and 25.3.3] using the imputation algorithm for missing values as described in Section 10.5.1 :

- point estimate and two-sided 99% CI for the difference of medians (selexipag minus placebo) for absolute change to Baseline in sub-scale ‘Breathlessness’ at Week 26
- point estimate (based on the Mann-Whitney statistic) for the probability to obtain a lower change to Baseline in sub-scale ‘Breathlessness’ at Week 26 for a patient treated with selexipag rather than with placebo.

18.5.2.1 Main analysis

The main analysis is performed by a non-parametric ANCOVA (described in Section 25.3.1) with sub-scale ‘Breathlessness’ at Baseline and imputation algorithm for missing values as described in Section 10.5.1.

18.5.2.2 Supportive analyses

The following supportive analyses are planned using the imputation of missing values as described in Section 10.5.1:

- non-parametric ANCOVA with additional stratification for modified NYHA/WHO functional class at Baseline (classes I/II and classes III/IV)
- non-parametric ANCOVA with additional stratification for concomitant PAH medication at Baseline (no/yes)

18.6 Absolute change from Baseline to Week 26 in CAMPHOR ‘Symptoms’ score

Absolute change from Baseline in CAMPHOR ‘Symptoms’ score at Week 26 is not assumed to be an interval-scaled variable and is analyzed as described in Section 25.3 with handling of missing values as described in Section 10.5.2. All analyses are based on the QoL analysis set.

18.6.1 Hypotheses

The null hypothesis

$H_{0,\text{Symp}}$: “Distributions of absolute change from Baseline in ‘Symptoms’ score at Week 26, adjusted for ‘Symptoms’ score at Baseline, are identical for selexipag and placebo”

is tested against the alternative hypothesis

$H_{A,\text{Symp}}$: “Distribution of absolute change from Baseline in ‘Symptoms’ score at Week 26, adjusted for ‘Symptoms’ score at Baseline, is more favorable for selexipag as compared to placebo”.

18.6.2 Statistical analysis

Statistical analysis is performed in analogy to Section 18.5.2.

19 STATISTICAL ANALYSIS OF EXPLORATORY EFFICACY ENDPOINTS

See Section 31 for an overview.

If not otherwise indicated, significance levels are set to one-sided 0.005 (equivalent to two-sided 0.01). However, two-sided 95% CIs are provided.

All analyses are based on the FAS, if not indicated otherwise.

Note: as mentioned in Section 11, in all the analyses of the exploratory efficacy endpoints CEC-confirmed morbidity/mortality events with onset date (as per CEC) up to 16 August

2011 are considered as events, and deaths with date of death up to 16 August 2011 are considered as deaths.

19.1 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure

Hypotheses and main statistical analysis are analogous to the ones for the primary efficacy endpoint except for the group-sequential method.

The following supportive analyses are planned:

- unstratified proportional hazards model.
- log-rank test and proportional hazards model stratified by geographical region (Asia, Eastern Europe, Latin America, North America, Western Europe + Australia).
- log-rank test and proportional hazards model stratified by PAH etiology ([idiopathic, heritable, drug or toxin induced, associated with HIV infection], associated with connective tissue disease, associated with congenital heart disease with corrected systemic-to-pulmonary shunts).
- log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline (classes I/II and classes III/IV).
- log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline (no/yes).
- log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline (classes I/II and classes III/IV) and concomitant PAH medication at Baseline (no/yes).
- unstratified log-rank test and proportional hazards model for time to first morbidity/mortality event (excluding “disease progression”) up to Study Closure reported by the investigator (irrespective of confirmation by the CEC).
- unstratified log-rank test and proportional hazards model restricted to patients with typical or consistent PAH as per blinded expert review.

19.2 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period

Hypotheses and main statistical analysis are analogous to the ones for the primary efficacy endpoint except for the group-sequential method.

The following supportive analyses are planned:

- unstratified proportional hazards model
- unstratified log-rank test and proportional hazards model restricted to patients with typical or consistent PAH as per blinded expert review.

19.3 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid

therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure

Hypotheses and main statistical analysis are analogous to the ones for the primary efficacy endpoint except for the group-sequential method.

The following supportive analyses are planned:

- unstratified proportional hazards model.
- log-rank test and proportional hazards model stratified by geographical region (Asia, Eastern Europe, Latin America, North America, Western Europe + Australia).
- log-rank test and proportional hazards model stratified by PAH etiology ([idiopathic, heritable, drug or toxin induced, associated with HIV infection], associated with connective tissue disease, associated with congenital heart disease with corrected systemic-to-pulmonary shunts).
- log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline (classes I/II and classes III/IV).
- log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline (no/yes).
- log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline (classes I/II and classes III/IV) and concomitant PAH medication at Baseline (no/yes).
- unstratified log-rank test and proportional hazards model for time to first morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure reported by the investigator (irrespective of confirmation by the CEC).
- unstratified log-rank test and proportional hazards model restricted to patients with typical or consistent PAH as per blinded expert review.

19.4 Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period

Hypotheses and main statistical analysis are analogous to the ones for the primary efficacy endpoint except for the group-sequential method.

The following supportive analyses are planned:

- unstratified proportional hazards model
- unstratified log-rank test and proportional hazards model restricted to patients with typical or consistent PAH as per blinded expert review.

19.5 Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period

Hypotheses and main statistical analysis are analogous to the ones for the primary efficacy endpoint except for the group-sequential method.

The following supportive analysis is planned:

- unstratified proportional hazards model
- unstratified log-rank test and proportional hazards model restricted to patients with typical or consistent PAH as per blinded expert review.

19.6 Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study Closure

Hypotheses and main statistical analysis are analogous to the ones for the primary efficacy endpoint except for the group-sequential method.

The following supportive analysis is planned:

- unstratified proportional hazards model

19.7 Time from randomization to first CEC-confirmed morbidity/mortality event up to Study Closure

Hypotheses and main statistical analysis are analogous to the ones for the primary efficacy endpoint except for the group-sequential method.

The following supportive analysis is planned:

- unstratified proportional hazards model

19.8 Time from randomization to CEC-confirmed death due to PAH up to Study Closure

Hypotheses and main statistical analysis are analogous to the ones for the primary efficacy endpoint except for the group-sequential method.

The following supportive analysis is planned:

- unstratified proportional hazards model.

19.9 Borg dyspnea index

Descriptive statistics and boxplots over time are used to present the observed data for each scheduled visit up to Month 36. The results for the EOS visit are summarized descriptively.

19.10 Other exploratory efficacy endpoints

For continuous data, descriptive statistics are used to present the observed data (up to Month 36) and are displayed over time in boxplots. The results for the EOS visit are summarized descriptively.

The absence of worsening from Baseline in modified NYHA/WHO functional class at scheduled visits (up to Month 36) is analyzed by frequency tables but without imputation of missing values. The point estimates for the probability of worsening are plotted over time with 95% CI up to Month 36. For each scheduled post-Baseline visit up to Month 36 and separately for the worst post-Baseline assessment, a transition table from modified NYHA/WHO functional class at Baseline is provided with no imputation of missing values. Number and percentage of patients in each functional class at Baseline and at each post-Baseline scheduled visit (up to Month 36) are displayed, as well as number and percentage of patients having an improvement/no change/worsening from Baseline at each post-Baseline scheduled visit (up to Month 36) together with 95% CI. The results for the EOS visit are summarized descriptively.

Absolute change from Baseline in Plasma NT pro-BNP levels over time (up to Month 36) are displayed using descriptive statistics by treatment group. The results for the EOS visit are summarized descriptively.

20 EXPLORATORY ANALYSIS OF DOSE-RESPONSE RELATIONSHIP

Interpretation of results from exploratory analyses of dose-response relationships (described below) is limited as the IMD of selexipag in study AC-065A302 has not been randomly assigned to patients but is itself a post-Baseline outcome. For patients randomized to placebo, IMD is substituted with 0.

The following patients are excluded from the statistical analyses described in this section:

- patients randomized to selexipag and with an IMD = 0 mcg according to the definition in Section 7.2.2
- patients randomized to selexipag and with an IMD set to ‘other’ according to the definition in Section 7.2.2.

20.1 Relationship between individual maintenance dose in study AC-065A302 and primary efficacy endpoint

Note: CEC-confirmed morbidity/mortality events with onset date (as per CEC) up to 16 August 2011 are considered as events.

Statistical analyses of the selexipag dose effect on time to first CEC-confirmed morbidity/mortality event (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) relative to placebo are performed on the FAS as follows:

- unstratified proportional hazards model with selexipag IMD in study AC-065A302 as continuous single covariate. Hazard ratio and two-sided 95% CI per increase of 200 mcg selexipag IMD are provided.
- unstratified log-rank test and proportional hazards model with selexipag IMD in study AC-065A302 as categorical single covariate (IMD categories: 200 to 500 µg, 600 to 1100 µg, 1200 to 1600 µg). Kaplan-Meier plots for the survival functions are provided (three individual figures with one selexipag IMD category and placebo as well as all four groups in one figure).
- unstratified proportional hazards model with selexipag IMD in study AC-065A302 as continuous covariate separately for patients with/without selexipag dose reductions or study drug discontinuation because of “prostacyclin-like associated AEs” as defined in Section 14.2.6 (both subgroups compared to all patients randomized to placebo). Hazard ratio and two-sided 95% CI per increase of 200 mcg selexipag IMD are provided.
- unstratified proportional hazards model with selexipag IMD in study AC-065A302 as continuous covariate separately for patients with/without treatment-emergent “prostacyclin-like associated AEs” (both subgroups compared to all patients randomized to placebo). Hazard ratio and two-sided 95% CI per increase of 200 mcg selexipag IMD are provided.
- unstratified log-rank test and proportional hazards model with selexipag IMD in study AC-065A302 as categorical covariate separately for patients with/without selexipag

dose reductions or study drug discontinuation because of “prostacyclin-like associated AEs” (both subgroups compared to all patients randomized to placebo). Kaplan-Meier plots for the survival functions are provided.

- unstratified log-rank test and proportional hazards model with selexipag IMD in study AC-065A302 as categorical covariate separately for patients with/without treatment-emergent “prostacyclin-like associated AEs” (both subgroups compared to all patients randomized to placebo).-Kaplan-Meier plots for the survival functions are provided.

20.2 Relationship between individual maintenance dose up to Week 26 in study AC-065A302 and absolute change from Baseline in 6MWD at Week 26

Statistical analyses of the selexipag dose effect on the absolute change from Baseline to Week 26 in 6MWD at trough relative to placebo (IMD of 0 mcg) are performed on the FAS as follows using the main imputation method for missing values at Week 26:

- non-parametric ANCOVA with selexipag IMD in study AC-065A302 as categorical covariate (IMD categories: 0 mcg, 200 to 500 mcg, 600 to 1100 mcg, 1200 to 1600 mcg) and usual descriptive statistics
- non-parametric ANCOVA with selexipag IMD in study AC-065A302 as categorical covariate separately for patients with/without treatment-emergent “prostacyclin-like associated AEs” with AE onset date prior to the Week 26 6MWT (both subgroups compared to all patients randomized to placebo) and usual descriptive statistics
- non-parametric ANCOVA with selexipag IMD in study AC-065A302 as categorical covariate separately for patients with/without selexipag dose reductions or study drug discontinuation (prior to the Week 26 6MWT) because of “prostacyclin-like associated AEs” (both subgroups compared to all patients randomized to placebo) and usual descriptive statistics.

21 STATISTICAL ANALYSIS OF PHARMACOECONOMIC ENDPOINTS

21.1 Annualized number of hospitalizations (for all causes) up to the EOS visit

A negative binomial model as described in Section 25.2.3 is used for the statistical analysis. The null hypothesis of no treatment effect ($\theta_{\text{treatment}}=0$) is tested by a two-sided Wald-type test at a two-sided significance level of 0.01. A two-sided 99% Wald CI is calculated for the relative reduction in mean annualized hospitalization rate for selexipag compared to placebo.

The main analysis is performed on the FAS with study treatment as the only covariate. Descriptive statistics are presented.

21.2 Annualized number of PAH-related hospitalizations up to the EOS visit

Statistical analysis is performed in analogy to Section 21.1.

21.3 Annualized number of days spent in hospital for all causes up to the EOS visit

The (annualized) number of days spent in hospital is not expected to follow a specific type of distribution and is therefore analyzed in a non-parametric way.

21.3.1 Hypotheses

The null hypothesis

$H_{0,ADH}$: “Distributions of annualized number of days spent in hospital for all causes up to the EOS visit are identical for selexipag and placebo”

is tested against the alternative hypothesis

$H_{A,ADH}$: “Distribution of annualized number of days spent in hospital for all causes up to the EOS visit is more favorable for selexipag as compared to placebo”.

21.3.2 Statistical analysis

The usual descriptive statistics for each treatment group are provided on the FAS; distributions by study treatment group are displayed graphically. The non-parametric one-sided Wilcoxon-Mann-Whitney test [see Section 25.3.2] is used to test $H_{0,ADH}$ at one-sided significance level of 0.005.

21.4 Annualized number of days spent in hospital for PAH-related causes up to the EOS visit

Statistical analysis is performed in analogy to Section 21.3.

22 STATISTICAL ANALYSIS OF PHARMACOKINETIC ENDPOINTS

Plasma trough concentrations of ACT-293987 (selexipag) and ACT-333679 per time point (after first study drug intake) are summarized by selexipag dose (last dose prior to PK sampling from Study Drug Log CRF). Descriptive statistics include the number of observations, arithmetic mean, geometric mean, minimum, median, maximum, standard deviation (SD), coefficient of variation (CV%), and two-sided 95% CIs of the means. The CI for the geometric mean is based on log-transformed data and presented back-transformed to the original scale.

For all PK summaries, values below the limit of detection (e.g. ' < 0.0100 ') are substituted with 0. The values as received are listed.

23 STATISTICAL ANALYSIS OF SAFETY AND TOLERABILITY ENDPOINTS

For quantitative safety endpoints the descriptive statistics are the following: number of patients with the assessment, mean, median, SD, quartiles, minimum, and maximum.

23.1 Analysis of adverse events

23.1.1 Standard display of adverse events

Crude incidence summaries (see subsequent paragraph) of treatment-emergent AEs are displayed separately for

- study AC-065A302 (comparing selexipag to placebo on an inter-patient basis) with treatment groups selexipag and placebo
- study AC-065A303 with treatment group selexipag
- intra-patient comparison for patients treated with placebo in study AC-065A302 and with selexipag in study AC-065A303 with treatment groups “placebo in AC-065A302” and “selexipag in AC-065A303”
- intra-patient comparison for patients treated with selexipag in both studies with treatment groups “selexipag in AC-065A302” and “selexipag in AC-065A303”

The number and percentage of patients who experienced treatment-emergent AEs are tabulated by treatment, by SOC, PT within each SOC and treatment. Patients with AEs coded with more than one PT are counted on each PT. Treatment-emergent AEs are also tabulated by PT (sorted by descending frequency in the selexipag group and separately [for study AC-065A302 only] by difference in frequency between selexipag and placebo in descending order) and treatment.

Further, treatment-emergent AEs are tabulated by IMD categories [see Section 20.1 for definitions], by maximum severity and by investigator’s assessment of relationship to study drug. If an AE is reported more than once within a patient, the worst category is used.

Treatment-emergent AEs leading to discontinuation of study drug and treatment-emergent SAEs are reported similarly to AEs. For study AC-065A303, AEs leading to discontinuation are presented overall and by treatment received in AC-065A302. For each study, a summary table for all SAEs with outcome death is provided as well as a table restricted to treatment-emergent SAEs with outcome death.

For patients who discontinued the study due to withdrawal of consent all AEs ongoing at study discontinuation date are listed. SAEs occurring before study drug start date and SAEs occurring after 7 days (3 days for AC-065A303) from last study drug intake in AC-065A302 are listed separately.

In addition, a table of non-serious treatment-emergent AEs (all AEs excluding SAEs) are tabulated by SOC and PT. Preferred terms are presented by descending order of

frequency for AEs with frequency $\geq 5\%$. All other AE PTs with frequency below 5% are combined. This table is a request from clinicaltrials.gov and is not to be included in the CSR.

For adverse events, causes of death, and previous/concomitant diseases at baseline, when a verbatim term is assigned to more than one preferred term, one of which is “DISEASE PROGRESSION”, the preferred term “DISEASE PROGRESSION” is not displayed in the summary tables but is provided in the patient listings. For instance, if the verbatim is “Worsening of dyspnea”, coded as “DYSPNEA” and “DISEASE PROGRESSION”, only “DYSPNEA” is displayed in the summary.

23.1.2 Reporting and analysis of AEs of special interest in study AC-065A302

23.1.2.1 General aspects

For patients with at least one AE of special interest, all concomitant medications ongoing at the time of the AE of special interest (i.e., start date of the medication is before onset of the AE and end date of the medication is after onset date of the AE) are listed separately for each category of AE of special interest.

For each defined type of treatment-emergent AEs of special interest, crude incidence estimates for selexipag and placebo as well as the relative risk estimator (selexipag relative to placebo) together with a two-sided 95% CI are provided and also displayed in a graphical form ordered by relative risk.

In addition crude incidence estimates for selexipag and placebo are provided for treatment-emergent AEs of special interest that:

- lead to discontinuation of study AC-065A302
- are serious
- have a fatal outcome in study AC-065A302.

The occurrence of (potentially recurrent) specific types of AEs of special interest is analyzed within the Andersen-Gill model [see Section 25.1.5], hazard ratios (relative to placebo) with two-sided 95% CIs are provided and also displayed in a graphical form. Patients not experiencing a specific type of an AE of special interest are censored as follows:

- for patients who did not discontinue GRIPHON study drug prior to study closure (i.e., reason for discontinuation is “end of treatment period”), censoring date is the last study drug intake in AC-065A302
- for patients who discontinued GRIPHON study drug prior to study closure (i.e., reason for discontinuation is not “end of treatment period”) and did not enter study AC-065A303, censoring date is minimum[date of last study drug intake of GRIPHON study drug plus 7 days, date of death]
- for patients who discontinued GRIPHON study drug before study closure (i.e., reason for discontinuation is not “end of treatment period”) and entered study AC-065A303,

censoring date is minimum[date of discontinuation of GRIPHON study drug plus 7 days, date of first selexipag dose in study AC-065A303, date of death].

23.1.2.2 Eye disorders

Crude incidences for treatment-emergent AEs of special interest “Eye disorders” are estimated overall.

Treatment-emergent AEs of special interest “Eye disorders” are presented, in addition, separately for patients included in the ophthalmology sub-study and separately by age at screening categories (18–40, 41–60, > 60 years old).

23.1.2.3 Hemorrhage

In order to explore the influence of potentially confounding factors [see Section 14.2.5.2], crude incidences for treatment-emergent AEs of special interest “Hemorrhage” are estimated overall as well as for two distinct time periods, defined for each patient as follows:

- time period without confounding factor(s):
 - for patients without any medical history of “Haemorrhage” and without any of the confounding medications concomitant at Baseline and without PAH associated with connective tissue disease: date of first dose of study medication to minimum(date before first dose of any of the confounding concomitant medications, date of last intake of study medication plus 7 days)
 - for patients with medical history of “Haemorrhage” or with any of the confounding medications concomitant at Baseline or with PAH associated with connective tissue disease: not applicable
- time period with confounding factor(s):
 - for patients without medical history of “Haemorrhage” and without any of the confounding medications concomitant at Baseline and without PAH associated with connective tissue disease: minimum(date of first dose of any of the confounding medications, date of last intake of study medication plus 7 days) to date of last intake of study medication plus 7 days
 - for patients with medical history of “Haemorrhage” or with any of the confounding medications concomitant at Baseline or with PAH associated with connective tissue disease: date of first dose of study medication to date of last intake of study medication plus 7 days.

When displaying crude incidences for selexipag and placebo, denominators are defined

- for time period without confounding factor(s): number of patients
 - without any medical history of “Haemorrhage”, and
 - without any of the confounding medications concomitant at Baseline, and
 - without PAH associated with connective tissue disease

- for time period with confounding factor(s): number of patients
 - with at least one medical history of “Haemorrhage”, or
 - with any of the confounding medications started before or at the date of last intake of study medication plus 7 days, or
 - with PAH associated with connective tissue disease.

In addition, the influence of potentially confounding medications (“Antithrombotic agents” or “Non-steroidal anti-inflammatory drugs (NSAIDs)” or “Corticosteroids”) is explored separately as follows:

- time period without confounding medications(s):
 - for patients without any of the confounding medications concomitant at Baseline: date of first dose of study medication to minimum(date before first dose of any of the confounding concomitant medications, date of last intake of study medication plus 7 days).
 - for patients with any of the confounding medications concomitant at Baseline: not applicable.
- time period with confounding medications(s):
 - for patients without any of the confounding medications concomitant at Baseline: minimum(date of first dose of any of the confounding medications, date of last intake of study medication plus 7 days) to date of last intake of study medication plus 7 days.
 - for patients with any of the confounding medications concomitant at Baseline: date of first dose of study medication to date of last intake of study medication plus 7 days.

When displaying crude incidences for selexipag and placebo, denominators are defined:

- for time period without confounding factor(s): number of patients without any of the confounding medications concomitant at Baseline.
- for time period with confounding factor(s): number of patients any of the confounding medications started before or at the date of last intake of study medication plus 7 days.

In addition, treatment-emergent AEs of special interest “Hemorrhage” are also presented by PAH etiology subgroup.

Treatment-emergent AEs of special interest “Hemorrhage” are also presented by maximum severity.

23.1.2.4 Hypotension

In order to explore the influence of potentially confounding factors [see Section [14.2.5.3](#)], crude incidences for treatment-emergent AEs of special interest “Hypotension” are

estimated overall as well as for two distinct time periods, defined for each patient as follows:

- time period without confounding factor(s):
 - for patients without any medical history event of special interest “Hypotension” and without any of the confounding medications concomitant at Baseline and without low blood pressure at Baseline: date of first dose of study medication to minimum(date before first dose of any of the confounding medications, date of last intake of study medication plus 7 days)
 - for patients with medical history event of special interest “Hypotension” or with any of the confounding medications concomitant at Baseline or with low blood pressure at Baseline: not applicable
- time period with confounding factor(s):
 - for patients without medical history of “Hypotension” and without any of the confounding medications concomitant at Baseline and without low blood pressure at Baseline: minimum(date of first dose of any of the confounding medications, date of last intake of study medication plus 7 days) to date of last intake of study medication plus 7 days
 - for patients with medical history of “Hypotension” or with any of the confounding medications concomitant at Baseline or with low blood pressure at Baseline: date of first dose of study medication to date of last intake of study medication plus 7 days.

When displaying crude incidences for selexipag and placebo, denominators are defined:

- for time period without confounding factor(s): number of patients
 - without any medical history of “Hypotension”, and
 - without any of the confounding medications concomitant at Baseline, and
 - without low blood pressure at Baseline.
- for time period with confounding factor(s): number of patients
 - with medical history of “Hypotension”, or
 - with any of the confounding medications started before or at the date of last intake of study medication plus 7 days, or
 - with low blood pressure at Baseline.

In addition, the influence of potentially confounding medications (PDE5-I or ERA or Riociguat or “Anti-hypertensives” or “Diuretics”) is explored separately as follows:

- time period without confounding medications(s):
 - for patients without any of the confounding medications concomitant at Baseline: date of first dose of study medication to minimum(date before first dose of any of the confounding medications, date of last intake of study medication plus 7 days).

- for patients with any of the confounding medications concomitant at Baseline: not applicable.
- time period with confounding medication(s):
 - for patients without any of the confounding medications concomitant at Baseline: minimum(date of first dose of any of the confounding medications, date of last intake of study medication plus 7 days) to date of last intake of study medication plus 7 days.
 - for patients with any of the confounding medications concomitant at Baseline: date of first dose of study medication to date of last intake of study medication plus 7 days.

When displaying crude incidences for selexipag and placebo, denominators are defined:

- for time period without confounding factor(s): number of patients without any of the confounding medications concomitant at Baseline.
- for time period with confounding factor(s): number of patients with any of the confounding medications started before or at the date of last intake of study medication plus 7 days.

23.1.3 Reporting and analysis of prostacyclin-like associated AEs

“Prostacyclin-like associated AEs”, as defined in Section 14.2.6, are summarized separately for Titration Period and Maintenance Period for patients who were treated in both periods (AEs started in the Titration Period and ongoing in the Maintenance Period are counted for both periods).

23.1.4 Reporting and analysis of AEs leading to dose reduction in the Titration Period

Treatment-emergent AEs with onset date up to the first time study drug dose is reduced or discontinued (i.e., up to the end date of the interval in study drug log after which the study drug dose is reduced) or up to Day 87 (whichever comes first) are summarized by PT for patients treated with placebo and for patients treated with selexipag by the following cumulative selexipag dose (all b.i.d.; in case two different doses were taken on the same day, the lower will be used):

- ≤ 200 mcg (i.e., all treatment-emergent AEs with onset date while treated with selexipag of 200 mcg or lower)
- ≤ 400 mcg (i.e., all treatment-emergent AEs with onset date while treated with selexipag of 400 mcg or lower)
- ≤ 600 mcg
- ≤ 800 mcg
- ≤ 1000 mcg
- ≤ 1200 mcg

- ≤ 1400 mcg
- ≤ 1600 mcg.

Treatment-emergent AEs leading to dose reduction [as defined in Section 14.2.3] or leading to study drug discontinuation with onset date up to Day 87 are summarized by PT.

23.1.5 Reporting of AEs denoting anemia or hemoglobin decrease

Crude incidence estimates for treatment-emergent AEs denoting “anemia or hemoglobin decrease” are presented for selexipag and placebo, as well as treatment-emergent AEs that

- lead to discontinuation of study AC-065A302
- are serious

In order to explore the influence of potentially confounding factors [see Section 14.2.8], crude incidences for treatment-emergent AEs denoting “anemia or hemoglobin decrease” are estimated for two distinct time periods, defined for each patient as follows:

- time period without confounding medications(s):
 - for patients without any of the confounding medications (ERAs or “Antithrombotic agents”) concomitant at Baseline: date of first dose of study medication to minimum(date before first dose of any of the confounding medications, date of last intake of study medication plus 7 days).
 - for patients with any of the confounding medications concomitant at Baseline: not applicable.
- time period with confounding medications(s):
 - for patients without any of the confounding medications concomitant at Baseline (ERAs or “Antithrombotic agents”): minimum(date of first dose of any of the confounding medications, date of last intake of study medication plus 7 days) to date of last intake of study medication plus 7 days.
 - for patients with any of the confounding medications concomitant at Baseline: date of first dose of study medication to date of last intake of study medication plus 7 days.

When displaying crude incidences for selexipag and placebo, denominators are defined:

- for time period without confounding medications(s): number of patients without any of the confounding medications concomitant at Baseline.
- for time period with confounding factor(s): number of patients with any of the confounding medications started before or at the date of last intake of study medication plus 7 days.

In addition, the separate influences of ERAs and “Antithrombotic agents” are explored as done above for the confounding medications “ERAs or Antithrombotic agents” but separately for ERAs and separately for “Antithrombotic agents”.

The treatment-emergent AEs denoting “anemia or hemoglobin decrease” are also presented for the patients with/without medical history denoting “anemia or hemoglobin decrease” as defined in Section 6.3.

23.2 Analysis of ECG data

ECG variables HR, PR, QRS, QT and QTcF are summarized by descriptive statistics for the absolute values, and for the changes from Baseline at each scheduled visit up to Month 36.

ECG variables are summarized separately for the absolute values at Visit 6 (Month 12) pre-dose, 2h post-dose and 4h post-dose for the absolute change from pre-dose to post-dose assessments (for these summaries the visit windowing described in Section 24.4 does not apply).

Number and percentage of patients who experienced treatment-emergent ECG abnormalities coded with the same PT are summarized by treatment group. ECG abnormalities coded with the preferred term “No code needed” are not displayed in the summary tables but are displayed in patient listings.

Number and percentage of patients with treatment-emergent QTcF prolongation [see Section 14.3.3] are summarized by treatment group. Change from Baseline to patient’s highest QTcF prolongation is presented in a shift table.

The ECG results of all patients having at least one of these QTcF prolongations are listed separately.

23.3 Analysis of laboratory test results

Laboratory test results are displayed separately for studies AC-065A302, AC-065A303 and for intra-patient comparison.

Laboratory tests are summarized by:

- descriptive statistics for the laboratory test results at all scheduled visits up to Month 36 (overall and separately by factors, e.g., sex or age at screening category, as detailed in Table 9 below) and boxplots over time for study AC-065A302

- descriptive statistics for absolute change from Baseline at all scheduled visits from Week 4 up to Month 36 (with boxplots over time for study AC-065A302).

Table 9 Laboratory tests: sex or age at screening categories

<i>Laboratory test</i>	<i>Sex or age at Screening categories</i>	
Hemoglobin	M: 18-64 year old M: ≥ 65 year old	F: 18-64 year old F: ≥ 65 year old
Hematocrit	M: 18-64 year old M: ≥ 65 year old	F: 18-64 year old F: ≥ 65 year old
Erythrocyte count	M: 18-64 year old M: ≥ 65 year old	F: 18-64 year old F: ≥ 65 year old
AST	M/F: < 65 year old M/F: ≥ 65 year old	
Serum creatinine	M: < 20 year old M: 20-49 year old M: 50-69 year old M: > 69 year old	F: < 20 year old F: 20-49 year old F: 50-69 year old F: > 69 year old
Urea	M/F: < 65 year old M/F: ≥ 65 year old	
Blood urea nitrogen	M/F: < 65 year old M/F: ≥ 65 year old	
Glucose	M/F: < 50 year old M/F: ≥ 50 year old	
Thyroid stimulating hormone (TSH)	M/F: < 21 year old M/F: ≥ 21 year old	
Bone alkaline phosphatase	M/F: < 50 year old M/F: ≥ 50 year old	
Carboxy-terminal telopeptide	M: <50 year old M: ≥ 50 year old	F: <50 year old F: ≥ 50 year old

Treatment-emergent (marked/alert) laboratory abnormalities (see [Table 8](#), but except for white blood cell differentials) are summarized separately for both directions, e.g., a patient with treatment-emergent HH and LL for the same laboratory test (at different visits) is counted for each direction in summary tables.

Patients with treatment-emergent (marked/alert) laboratory abnormalities LL or LLL in hemoglobin in AC-065A302 are listed. The listing includes the hemoglobin values at baseline and at screening, the lowest and the last hemoglobin value observed during the treatment-emergent period in AC-065A302, and whether the patient had concomitant (at Baseline or during treatment) “Antithrombotics agents” (as defined by the SDG), ERAs [as defined in [Section 8.1](#)], had a medical history denoting “anemia or hemoglobin

decrease” [as defined in Section 6.3], and had a treatment-emergent AE denoting “anemia or hemoglobin decrease” [as defined in Section 14.2.8] in AC-065A302.

Patients with treatment-emergent (marked/alert) laboratory abnormalities LL or LLL in leukocytes in AC-065A302 are listed. The listing includes the leukocyte values at baseline and at screening, the lowest and the last leukocyte values observed during the treatment-emergent period in AC-065A302, and whether the patient had concomitant (at Baseline or during treatment) “Immunosuppressant” (Therapeutic class).

23.3.1 Analysis of drug-induced serious hepatotoxicity (eDISH)

A graphical representation of total bilirubin versus ALT is produced to identify possible cases of Hy’s Law. The graph displays the peak of total bilirubin times $\times$ upper limit of normal (ULN) against the peak ALT $\times$ ULN, on a $\log_{10}$ scale for all patients having assessments $> 0.0625 \times$ ULN for both peaks [Watkins 2011]. Two reference lines are plotted identifying the $2 \times$ ULN for total bilirubin and $3 \times$ ULN for ALT.

Normal patients are on the left lower quadrant, possible Hy’s Law cases appear on the right upper quadrant. The latter patients are listed in addition.

23.4 Analysis of vital signs and body weight

Vital signs and body weight are summarized by descriptive statistics for the observed values at each scheduled visit and for absolute changes from Baseline at each scheduled visit (from Week 4 to Week 36).

Number and percentage of patients with treatment-emergent low blood pressure are tabulated for the categories defined in Section 14.5.2 separately for studies AC-065A302 and AC-065A303 and in addition for the intra-patient comparison.

23.5 Analysis of medications and PAH-specific medication

For each study treatment, medications concomitant at Baseline and medication started during treatment period are summarized on the FAS and on the OAS by number and percentage of patients having any medication, having a medication in each ATC class, and having each individual medication (preferred term) separately for each type of medication: PAH-specific, PAH-non-specific and medication not for PAH (sorted by ATC class and preferred term). PAH-specific medications concomitant at Baseline are summarized also by geographical region. PAH-specific medication started after study drug discontinuation (in study AC-065A302 or study AC-065A303, whichever is the latest for a patient) is summarized for the FAS.

In the total number of treatments the preferred term / medication linked to more than one class within the same patient is counted only once. Thus total number of treatments in the main total may not equal the sum of the subtotals by class.

For each preferred term the class/es are allocated using the 3 digits of the ATC code.

23.6 Ophthalmologic sub-study

Baseline findings, post-Baseline findings, change from Baseline findings and change from Baseline in qualitative severity of retinal tortuosity are summarized descriptively by study treatment. For the qualitative changes from Baseline, only patients with Visit 1 assessment taken prior to or on start date of study drug intake are included.

24 DEFINITIONS

24.1 Formulas

Month = 30.4 days

Weight (kg) = weight (lbs)*0.4536

Height (cm) = height (inch)*2.54

Body Mass Index (BMI) = weight(kg) / (height(m))²

Mean arterial pressure (MAP) = DBP + 1/3(SBP-DBP)

24.2 Dates

24.2.1 Randomization date in study AC-065A302

The randomization date in study AC-065A302 is taken from the IWRS/IVRS database (ICON) as the date of randomization with VisitCode="V1".

24.2.2 Study drug start date and study drug end date in study AC-065A302

Study drug start date in study AC-065A302 is taken from the "Start Date" of the first interval (sorted by chronological order) in the Study Drug Log CRF.

Study drug end date in study AC-065A302 is taken from the "End Date" of the last interval (sorted by chronological order of all records not completely empty) in the Study Drug Log CRF (with missing at the end of the ordering). If the study drug end date is missing, study drug is imputed by the earliest between (date of last contact, date of death, analysis cut-off date of AC-065A302 [27 Apr 2014]).

24.2.3 Study drug start date and study drug end date in study AC-065A303

Study drug start date in study AC-065A303 is taken from the "Start Date" of the first interval (sorted by chronological order) in the Study Drug Log CRF.

Study drug end date in study AC-065A303 is taken from the "End Date" of the last interval (sorted by chronological order) in the Study Drug Log CRF (with missing at the end of the ordering). If the study drug end date is missing, study drug is considered as ongoing at the analysis cut-off date and study drug end date in study AC-065A303 is set to the earliest between (date of last contact, date of death, analysis cut-off date of AC 065A303 [10 Mar 2014]).

24.2.4 Date of last contact

The date of last contact is the last date the patient was known to be alive (irrespective of study), i.e., the maximum of [visit dates, sample dates, AE onset dates, morbidity events, date of last contact from the Survival Follow-Up CRF page – excluding any dates that originate from the ARGUS database]. Dates originated from the ARGUS database can be identified in SDTM domain LB by laboratory name (variable LB.LBNAM) equal to "ARGUS".

24.2.5 Patient-specific Date of study closure

The patient-specific date of study closure is either the date of contact, date of death or date of last contact reported on ‘Survival Follow-up at study closure’ CRF page (only one of these three dates can be reported for a patient).

24.2.6 Date of CEC-confirmed morbidity/mortality event (including PTOP morbidity/mortality events)

The date of CEC-confirmed morbidity/mortality event is the date as confirmed by the CEC. If the date is incomplete it is set to the lower limit, unless the lower limit is before the randomization date in which case it is set to the randomization date. The same rule is applied to incomplete onset dates for morbidity/mortality events reported by the investigator.

24.3 Study Days

Study Day in study AC-065A302

AC-065A302 Study Day refers to the number of days elapsed since the day of study drug start in AC-065A302 plus 1 (i.e., AC-065A302 Study Day 1 is the day of study drug start in study AC-065A302). For dates prior to start of study drug in study AC-065A302, Study Day is the negative number of days elapsed between the date under consideration and the day of study drug start in study AC-065A302. Therefore, the Study Day is always different from 0.

Study Day in study AC-065A303

AC-065A303 Study Day refers to the number of days elapsed since the day of study drug start in AC-065A303 plus 1 (i.e., AC-065A303 Study Day 1 is the day of study drug start in study AC-065A303). For dates prior to start of study drug in study AC-065A303, Study Day is the negative number of days elapsed between the date under consideration and the day of study drug start in study AC-065A303. Therefore, the Study Day is always different from 0.

Study Day in combined studies AC-065A302 and AC-065A303

For the combined studies AC-065A302 and AC-065A303, Overall Study Day refers to the number of days elapsed since the day of study drug start in AC-065A302 plus 1 (i.e., Overall Study Day 1 is the day of study drug start in study AC-065A302). For dates prior to start of study drug in study AC-065A302, Overall Study Day is the negative number of days elapsed between the date under consideration and the day of study drug start in study AC-065A302. Therefore, the Overall Study Day is always different from 0.

24.4 Time windows

In order to summarize data descriptively over time in an at least approximate order, all recorded relevant assessments (for both studies AC-065A302 and AC-065A303, if applicable) are assigned to the most appropriate “visit window” (except post-dose ECG

assessments). These visit windows are based on respective Study Day [see Section 24.3] as described in the tables below³.

Should more than one assessment fall within the same time window, then the closest value to the nominal planned time point is assigned to the respective visit window. If values are equidistant to the planned time point, the mean of these values is used for the summaries over time (by visit) in the case of continuous data, and the maximum of these values in the case of ordered categorical data (except for the summary of marked laboratory abnormalities as detailed in Section 23.3).

Table 10 Visit windows for study AC-065A302

Visit window	AC-065A302 Study Day (nominal value)	Lower limit for AC-065A302 Study Day	Upper limit for AC-065A302 Study Day
Baseline	1	not applicable	1
Week 4	28	2	42
Week 8	56	43	84
Week 16	112	85	147
Week 26	182	148	271
Month 12	360	272	450
Month 18	540	451	630
Month 24	720	631	810
Month 30	900	811	990
Month 36	1080	991	1170
Month 42	1260	1171	1350
Month 48	1440	1351	1530
Month 54	1620	1531	1710
Month 60	1800	1711	1890

There are additional scheduled phone calls without explicit data collection on a respective CRF page. However, during these phone calls information on adverse events or concomitant medications may be recorded on respective CRF pages.

³ Values not retained in summaries over time are kept in the datasets and used as appropriate.

Table 11 Visit windows for study AC-065A303

Visit window	AC-065A303 Study Day (nominal value)	Lower limit for AC-065A303 Study Day	Upper limit for AC-065A303 Study Day
Day 1	1	1	1
Week 4	28	2	42
Week 8	56	43	84
Week 16	112	85	147
Week 26	182	148	271
Month 12	360	272	450
Month 18	540	451	630
Month 24	720	631	810
Month 30	900	811	990
Month 36	1080	991	1170
Month 42	1260	1171	1350
Month 48	1440	1351	1530
Month 54	1620	1531	1710
Month 60	1800	1711	1890

Table 12 Visit windows for combined studies AC-065A302 and AC-065A303

Visit window	Overall Study Day (nominal value)	Lower limit for Overall Study Day	Upper limit for Overall Study Day
Baseline	1	not applicable	1
Week 4	28	2	42
Week 8	56	43	84
Week 16	112	85	147
Week 26	182	148	271
Month 12	360	272	450
Month 18	540	451	630
Month 24	720	631	810
Month 30	900	811	990
Month 36	1080	991	1170
Month 42	1260	1171	1350
Month 48	1440	1351	1530
Month 54	1620	1531	1710
Month 60	1800	1711	1890

24.5 Enrollment in AC-065A303

A patient is considered enrolled in study AC-065A303 if date of Visit 1 is not missing in IVRS.

25 STATISTICAL ANALYSIS METHODS

This section describes the statistical analysis methods (models, tests, and point and interval estimation) which are applied to endpoints in the subsequent sections.

In general, data is listed and summarized by appropriate descriptive statistics (tables or figures), typically including:

- for continuous variables: number of non-missing observations, number of missing observations, mean, SD, standard error, minimum, Q1, median, Q3 and maximum
- time-to-event variables: number of events, number of censored observations and Kaplan-Meier estimates of the survival function
- categorical variables: number of non-missing observations, number of missing observations and frequency with percentage per category (percentages based on the number of non-missing observations).

25.1 Statistical analysis methods for event history endpoints

25.1.1 Kaplan-Meier estimation and display of survival distributions

A graphical estimate of the survival function for both treatment groups are obtained by the Kaplan-Meier (KM) product-limit method as implemented in SAS PROC LIFETEST.

The graphical presentation follows the recommendations from [\[Pocock 2002\]](#) on the following aspects:

- rules for KM curves going upwards or downwards
- termination of the vertical axis.

KM curves were also truncated at Month 36 or at Month 42 in order to guarantee sufficient numbers of patients at risk in the plot. KM estimates with two-sided 95% CIs at specific time points (Weeks 26, 52, 78) are provided and may be added to the plot. The CIs are constructed using Greenwood's formula [\[Collett 1994\]](#) for the standard error of the Kaplan-Meier estimate. If available, median time to event (as well as 25th and 75th percentiles) for each treatment group are provided along with two-sided CIs calculated using the method of [\[Brookmeyer 1982\]](#).

Standard statistics to be displayed with Kaplan-Meier graphs are given below.

Per treatment group:

- number of events and number of censored observations (reasons for censoring are provided in a separate listing)
- number of patients at risk for specific time points (Weeks 0, 26, 52, 78, 104, etc.)

For comparison of treatment groups:

- one-sided *p*-value of the (stratified, if relevant) log-rank test and list of stratification variables (if used)

- hazard ratio (HR) point estimate with two-sided CI based on Wald's method and list of list of stratification variables / covariates (if used).

See Sections 25.1.2 and 25.1.3 for details on these characteristics.

25.1.2 Log-rank tests

25.1.2.1 Unstratified log-rank test

Let $S_{\text{sel}}(t)$ and $S_{\text{pla}}(t)$ denote the survival functions for selexipag and placebo, respectively.

The null hypothesis

$H_0: S_{\text{sel}}(t) = S_{\text{pla}}(t)$ for all $t \geq 0$ "identical survival functions for both treatments"

is tested against the one-sided alternative hypothesis

$H_A: S_{\text{sel}}(t) \geq S_{\text{pla}}(t)$ for all $t \geq 0$ and $S_{\text{sel}}(t) > S_{\text{pla}}(t)$ for at least some $t > 0$

"survival function in the selexipag group superior to the survival function in the placebo group".

The unstratified log-rank test is conducted by SAS PROC LIFETEST where the STRATA statement includes only the treatment group variable (*treat*). The TIME statement includes a variable with times to event (*survtime*) and an indicator variable for right censoring (*censor*) with 0 representing censoring (additional options controlling the output may be added):

```
PROC LIFETEST DATA=dataset METHOD=KM;  
  TIME survtime*censor(0);  
  STRATA treat;  
RUN;
```

As an output of the procedure, the rank statistic S and variance $Var(S)$ are obtained. Under the null hypothesis, the test statistic $Z = S/\sqrt{Var(S)}$ is approximately normally distributed. The one-sided p -value is therefore obtained from normally distributed Z statistic and H_0 is rejected if the p -value does not exceed the (nominal) significance level assigned to the test.

25.1.2.2 Stratified log-rank test

Let $S_{\text{sel},k}(t)$ and $S_{\text{pla},k}(t)$ denote the survival functions for selexipag and placebo in stratum k , $k=1,\dots,K$, $K = m_1 \times m_2 \times \dots \times m_j$ where m_i denotes the number of categories for stratification factor i , $1 \leq i \leq j$, respectively. The null hypothesis

$H_0: S_{\text{sel},k}(t) = S_{\text{pla},k}(t)$ for all $t \geq 0$ and all k ("identical survival functions for both groups in each stratum")

is tested against the one-sided alternative hypothesis

$H_A: S_{\text{sel},k}(t) \geq S_{\text{pla},k}(t)$ for all $t \geq 0$ and all $k=1,\dots,K$ and $S_{\text{sel},m}(t) > S_{\text{pla},m}(t)$ for at least some $t > 0$ and some m ("survival function in the selexipag superior to the survival in the placebo group in at least one stratum").

Log-rank tests are performed for each of the strata separately, obtaining the rank statistic S_k and variance $Var(S_k)$ where $k=1, 2, \dots, K$. The stratified log-rank test statistic is constructed as $Z = [S_1 + \dots + S_K] / \sqrt{[Var(S_1) + \dots + Var(S_K)]}$. Under the null hypothesis, Z is approximately normally distributed. The one-sided stratified log-rank p -value is therefore obtained from normally distributed Z statistic and H_0 is rejected if p does not exceed the (nominal) significance level assigned to the test.

The stratified log-rank test is conducted with SAS PROC LIFETEST where the STRATA statement includes the j strata variables ($strat\_1, \dots, strat\_j$) and the GROUP option includes the treatment variable ($treat$). The TIME statement includes a variable with times to event ($survtime$) and an indicator variable for right censoring ($censor$) with 0 representing censoring (additional options controlling the output may be added):

```
PROC LIFETEST DATA=dataset METHOD=KM;  
    TIME survtime*censor(0);  
    STRATA strat_1 .. strat_j GROUP=treat;  
RUN;
```

25.1.3 Proportional hazards model

25.1.3.1 Unstratified unadjusted proportional hazards regression model

The unstratified unadjusted proportional hazards regression model and its assumptions are illustrated by:

$$h(t, x_{j1}, \beta_1) = h_0(t) \cdot \exp(x_{j1} \cdot \beta_1)$$

$h(.)$ hazard function as a function of time (relative to the start date), the patient's treatment and the unknown regression parameter

$h_0(t)$ unspecified baseline hazard function at time t

x_{j1} treatment for patient j coded as 0 (placebo) or 1 (selexipag); this coding leads to a hazard ratio < 1 if the estimated effect suggests a lower hazard in the selexipag group relative to the placebo group

β_1 unknown regression parameter for the treatment effect on the log-scale (the log hazard ratio).

The HR is a multiplicative constant $\lambda_1 = \exp(\beta_1)$ comparing the hazard function in the selexipag group relative to the hazard function in the placebo group (identical to the baseline hazard function). A $HR < 1$ indicates decreased hazard for the event of interest in the selexipag group compared to the placebo group.

SAS PROC PHREG (with the TIES=EXACT option for the "exact" handling of ties) is used to estimate the hazard ratio based on the partial maximum likelihood function; a Wald-test based two-sided CI is requested by the RISKLIMITS option (additional options controlling the output may be added):

```
PROC PHREG DATA=dataset;  
  MODEL survtime*censor(0)=treat / TIES=EXACT RISKLIMITS ALPHA=;  
RUN;  
  
* survtime represents variable containing event/censoring times;  
* censor represents censoring variable (0=censored, 1=event);  
* treat represents treatment group variable (0=placebo, 1=selexipag);
```

25.1.3.2 Stratified unadjusted proportional hazards regression

The stratified unadjusted proportional hazards regression model and its assumptions are described by:

$$h(t, x_{jk1}, \beta_1) = h_{0k}(t) \cdot \exp(x_{jk1} \cdot \beta_1)$$

$h(.)$ hazard function as a function of time (relative to the start date), the patient's stratum and treatment and the unknown regression parameter

$h_{0k}(t)$ unspecified baseline hazard function for stratum k at time t

x_{jk1} treatment for patient j in stratum k coded as 0 (placebo) or 1 (selexipag); this coding leads to a hazard ratio < 1 if the estimated effect suggests a lower hazard in the selexipag group relative to the placebo group

β_1 unknown regression parameter for the treatment effect on the log-scale (the log hazard ratio).

The hazard ratio is a multiplicative constant $\lambda_1 = \exp(\beta_1)$ comparing the hazard functions in the selexipag group relative to the hazard functions in the placebo group. The latter are allowed to vary across strata. However, the hazard ratio is assumed to be common across strata. A HR < 1 indicates decreased hazard for the event of interest in the selexipag group compared to the placebo group.

SAS PROC PHREG (with the TIES=EXACT option for the "exact" handling of ties) is used to estimate the hazard ratio based on the partial maximum likelihood function; a Wald-test based two-sided CI is requested by the RISKLIMITS option (additional options controlling the output may be added):

```
PROC PHREG DATA=dataset;  
  MODEL survtime*censor(0)=treat / TIES=EXACT RISKLIMITS ALPHA=;  
  STRATA strat_1 .. strat_j;  
RUN;  
  
* survtime represents variable containing event/censoring times;  
* censor represents censoring variable (0=censored, 1=event);  
* treat represents treatment group variable (0=placebo, 1=selexipag);  
* strat_1 to strat_j represent stratification variables;
```

25.1.3.3 Stratified adjusted proportional hazards regression

The stratified adjusted proportional hazards regression model and its assumptions are illustrated by:

$$\begin{aligned}h(t, \mathbf{x}_{jk}, \boldsymbol{\beta}) &= h_{0k}(t) \cdot \exp(\mathbf{x}'_{jk} \cdot \boldsymbol{\beta}) \\ &= h_{0k}(t) \cdot \exp(x_{jk1} \cdot \beta_1 + \dots + x_{jkn} \cdot \beta_n)\end{aligned}$$

- $h(.)$ hazard function as a function of time (relative to the start date), the patient's stratum and covariates, and the unknown vector of regression parameters
- $h_{0k}(t)$ unspecified baseline hazard function for patients with covariate vector (0, ..., 0) for stratum k at time t
- $\mathbf{x}_{jk}$ vector of Baseline covariates for patient j in stratum k , with x_{jk1} representing treatment coded as 0 (placebo) or 1 (selexipag)
- $\boldsymbol{\beta}$: unknown regression parameter vector on the log-scale (β_1 represents the log hazard ratio for treatment).

The hazard ratio for the i -th covariate is a multiplicative constant $\exp(\beta_i)$ comparing the hazard functions between the levels of the i -th covariate. Baseline hazard functions are allowed to vary across strata without any restrictions. However, the hazard ratio comparing a covariate (including treatment) is assumed to be common across strata. The estimates of β_i are adjusted for the other covariates in the model.

SAS PROC PHREG (with the TIES=EXACT option for the "exact" handling of ties) is used to estimate the hazard ratios based on the partial maximum likelihood function; a Wald-test based two-sided CI is requested by the RISKLIMITS option (additional options controlling the output may be added):

```
PROC PHREG DATA=dataset;  
  MODEL survtime*censor(0)=treat cov_1 .. cov_k /  
  TIES=EXACT RISKLIMITS ALPHA;  
  STRATA strat_1 .. strat_j;  
RUN;  
  
* survtime represents variable containing event/censoring times;  
* censor represents censoring variable (0=censored, 1=event);  
* treat represents treatment group variable (0=placebo, 1=selexipag);  
* cov_1 to cov_k represent covariates other than treatment group;  
* strat_1 to strat_j represent stratification variables;
```

The unstratified adjusted proportional hazards regression model is a special case with $h_0(t)$ denoting the unspecified baseline hazard function for all patients with covariate vector (0, ..., 0) at time t . In SAS PROC PHREG the STRATA statement is omitted.

25.1.3.4 Examination of proportional hazards assumption

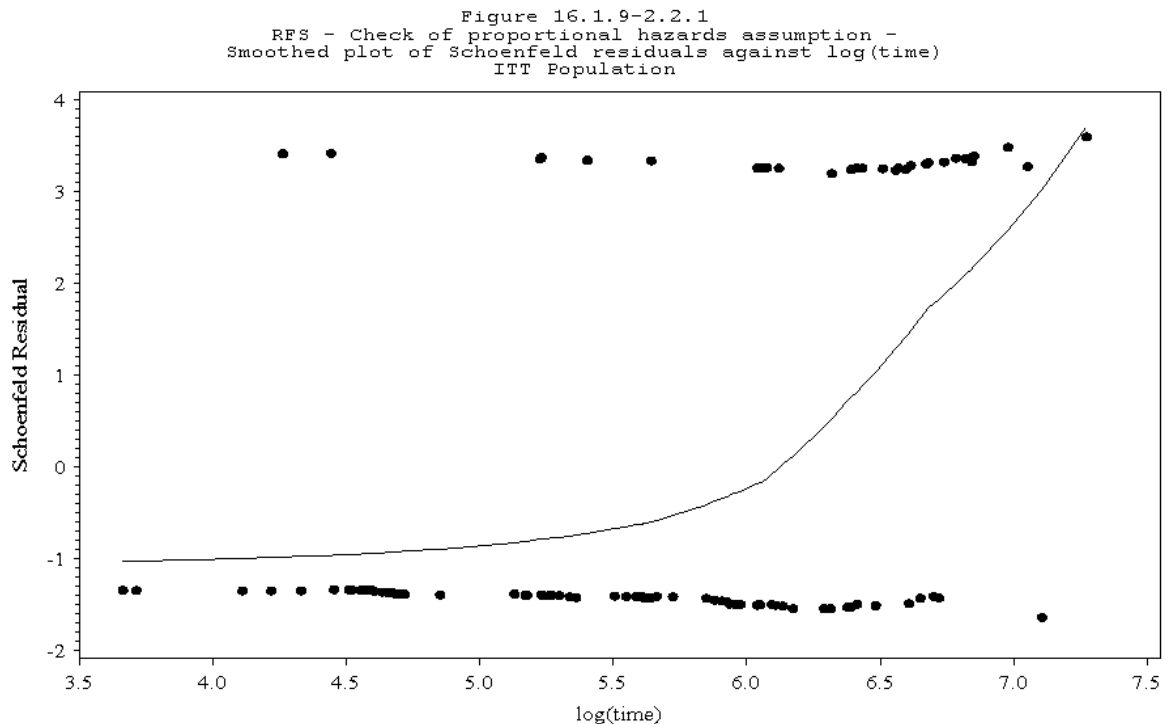
An investigation into the assumption of proportional hazards for treatment is performed informally using graphical means and more formally by a statistical test.

Using an output dataset from SAS PROC LIFETEST a plot of $\log(-\log[S(t)])$ against $\log(t)$ showing values for each treatment group separately is of help to identify the presence of non-proportional hazards. If the hazards are proportional over time the lines formed from joining up the values for each treatment group should be approximately parallel.

A smoothed plot (e.g., incorporating a LOESS curve) of scaled Schoenfeld residuals against time t , $\log(t)$ or some other transformation $g(t)$, can also indicate evidence of non-proportional hazards [Therneau 2000, chapter 6]. Within SAS PROC PHREG, the scaled Schoenfeld weighted residuals are obtained by using the keyword WTRESSCH within the OUTPUT statement. A linear regression line is fitted (e.g., by SAS PROC REG) to the plot along with a test of zero slope. Non-zero slope indicates non-proportional hazards. This formal test corresponds to testing an additional time-dependent variable $g(t)$ to the original model.

Figure 3 below is an example of a Schoenfeld residual plot with spline curve fitted showing definite non-proportional hazards with respect to the effect of treatment (active vs placebo). In this example the treatment effect appears fairly stable up to around one year ($\log(6)$) before decreasing notably afterwards.

Figure 3 Schoenfeld residuals plot



If there is strong evidence against the proportional hazards assumption, the estimated hazard ratio and related confidence interval is not reported (reason mentioned) and an alternative method, the restricted mean survival time approach [Royston 2011] is used instead, reporting the point estimated and a two-sided confidence interval for the ratio of two “survival losses”.

25.1.4 Competing risks analysis

Competing risks analysis is described below for the primary efficacy endpoint but the underlying method can be applied for time-to-event analysis for other composite endpoints as well.

25.1.4.1 Description of the underlying stochastic process

For each patient, a multistate stochastic process $(X_t)_{t \geq 0}$ is considered where X_t denotes the state a patient is at day t , $0 \leq t \leq$ date of last study drug intake in the AC-065A302 Treatment Period plus 7 days. Five states are defined as follows:

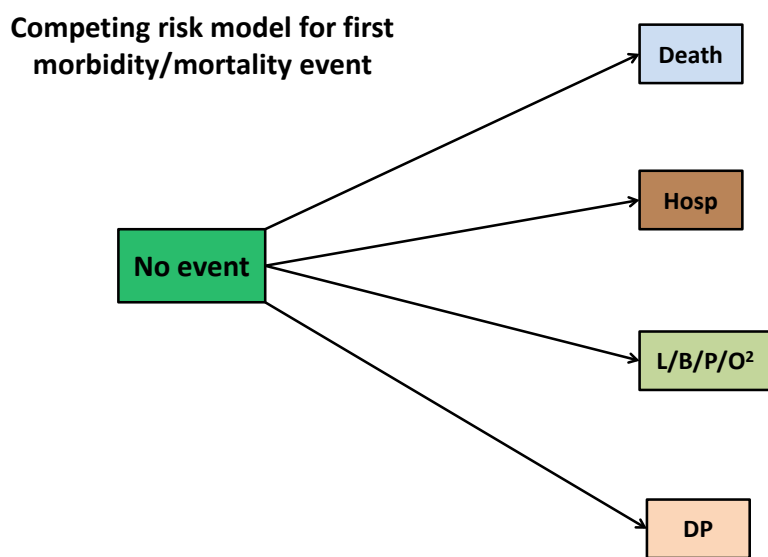
- [Death] death (all-cause mortality)
- [Hosp] hospitalization for worsening of PAH based on predefined criteria
- [L/B/P/O²] worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy, parenteral prostanoid treatment or chronic oxygen therapy

[DP] disease progression
[No event] no event

According to the study protocol patients start in state [No event] at time of randomization $t=0$, i.e., $P(X_0 = [\text{No event}]) = 1$. As the process $(X_t)_{t \geq 0}$ is discrete in time (days) it may happen that two states are associated with the same date, e.g., disease progression and hospitalization at the same day. In such cases, the state higher in the list above is used.

States and possible transitions between states are illustrated by [Figure 4](#) below.

Figure 4 Multi-state competing risks model for primary efficacy endpoint



Observation of the competing risks process are subject to right-censoring (assumed to be independent from the risk process), i.e., observation was stopped (for the primary efficacy endpoint typically 7 days after last study drug intake in the AC-065A302 Treatment Period) while the patient was still in state [No event].

25.1.4.2 Gray's test

The event components of the primary endpoint are analyzed by a competing risk methodology as proposed by Gray [\[Gray 1988\]](#).

Cumulative incidence functions for the time to first event and Gray's test will be calculated using the R-package *cmprsk*.

25.1.5 Andersen-Gill model for recurrent events

Data on recurrent events is to be arranged in the counting process structure [Therneau 2000]. There is one record (row) for each time interval a patient is at risk to experience an event. In general, there is more than one of such time intervals per patient, so that each patient is represented by a series of records (rows of data). The first interval starts with the date of randomization (for an efficacy event) or the date of first study drug intake (for safety events). Intervals ending without an event are indicated by a censoring variable: 0 indicates censored, 1 indicates event. A time dependent covariate for study treatment (selexipag, placebo, none) may be added.

Example 1 Patient 1 experienced no event and observation ended at Day 450; Patient 2 had events at Day 87, 200, and 510 and observation ended without further events at Day 610. This would result in following counting process data representation:

	Event-risk period		Event (1)/ Censoring (0)
	Start day	Stop day	
Patient 1	1	450	0
Patient 2	1	87	1
	88	200	1
	201	510	1
	511	610	0

If a patient experienced an event on the same day as the start day of the event-risk period (i.e. start day=stop day), stop day is set to start day + 0.5 for this given start-stop interval .

There may be types of events for which patients are off-risk for a number of days before they are back at risk. An example is the event of hospitalization: during the time when hospitalized a patient is not at risk for hospitalization.

Example 2 Patient 3 was never hospitalized and observation ended at Day 475; Patient 4 was hospitalized at Day 60 and discharged at Day 75, hospitalized at Day 180 and discharged at Day 190, and observation ended without further hospitalizations at Day 560. This would result in following counting process data representation:

	Event-risk period		Event (1)/ Censoring (0)
	Start day	Stop day	
Patient 3	1	475	0
Patient 4	1	60	1
	75	180	1
	190	560	0

The (stratified) Andersen-Gill model [Andersen 1982] for recurrent events is an extension of the (stratified) proportional hazards model. It can be described by:

$$\begin{aligned}\lambda_{jk}(t, x_{jk1}, \beta_1) &= \lim_{h \downarrow 0} \frac{1}{h} P(N_{jk}(t+h) - N_{jk}(t) = 1 | F_{jk}(t)) \\ &= Y_{jk}(t) \cdot h_{0k}(t) \cdot \exp(x_{jk1} \cdot \beta_1)\end{aligned}$$

$\lambda_{jk}(\cdot)$ intensity function depending on time (relative to the start date), the treatment of patient j in stratum k and the unknown regression parameter

$N_{jk}(\cdot)$ stochastic process counting the number of events for patient j in stratum k (right continuous process with jumps of height 1)

$F_{jk}(t)$ Filtration (a collection of σ -algebras with $F_{jk}(s)$ subset of $F_{jk}(t)$ for all $0 \leq s \leq t$) containing all relevant information on patient j in stratum k collected up to time t

$Y_{jk}(t)$ left continuous predictable stochastic process indicating patient j in stratum k is at risk, i.e., $Y_{jk}(t)=1$, or not, i.e., $Y_{jk}(t)=0$, for the event at time t

$h_{0k}(t)$ unspecified baseline hazard function for stratum k at time t

x_{jk1} treatment for patient j in stratum k coded as 0 (placebo) or 1 (selexipag); this coding leads to a hazard ratio < 1 if the estimated effect suggests a lower hazard in the selexipag group relative to the placebo group

β_1 : unknown parameter for the treatment effect on the log-scale (the log hazard ratio).

The hazard ratio is a multiplicative constant $\exp(\beta_1)$ comparing the hazard functions in the selexipag group relative to the hazard functions in the placebo group. The latter are allowed to vary across strata. However, the HR is assumed to be common across strata. A $HR < 1$ indicates decreased hazard for the event of interest in the selexipag group compared to the placebo group. Note that the model equation does not assume a change in the intensity function caused by an event and the argument of the baseline hazard function remains relative to the date of randomization, see [Kelly 2000].

Statistical analysis

The regression parameter β_1 is estimated by maximum likelihood method first ignoring possible correlation followed by a Wald test-based two-sided CI for the HR using a robust sandwich-type variance estimate taking into account correlation between recurrent events within a patient [Therneau 2000, sections 7.2 and 8.2.1].

SAS PROC PHREG using COVSANDWICH(AGGREGATE) option and the ID statement is used (additional options controlling the output may be added):


```
PROC PHREG DATA=dataset COVSANDWICH(AGGREGATE);  
  MODEL (start stop)*censor(0)=treat  
    / TIES=EXACT RISKLIMITS ALPHA=;  
  ID subjid;  
  STRATA strat_1 .. strat_j;  
RUN;  
  
* start represents the variable containing start day of event-risk periods;  
* stop represents the variable containing stop day of event-risk periods;  
* censor represents the censoring variable (0=censored, 1=event);  
* treat represents the treatment group variable (0=placebo, 1=selexipag);  
* subjid represents the patient identifier  
* strat_1 .. strat_j represent stratification variables (if applicable);
```

25.2 Statistical analysis methods for categorical endpoints

25.2.1 Unstratified analysis method for binary endpoints

Let π_{sel} and π_{pla} denote the unknown probabilities for an outcome of interest in the selexipag and placebo group, respectively.

The null hypothesis

$H_0: \pi_{sel} = \pi_{pla}$ “identical probabilities for an outcome in both treatment groups”

is tested against the one-sided alternative hypothesis

$H_A: \pi_{sel} > \pi_{pla}$ “probability for an outcome is higher in the selexipag group”

The Mantel-Haenszel test is used to test the null hypothesis: H_0 is rejected if the two-sided p -value is not exceeding the two-sided significance level assigned to the test (typically 0.01) and the observed proportions fulfill $p_{sel} > p_{pla}$.

The effect of selexipag relative to placebo is expressed by the odds ratio estimate and a two-sided CI.

SAS PROC FREQ is used (additional options controlling the output may be added):

```
PROC FREQ DATA=dataset;  
  TABLES treat*response / CHISQ MEASURE ALPHA=0.01;  
RUN;  
  
* response represents binary endpoint (outcome of interest in first column);  
* treat represents the treatment group (selexipag in first row);
```

25.2.2 Stratified analysis method for binary endpoints

Let $\pi_{sel,k}$ and $\pi_{pla,k}$, $k=1,\dots,K$, denote the unknown probabilities for an outcome of interest in stratum k for the selexipag and placebo group, respectively.

The null hypothesis

$H_0: \pi_{sel,k} = \pi_{pla,k}$ for all $k=1,\dots,K$ “in all K strata the probabilities for an outcome are the same for both treatment groups”

is tested against the two-sided alternative hypothesis

$H_A: \pi_{\text{sel},j} \neq \pi_{\text{pla},j}$ for at least one stratum j with $1 \leq j \leq K$ “for at least one stratum the probabilities for an outcome are different between selexipag and placebo”.

The Cochran-Mantel-Haenszel test is used to test the null hypothesis: H_0 is rejected if the two-sided p -value is not exceeding the two-sided significance level assigned to the test (typically 0.01).

If the assumption of a common odds ratio is not rejected by the Breslow-Day test using a two-sided significance level of 0.05, the effect of selexipag relative to placebo is expressed by the common odds ratio estimate and a two-sided CI.

SAS PROC FREQ is used (additional options controlling the output may be added):

```
PROC FREQ DATA=dataset;
  TABLES strata*treat*response / CMH ALPHA=0.01;
RUN;

* strata represents the stratification factor(s);
* response represents the binary endpoint (e.g. yes/no);
* treat represents the treatment group (selexipag as first row);
```

25.2.3 Analysis method for counts and rates

For statistical analysis of counts and rates (for example the annualized hospitalization rate), the following individual patient data is used:

- the patient’s number of events (e.g., hospitalizations) up to the EOS visit
- the patient’s length of observation expressed in years, defined as: [EOS visit date minus randomization date +1] divided by 365.25.

A generalized linear model with negative-binomial distribution for the number of events up to the EOS visit is assumed.

t_j denotes the length of observation (see above) for patient j

Y_j denotes the number of events for patient j during t_j

μ_j denotes the mean of the negative binomial distribution of Y_j .

The mean for the distribution of the annualized hospitalization rate for patient j , denoted by μ_j/t_j , is modeled by the following equation:

$$\log(\mu_j/t_j) = \mathbf{x}'_j \boldsymbol{\theta}, \quad \text{i.e.,} \quad \log(\mu_j) = \mathbf{x}'_j \boldsymbol{\theta} + \log(t_j), \quad \text{where}$$

$\mathbf{x}_j$ is the vector denoting treatment (and other Baseline covariates, if applicable) for patient j

$\boldsymbol{\theta}$ is the vector of unknown fixed model parameters (treatment and other Baseline covariates, if applicable).

Within the negative binomial regression model, the null hypothesis of no treatment effect ($\theta_{\text{treatment}}=0$) is tested by a two-sided Wald-type test (typically at a two-sided significance level of 0.01). A two-sided Wald CI is calculated for the relative reduction in mean annualized event rate for selexipag compared to placebo.

25.3 Nonparametric statistical analysis methods for endpoints with a continuous distribution

25.3.1 Nonparametric analysis of covariance for univariate endpoints

Non-parametric ANCOVA similar as described in section 7.7 of [\[Stokes 2000\]](#) is performed.

Null hypothesis H_0 : “Distributions of the post-Baseline endpoint, adjusted for its Baseline value, are identical for selexipag and placebo”

is tested against the alternative hypothesis H_A : “Distribution of the post-Baseline endpoint, adjusted for its Baseline value, is more favorable for selexipag as compared to placebo”.

The non-parametric ANCOVA procedure incorporates three steps:

1. Transformation of Baseline and post-Baseline values for all patients (regardless of treatment groups) to standardized ranks (i.e., ranks divided by the number of patients ranked plus 1, mean ranks in case of ties)
2. Determination of residuals from the linear regression of the response variable standardized ranks on Baseline variable standardized ranks.
3. Application of the one-sided Wilcoxon-Mann-Whitney test to these residuals. The standardized test statistic with a continuity correction of 0.5 is asymptotically standard normally distributed under the null hypothesis. One-sided significance level of 0.005 is used.

SAS code for the analysis:

```
PROC RANK DATA=dataset TIES=MEAN NPLUS1 OUT=stdrank;  
    VAR base outcome;  
RUN;  
  
PROC GLM DATA=stdrank;  
    MODEL outcome=base / PREDICTED;  
    ODS OUTPUT PredictedValues=pred;  
    ID treat;  
RUN;  
  
PROC NPAR1WAY DATA=pred WILCOXON;  
    CLASS treat;  
    VAR residual;  
RUN;  
  
* base represents the Baseline value of the endpoint;  
* outcome represents the post-Baseline endpoint;  
* treat represents the treatment group;
```

Further options to control the output may be added.

In case of a stratified non-parametric ANCOVA, the linear regression in step 2 is stratified, and in step 3 a two-sided stratified van Elteren test with two-sided significance level 0.01 is performed.

SAS code for the analysis:

```
PROC RANK DATA=dataset TIES=MEAN NPLUS1 OUT=stdrank;  
  BY strata;  
  VAR base outcome;  
RUN;  
  
PROC GLM DATA=stdrank;  
  BY strata;  
  MODEL outcome=base / PREDICTED;  
  ODS OUTPUT PredictedValues=pred;  
  ID treat;  
RUN;  
  
PROC FREQ DATA=pred SCORES=MODRIDIT;  
  TABLES strata*treat*residual / CMH2;  
RUN;  
  
* base represents the Baseline value of the endpoint;  
* outcome represents the post-Baseline endpoint;  
* strata represents the stratification variable(s);  
* treat represents the treatment group;
```

Further options to control the output may be added.

25.3.2 Nonparametric analysis of distribution shift and non-parametric Wilcoxon-Mann-Whitney test

Non-parametric estimation of the distribution shift (between selexipag and placebo) for a univariate endpoint is performed by the Hodges-Lehmann method [Lehmann 1998, section 2.5]. Apart from the shift, the distributions for both treatment groups are assumed to be the same. Two-sided CIs for the location shift are provided with the method described in [SAS Institute 2009].

SAS code for the analysis (also to be used to perform the Wilcoxon-Mann-Whitney test):

```
PROC NPAR1WAY DATA=dataset WILCOXON HL ALPHA=;
  CLASS treat;
  VAR outcome;
RUN;

* outcome represents the post-Baseline endpoint;
* treat represents the treatment group;
```

Further options to control the output may be added.

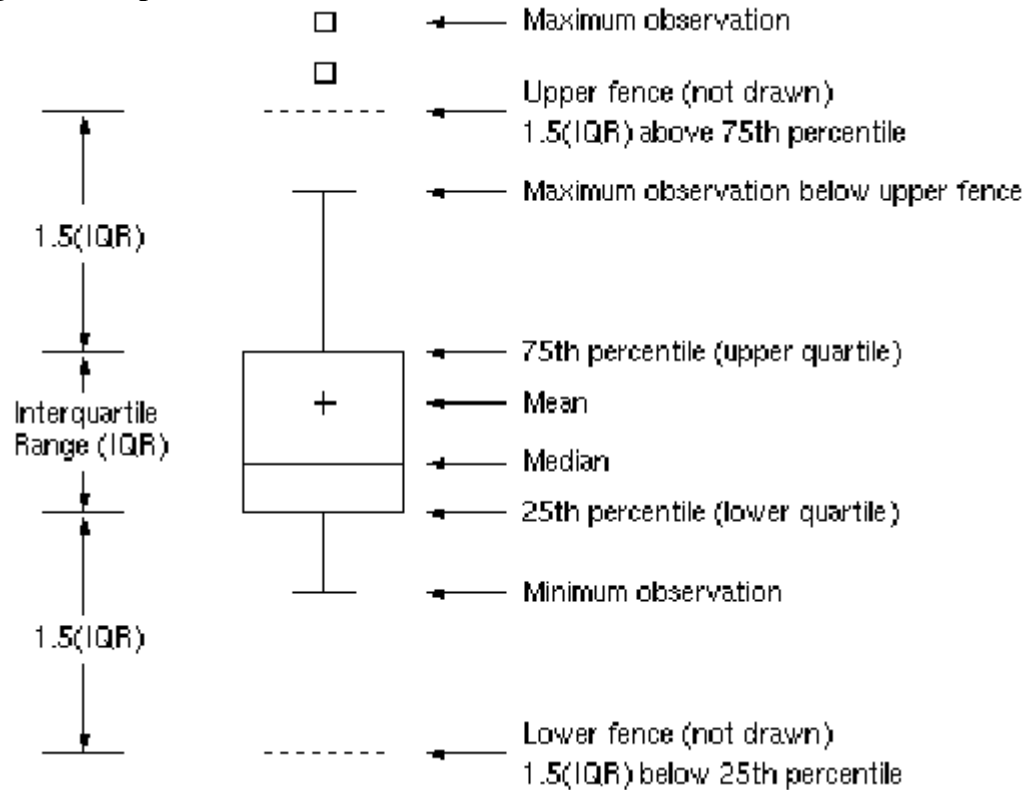
25.3.3 Nonparametric comparative probabilities

As distributions may not simply differ by a shift, a further method is to express the difference (or similarity) by the terms $P(X_{\text{sel}} < X_{\text{pla}})$, $P(X_{\text{sel}} = X_{\text{pla}})$ and $P(X_{\text{sel}} > X_{\text{pla}})$. These quantities are estimated by comparing all n_{sel} to all m_{pla} observations, counting the pairs falling in each of the 3 categories and dividing by $n_{\text{sel}} \times m_{\text{pla}}$. For example, $P(X_{\text{sel}} > X_{\text{pla}})$ can be interpreted as the probability to achieve a larger result (e.g., 6MWD) for a randomly chosen patient treated with selexipag rather than treated with placebo.

25.4 Boxplots

[Figure 5](#) below illustrates the boxplot elements.

Figure 5 Boxplots elements



26 AMOUNT OF AND REASON FOR MISSING DATA

Missing data is expected due to the PAH patient population, some specific design features of studies AC-065A302 and AC-065A303 and general features of clinical studies:

- (D) patient died
- (E) patient with a CEC-confirmed morbidity event in study AC-065A302 entered the AC-065A302 Post-Treatment Observation Period with reduced efficacy data collection or was not followed-up any further (with the possible exception of survival status)
- (P) patient discontinued study drug in AC-065A302 without a CEC-confirmed morbidity/mortality event (e.g., because of intolerability or an administrative reason) entered the AC-065A302 Post-Treatment Observation Period with reduced efficacy data collection – or were not followed-up any further (with the possible exception of survival status)
- (L) at the analysis cut-off date the patient has not reached the visit for which an assessment is scheduled according to the study protocol (a feature more prominent for the interim analysis and for patients randomized during the final part of the recruitment phase)
- (W) patient withdrew informed consent or became lost to follow-up either in the treatment period or in the PTOP
- (M) assessment (may be a complete visit) could not be performed for a reason not covered by one of the reasons above.

Number and percentage (based on the number of randomized patients) of missing values and reasons (categories as defined above) are summarized by treatment and visit for 6MWD at Week 26 and modified NYHA/WHO functional class at Week 26.

Censoring for time-to-event endpoints

For all time-to-event endpoints (including the primary efficacy endpoint), the censoring is defined in the respective SAP section for endpoint definitions. The analysis methods for time-to-event endpoints are taking into account the censoring, typically assuming independent censoring but also allowing for sensitivity analyses where the assumption of independent censoring is doubtful and interpretation is difficult.

Number and percentage (based on the number of randomized patients) of censored observations and reasons (categories as defined above) are summarized by treatment for the primary and secondary time-to-event endpoints.

27 STATISTICAL METHODS FOR SUBGROUP ANALYSIS

27.1 General remarks

Subgroup analyses are performed by

- (A) separate analyses for each of the respective subgroups using the same statistical methods, e.g.,
 - o log-rank test and proportional hazards model for time-to-event endpoints
 - o (non-parametric) ANCOVA for continuous endpointsas for the statistical analysis in the overall Full Analysis Set.
- (B) modified statistical models that allow incorporation of treatment-by-subgroup interaction of, e.g.,
 - o proportional hazards model with study treatment, subgroup and treatment-by-subgroup interaction terms for time-to-event endpoints
 - o (non-parametric) ANCOVA with study treatment and subgroup terms for continuous endpoints.

27.2 Display of subgroup analysis results

Point estimates and corresponding two-sided 99% CIs for treatment effect in each subgroup – method (A) described above – are presented in a forest-plot as descriptive evidence about consistency of estimated treatment effect across subgroups.

These plots are prepared with a vertical reference line displayed for the treatment effect in the overall Full Analysis Set, see [\[Cuzick 2005\]](#). In addition the two-sided p-value for the respective test of treatment-by-subgroup interaction is displayed on the plots (no formal significance level is employed for the interaction test).

28 GROUP-SEQUENTIAL DESIGN AND ANALYSIS

28.1 Group-sequential design

Study AC-065A302 employs a group-sequential design for the primary efficacy endpoint with options to recommend stop for futility or for compelling and robust efficacy at the interim analysis.

28.1.1 Concept of alpha-spending functions

Group-sequential designs based on the concept of alpha-spending functions have been introduced by [Lan 1983] and are described in more detail in [DeMets 1995]. The alpha-spending function allocates some fractions of the pre-specified overall type-I-error probability (one-sided 0.005 in this study) to interim and final analyses over the course of the study. This is achieved by a mathematical function with certain properties; argument of such a function is the information fraction f observed at a particular analysis out of the total amount of information the study has been designed for. In other words, the information fraction f indicates how much of the study has been completed in terms of the accumulated information (observed mortality/morbidity events), and thus indicates how much of the overall α should be allocated up to (and including) that analysis.

Formally, the equation below defines the information fraction f :

$$f = \frac{\text{amount of information available at time of analysis}}{\text{amount of total information planned for the entire study}}$$

Any alpha spending function is equal to 0 at $f = 0$ and equal to α at $f = 1$, and it is non-decreasing in-between.

The alpha spending approach requires neither a specific number of interim analyses nor specific times when they have to occur. It does however require that the particular spending function is specified in advance and that the maximum information is specified at the design stage.

28.1.2 Application of the alpha-spending function principle in study AC-065A302

The alpha-spending function principle is applied in study AC-065A302 in a slightly modified fashion: the interim nominal significance level has been fixed in the study protocol rather than the type of alpha-spending function.

The design features are:

- the one-sided overall type-I-error probability is fixed to $\alpha = 0.005$
- the maximum information is specified as 331 morbidity/mortality events⁴ confirmed by the CEC

⁴ Morbidity/mortality events in this section exclude events with CEC-determined onset date up to 16 Aug 2011

- the one-sided type-I-error probability at the interim analysis is fixed to 0.00005
- the interim analysis is planned with 202 morbidity/mortality events (an information fraction of $f = 202/331 = 0.61$) confirmed by the CEC; however, if there are less or more events available for the interim analysis, the one-sided significance level used for the interim analysis is kept unchanged at 0.00005
- calculation of the one-sided type-I-error probability / required Z-score for the final analysis are performed once the number of morbidity/mortality events confirmed by the CEC at the interim analysis is known (this number together with the other characteristics described above determines the necessary characteristic of the alpha spending function in this modified approach).

The one-sided log-rank statistic Z (which fulfills the condition of independent increments) is used to test the null hypothesis for time to first morbidity/mortality event described in Section 17.1. In addition, a non-binding interim futility stopping rule is foreseen as outlined in Table 13 below.

Table 13 Summary of group-sequential design

Analysis stage (anticipated cumulative number of events ¹)	Efficacy			Futility		
	Cumulative alpha ² spent	Guidance ³ to reject H_0		Cumulative beta spent	Guidance ³ to accept H_0	
		p -value	Z-score		p -value	Z-score
Interim (202 events)	0.00005	≤ 0.00005	≥ 3.8906	0.0013	≥ 0.5	≤ 0
Final (331 events)	0.005	≤ 0.004991	≥ 2.5764	0.1	> 0.004991	< 2.5764

¹ If number of events observed at the interim analysis differs from 202, the interim boundaries are not to be changed.

² All significance levels (alpha) are one-sided.

³ The boundaries for the final analysis are definite whereas they are only guidelines for the DMC at the interim stage.

28.2 Group-sequential statistical analysis

In past experience with group-sequential studies FDA/EMA recommended not to modify efficacy boundaries because of the presence of any futility rules (from theoretical point of view, efficacy stopping boundaries [on the Z-scale] are affected slightly towards 0 by the presence of futility stopping rules). Therefore, the group-sequential analysis (with software East, details of the individual steps in East are to be described in a separate document) is performed by using a design employing the stopping rule for a stopping philosophy outlined by [Haybittle 1971] but formally ignoring the stopping rule for futility. However, the DMC may apply the futility stopping rule as given in the table above.

At the interim and final analysis stage, the following statistics are calculated based on the methods described in Sections 25.1.2.1 and 25.1.3.1:

- Z statistic for the log-rank test
- point estimate and standard error of the log hazard ratio β from the proportional hazard model.

These quantities are entered in the East monitoring sheet and the following results are reported:

- a comparison of the observed Z-score to the efficacy boundary given
- two-sided repeated 99% CI for the log hazard ratio β as well as for the hazard ratio $\exp(\beta)$.

If the observed Z-score is greater or equal the efficacy stopping boundary for rejection of the null hypothesis, the DMC may nevertheless recommend to continue the trial to its end, i.e., when 331 morbidity/mortality events have been confirmed by the CEC. In addition, Actelion may decide to continue the trial to its end despite the DMC recommending to stop it at the interim stage.

28.2.1 Repeated CIs

In general, multiplicity introduced by interim analyses affects construction of CIs just as it affects significance levels of hypothesis tests. If naïvely using standard two-sided $(1-2\alpha)\times 100\%$ CIs like $\hat{\beta}(f_k) \pm z_{1-\alpha} \cdot SE(\hat{\beta}(f_k))$ for a parameter β of interest based on observations accumulated up to analysis stages $k = 1, \dots, K$ with information fractions $f_1, \dots, f_K$, then the overall coverage probability of all these K intervals would be less than $(1-2\alpha)\times 100\%$.

Following [Jennison 1989], a repeated CI (RCI) for β is defined as a sequence of intervals

$I(f_k) = \left(\beta(f_k), \beta(\bar{f}_k) \right)$, with $k = 1, \dots, K$, for which a simultaneous coverage probability is maintained at level $1-2\alpha$.

As both $\beta(f_k)$ and $\beta(\bar{f}_k)$ are random variables, the RCI definition can be formalized by

$$P_{\beta}(\beta \in I(f_k) \text{ for all } k = 1, \dots, K) = 1 - 2\alpha \quad \text{for all } \beta.$$

Hence, the RCI $I(f_k)$

- provides a statistical summary of the information about the parameter β available at the k -th analysis, adjusted to compensate for repeated (past, present and planned future) looks at the accumulating data
- is valid regardless of how the decision to stop the study may have reached, in particular if group-sequential stopping guidelines are or are not followed by the DMC.

Typically, two-sided repeated $(1-2\alpha)\times 100\%$ CIs are obtained from inverting a family of two-sided group-sequential tests (called parent test) with type-I-error probability 2α by using the familiar duality between CIs and hypothesis tests. Therefore, the construction of a sequence of RCIs depends on the group-sequential parent test (here the Wald-type test for the (log) hazard ratio) and the type-I-error probability available at the analysis stage.

This allows calculation of two-sided RCIs by replacing the standard normal quantile $z_\alpha = \Phi^{-1}(1-\alpha)$ in the formula for the unadjusted two-sided $(1-2\alpha)\times 100\%$ CI $\hat{\beta}(f_k) \pm z_\alpha \cdot SE(\hat{\beta}(f_k))$ by the critical value $c_\alpha(f_k)$ from the two-sided level 2α parent test: $I(f_k) = \hat{\beta}(f_k) \pm c_\alpha(f_k) \cdot SE(\hat{\beta}(f_k))$.

28.2.2 Supplementary statistical analysis after study termination

This section deals with the supplementary computation of p -values and estimates (including CIs) for log hazard ratio β and hazard ratio $\exp(\beta)$ after terminating the group-sequential trial, see [Whitehead 1986a], [Whitehead 1986b], [Kim 1987], [Kim 1989]. Computing these quantities ignoring that a sequential monitoring procedure with an option for an early stop is used, would fail to preserve the desired type-I-error probability of the significance test, the desired coverage probability of the CI and the lack of bias of the point estimate.

Rather, there is a need first to order the sample space to reflect the sequential nature of the test procedure, and then obtain p -values and CIs on the basis of this ordering. Software East is used to obtain supplementary statistical results by applying the stage-wise ordering, [Tsiatis 1984] and [Cytel 2009], of the sample space. This ordering is recommended because it does not require knowledge about the interim monitoring time-points that would have been adopted in the future, had the study not stopped early. In addition, stage-wise ordering ensures consistency between the p -value and the CI: the upper limit of the two-sided $(1-2\alpha)\times 100\%$ CI for the hazard ratio excludes 1 if and only if the corresponding one-sided p -value is smaller than α .

If the study continues to its planned end the data observed before and after the interim analysis are compared [Friede 2009].

28.2.3 Analyses when statistical stopping guidance has been overruled

If the study has been continued despite the statistical efficacy guidance boundary having been crossed, the overall p -values, overall CIs and point estimates adjusted for the original group-sequential design are not valid anymore [Jennison 1989]. Instead, the more conservative repeated CI is used for reporting.

28.2.4 Over-running and under-running

If Actelion and the Steering Committee decide – without having any access to unblinded results restricted to the DMC – that the study is not to be continued to its planned end,

then all the remaining alpha, i.e., $\alpha - \alpha(t_{j-1})$ is spent for this now final analysis. An example for such reasons would be lack of ethical justification for randomized assignment of placebo caused by approval of another treatment with demonstrated superiority over placebo.

Using all the remaining alpha is thereby a way to deal with the problems of

- “**under-running**”, i.e., reaching the final analysis with less than 331 events, at the cost of statistical power;
- “**over-running**”, i.e., performing the final analysis with more than 331 events.

The latter scenario is not to be confused by the fact that there are additional data (therefore also more events) obtained within the timeframe from the interim analysis cut-off date to the date when an ultimate decision to close the study is communicated to investigators. [CHMP 2007] states that “in such a situation, it is accepted regulatory practice to base decision making on the final results of the trial (not the interim analysis). This is also in accordance with the intention to treat principle that all randomized patients⁵ should be analyzed. Obviously, overrunning patients need to be treated and observed according to the protocol and due attention should be given to this at the planning stage of the trial.”

Estimates of the treatment effects including and excluding such extra information is provided in the Clinical Study Report.

28.3 Required number of events and power

In order to determine sample size and power, the following assumptions have been made in addition to the group-sequential design features described in Section 28.1:

- Constant hazard rate of 0.2231 per year for placebo
- Constant hazard rate of 0.145 per year for selexipag (hazard ratio of 0.65)
- Constant hazard rate of 0.051 per year for drop-out (end of study without a morbidity/mortality event) in both treatment groups

These lead to a total of 331 morbidity/mortality events confirmed by the CEC in order to obtain an overall power of 90% for rejection of the null hypothesis.

Under these assumptions, the probability to (correctly) reject the null hypothesis already at the interim stage is approximately 19%, and to (falsely) accept the null hypothesis at the interim stage is less than 0.2%.

If the true hazard ratio is 1, then the probability of (correctly) accepting the null hypothesis at the interim stage is approximately 50%.

⁵ and all available data from these patients

29 MODIFICATIONS FROM STUDY PROTOCOL TO SAP

As usual, Statistical Analysis Plans are more detailed than relevant sections of the Study Protocols; such additions and refinements are therefore not mentioned in this section. Instead, only true deviations from statements in the study protocol (last amended version) to the SAP are listed (in the sequence of SAP sections) together with a brief rationale.

Section 5: An additional condition for all analysis sets was added to reflect that only patients with signed informed consent for study AC-065A302 will be included. Although no patients without a signed informed consent have been identified so far, this potential major protocol violation has been added now to avoid later amendment of the SAP.

Section 5.5: A “QoL analysis set” has been added as the CAMPHOR questionnaire has not been available in a suitable language for all patients. This implied changes in subsequent sections, e.g., Sections 5.7, 18.5 and 18.6.

Section 6.4: Because of a sub-optimally designed CRF the categories for race (Caucasian, Asian, Black, other) are partly mixed up with ethnicity (Hispanic). Therefore, the related subgroups in the SAP are defined: “race/ethnicity: Caucasian/Hispanic versus Asian versus Black versus other”.

Sections 9, 10, 11, 17, 18 and 19: The protocol states that for the primary, secondary and all exploratory endpoints, CEC-confirmed morbidity/mortality events or death with onset date up to 16 August 2011 are considered as censored at the time of event/death onset. Following an agreement with the FDA (meeting held on 11 July 2014), it was decided to exclude events with an onset date up to 16 August 2011 only for the main analysis of the primary endpoint and to include events with an onset date up to 16 August 2011 in all sensitivity and subgroup analyses of the primary endpoint as well as in all secondary and exploratory time-to-event endpoints analyses.

Section 10.1: The study protocol defined the secondary endpoint “absolute change from baseline to Week 26 in 6MWD measured at trough level of study drug” for which 6MWTs not done at trough were to be considered as missing data in the main analysis of this secondary endpoint. In the SAP, if all the 6MWTs at Week 26 are not performed at trough, these non-missing 6MWD values are included in the main analysis. Hence all available 6MWT data at Week 26 are included in the main analysis of this endpoint. Rationale: During the Pre-NDA meeting, FDA advised to include 6MWTs not performed at trough in the main analysis of the secondary endpoint.

Section 10.3 and Section 11.11: The study protocol defined the endpoint “Borg dyspnea index at Week 26” as a secondary efficacy endpoint and “Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period” as an exploratory efficacy endpoint. In the SAP, these two endpoints are

switched, i.e., “Borg dyspnea index at Week 26” becomes an exploratory endpoint and “Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period” is a secondary endpoint. Rationale: Regulatory interactions following the macitentan filing made it evident that the composite of PAH-death and hospitalization (as reflected in the efficacy endpoint “Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period”) bears a high level of relevance for regulatory agencies based on the association with disease-specific survival and morbidity. The Borg dyspnea index has not been linked to any other outcome parameter and is therefore perceived as bearing little clinical relevance.

Sections 10.4, 11.1, 11.3, 11.6, 11.7 and 11.8: For all the endpoints analyzed up to Study Closure, the definition of the censoring rules in the protocol included the EOS visit date as one of the potential censoring dates. In some specific cases, this rule resulted in premature censoring of patients who should have been censored later i.e., at their date of last contact. In the post-hoc SAP, the rules are updated and all patients are censored at their date of last contact if applicable.

Removed section: The study protocol defined the exploratory efficacy endpoint “CEC-confirmed (potentially recurrent) hospitalization due to worsening of PAH up to Study Closure”. This endpoint is no longer included in the SAP. Rationale: the endpoint is no longer considered relevant for the Clinical Study Report.

Removed section: The study protocol defined the exploratory endpoint “Time course of CEC-confirmed (potentially recurrent) hospitalization due to worsening of PAH, initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH, and death up to Study Closure”. This endpoint is no longer included in the SAP. Rationale: the endpoint is no longer considered relevant for the Clinical Study Report.

Removed section: The study protocol defined the pharmacoeconomic endpoint “Occurrence of recurrent hospitalizations (all-cause and PAH-related) up to the EOS visit”. This endpoint is no longer included in the SAP. Rationale: the endpoint is no longer considered relevant for the Clinical Study Report.

Section 13: The definition of trough plasma sample has been changed from “before the morning dose” (in the study protocol) to “before the morning dose, with the last study drug administration one day prior to the PK sampling” in the SAP. Rationale: interruption of study drug administration prior to PK sampling needs to be taken into account.

Section 14.1: The study protocol AC-065A302 stated that for patients who discontinue due to a CEC-confirmed morbidity/mortality event and then enroll in study AC-065A303, the treatment-emergent safety events will be counted until last study drug intake in the Treatment Period of study AC-065A302. In the SAP, for these patients,

treatment-emergent safety events in AC-065A302 are defined up to last study drug intake in the Treatment Period of study AC-065A302 plus 7 days or up to first study drug intake in AC-065A303, whichever comes first. This is done in order to be consistent with patients not enrolled in study AC-065A303.

Section 19: For exploratory efficacy endpoints, the study protocol stated that two-sided 99% confidence intervals will be provided. This has been changed in the SAP to two-sided 95% confidence intervals as it is felt this is more appropriate for exploratory endpoints even for submissions with one single pivotal study.

Section 19: The protocol stated that the pharmaco-economic endpoints 'number of days spent in hospital for all causes and PAH-related causes up to EOS Visit' are analyzed with the negative binomial model. In the *post-hoc* CSR SAP version 6.0 this is changed to non-parametric model. Rationale: the negative binomial model did not fit the data properly.

Section 23: For the analysis of safety endpoints the protocol stated that in the event of missing values the last valid post-Baseline value will be carried forward. This was a typographical error and in the SAP all safety endpoints are analyzed descriptively without imputation for missing data (with the exception of the analysis of occurrence of [potentially recurrent] AEs of special interest in which censoring rules are applied).

Section 23.6: The protocol stated that the absolute change from Baseline up to EOS in retinal arterial tortuosity will be summarized with a two-sided 95% confidence interval for the difference of selexipag and placebo means (assuming normal distribution). This quantitative analysis is not included in the SAP. The rationale is that based on expert recommendation such analysis would be without scientific merit, given that the degree of tortuosity is not necessarily associated with clinical relevance. Upon clinically relevant findings, quantitative analysis of tortuosity may be considered in patients with relevant ophthalmology findings.

Section 28.1: Table 3 of the study protocol contains a typo: a 0 is missing in the criterion for p-value for the final analysis. The value 0.04991 has been corrected to 0.004991 in [Table 13](#) of the SAP.

30 REFERENCES

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31 OVERVIEW OF ANALYSES FOR EFFICACY ENDPOINTS

Primary efficacy endpoint:

Time to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in the AC-065A302 Treatment Period [defined in Section 9]

Primary analysis: group-sequential unstratified log-rank test on the FAS (overall one-sided significance level 0.005); CEC-confirmed morbidity/mortality events with onset date (as per CEC) up to 16 August 2011 are excluded/censored

Supportive analyses (on the FAS if not otherwise specified):

- unstratified proportional hazards model (CEC-confirmed morbidity/mortality events with onset date (as per CEC) up to 16 August 2011 are excluded/censored)
- unstratified log-rank test and proportional hazards model handling morbidity/mortality events confirmed by the CEC with onset date up to 16 August 2011 as events (same applies to all subsequent bullet points)
- log-rank test and proportional hazards model stratified by geographical region
- log-rank test and proportional hazards model stratified by PAH etiology
- log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline
- log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline
- log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline and concomitant PAH medication at Baseline
- proportional hazards model adjusted for modified NYHA/WHO functional class at Baseline (classes I/II and classes III/IV), concomitant PAH medication at Baseline (no and yes), geographic regions [as defined in Section 6.4], PAH etiology [as defined in Section 6.4], sex, race/ethnicity Caucasian/Hispanic (Yes and No), age categories [as defined in Section 6.4] – see Section 25.1.3.3 for methodology.
- models attempting to address potential informative censoring, with the following circumstances identified as potentially informative censoring for the morbidity/mortality event:
 - morbidity/mortality events not confirmed by the CEC but study drug discontinued because of this event
 - patient lost-to follow-up
- log-rank tests and proportional hazards models for the originally planned number (202) of first CEC-confirmed morbidity/mortality events observed in the originally planned number (first 670) randomized patients
- competing risk analysis as described in Section 25.1.4
- subgroup analyses as specified in Section 6.4 and Section 27
- unstratified log-rank test and proportional hazards model based on the PPS

- unstratified log-rank test and proportional hazards model for time to first morbidity/mortality event (up to 7 days after last study drug intake in the AC-065A302 Treatment Period) reported by the investigator (irrespective of confirmation by the CEC)
- unstratified log-rank test and proportional hazards model restricted to patients with typical or consistent PAH as per blinded expert review
- analysis restricted to patients with typical PAH as per blinded expert review
- unstratified log-rank test and proportional hazards model ignoring CEC-confirmed “disease progression” event component when the second 6MWT was not performed.
- descriptive comparison of data before and after the interim analysis.
- unstratified log-rank test and proportional hazards model handling premature discontinuation from study drug with signs of disease worsening as event.

Secondary efficacy endpoints
(on the FAS if not otherwise specified)

Secondary efficacy endpoint:

Absolute change from Baseline at Week 26 in 6MWD at trough [defined in Section 10.1]

Main analysis: non-parametric ANCOVA (covariate: 6MWD at Baseline)

Supportive analyses:

- non-parametric ANCOVA with additional stratification for geographical region
- non-parametric ANCOVA with additional stratification for PAH etiology
- non-parametric ANCOVA with additional stratification for modified NYHA/WHO functional class at Baseline
- non-parametric ANCOVA with additional stratification for concomitant PAH medication at Baseline
- subgroup analyses as specified in Section 6.4 and Section 27
- analysis restricted to patients with typical or consistent PAH as per blinded expert review.

In addition: non-parametric ANCOVA on the PPS excluding patients randomized to selexipag with no 6MWT at Week 26 performed at trough.

Secondary efficacy endpoint:

Absence of worsening from Baseline to Week 26 in modified NYHA/WHO functional class [defined in Section 10.2]

Main analysis: Cochran-Mantel-Haenszel test stratified by modified NYHA/WHO functional class at Baseline

Supportive analyses:

- common odds ratio estimate and a two-sided 99% CI (if assumption of common odds ratio is not rejected by a Breslow-Day test)
- Cochran-Mantel-Haenszel test and two-sided 99% CI for common odds ratio with additional stratification for geographical region
- Cochran-Mantel-Haenszel test and two-sided 99% CI for common odds ratio with additional stratification for PAH etiology
- Cochran-Mantel-Haenszel test and two-sided 99% CI for common odds ratio with additional stratification for concomitant PAH medication at Baseline

Secondary efficacy endpoint:

Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period

Main analysis: unstratified log-rank test

Supportive analyses:

- unstratified proportional hazards model
- log-rank test and proportional hazards model stratified by geographical region
- log-rank test and proportional hazards model stratified by PAH etiology
- log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline
- log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline
- unstratified log-rank test and proportional hazards model restricted to patients with typical or consistent PAH as per blinded expert review
- log-rank test and proportional hazards model based on the PPS.

Secondary efficacy endpoint:

Time from randomization to death up to Study Closure [defined in Section 10.4]

Main analysis: unstratified log-rank test

Supportive analyses (on the FAS if not otherwise specified):

- unstratified proportional hazards model
- log-rank test and proportional hazards model stratified by geographical region
- log-rank test and proportional hazards model stratified by PAH etiology
- log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline
- log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline

- analysis restricted to patients with typical or consistent PAH according to the blinded expert review
- analysis restricted to patients with typical PAH as per blinded expert review.
-

Secondary efficacy endpoint:

Absolute change from Baseline to Week 26 in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score [defined in Section [10.5.1](#)]

Main analysis: non-parametric ANCOVA (covariate: sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score at Baseline) on the QoL analysis set

Supportive analyses (on the QoL analysis set):

- non-parametric ANCOVA with additional stratification for modified NYHA/WHO functional class at Baseline
- non-parametric ANCOVA with additional stratification for concomitant PAH medication at Baseline

Secondary efficacy endpoint:

Absolute change from Baseline to Week 26 in CAMPHOR 'Symptoms' score [defined in Section [10.5.1](#)]

Main analysis: non-parametric ANCOVA (covariate: CAMPHOR 'Symptoms' score at Baseline)

Supportive analyses: same as for previous secondary efficacy endpoint.

Exploratory efficacy endpoints (all analyses are exploratory by definition) all analyses on the FAS if not otherwise specified	
Endpoint	Statistical methods
Exploratory efficacy endpoints related to morbidity/mortality [defined in Section 11.10 to Section 11.8]	
Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure	<u>Main analysis</u>: unstratified log-rank test <u>Supportive analyses</u>: • unstratified proportional hazards model • log-rank test and proportional hazards model stratified by geographical region • log-rank test and proportional hazards model stratified by PAH etiology • log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline • log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline • log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline and concomitant PAH medication at Baseline • unstratified log-rank test and proportional hazards model for time to first morbidity/mortality event (excluding “disease progression”) up to Study Closure reported by the investigator (irrespective of confirmation by the CEC) • unstratified log-rank test and proportional hazards model restricted to patients with typical or consistent PAH as per blinded expert review

Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period	<u>Main analysis:</u> unstratified log-rank test on the FAS <u>Supportive analyses:</u> • unstratified proportional hazards model • unstratified log-rank test and proportional hazards model restricted to patients with typical or consistent PAH as per blinded expert review
Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure	<u>Main analysis:</u> unstratified log-rank test <u>Supportive analyses:</u> • unstratified proportional hazards model • log-rank test and proportional hazards model stratified by geographical region • log-rank test and proportional hazards model stratified by PAH etiology • log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline • log-rank test and proportional hazards model stratified by concomitant PAH medication at Baseline • log-rank test and proportional hazards model stratified by modified NYHA/WHO functional class at Baseline and concomitant PAH medication at Baseline • unstratified log-rank test and proportional hazards model for time to first morbidity/mortality event (excluding “disease progression” and initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to Study Closure reported by the investigator (irrespective of confirmation by the CEC) • unstratified log-rank test and proportional hazards model restricted to patients with typical or consistent PAH as per blinded expert review
Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and initiation of	<u>Main analysis:</u> unstratified log-rank test <u>Supportive analyses:</u> • unstratified proportional hazards model • unstratified log-rank test and proportional hazards

parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH) up to 7 days after last study drug intake in the AC-065A302 Treatment Period	model restricted to patients with typical or consistent PAH as per blinded expert review.
Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period	<u>Main analysis:</u> unstratified log-rank test <u>Supportive analyses:</u> - unstratified proportional hazards model - unstratified log-rank test and proportional hazards model restricted to patients with typical or consistent PAH as per blinded expert review.
Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study closure	<u>Main analysis:</u> unstratified log-rank test <u>Supportive analyses:</u> unstratified proportional hazards model
Time from randomization to first CEC-confirmed morbidity/mortality event up to Study Closure	<u>Main analysis:</u> unstratified log-rank test <u>Supportive analyses:</u> unstratified proportional hazards model
Time from randomization to CEC-confirmed death due to PAH up to Study Closure	<u>Main analysis:</u> unstratified log-rank test <u>Supportive analyses:</u> unstratified proportional hazards model
Exploratory efficacy endpoints related to 6MWD [defined in Section 11.9]	
Absolute changes in 6MWD from Baseline to all scheduled visits (other than Week 26) at trough	descriptive summary
Absolute change in 6MWD from Baseline to EOS	descriptive summary

Exploratory endpoints related to modified NYHA/WHO functional class [defined in Section 11.10]	
Absence of worsening from Baseline at scheduled visits other than Week 26	transition table from Baseline visit to post-Baseline visits
Absence of worsening from Baseline to EOS	frequency table
Exploratory efficacy endpoints related to Borg dyspnea index [defined in Section 11.11]	
Borg dyspnea index at scheduled visits	descriptive summary
Borg dyspnea index at EOS	descriptive summary
Exploratory efficacy endpoints related to plasma NT pro-brain natriuretic peptide [defined in Section 11.12]	
Absolute change in plasma NT pro-BNP from Baseline at scheduled visits	descriptive summary
Absolute change in plasma NT pro-BNP from Baseline to EOS	descriptive summary
Exploratory efficacy endpoints related to CAMPHOR [defined in Section 11.13] on the QoL analysis set	
Absolute change from Baseline to scheduled visits other than Week 26 in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score	descriptive summary
Absolute change from Baseline to EOS in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score	descriptive summary
Absolute change from Baseline to scheduled visits other than Week 26 in CAMPHOR 'Symptoms' score	descriptive summary
Absolute change from Baseline to EOS in CAMPHOR 'Symptoms' score	descriptive summary

32 APPENDIX

Appendix A List of planned outputs including *post-hoc* changes

Appendix A to Statistical Analysis Plan for CSR version 6.0

Purpose of Analysis:	Clinical Study Report including <i>post-hoc</i> changes
Investigational Drug:	Selexipag
Protocol Number:	AC-065A302 / GRIPHON AC-065A303 / GRIPHON OL
Date:	22 September 2014

LIST OF PLANNED OUTPUTS INCLUDING *POST-HOC* CHANGES

MULTICENTER CLINICAL INVESTIGATIONS TO EVALUATE EFFICACY AND SAFETY OF SELEXIPAG IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

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Display: L=Listing, F=Figure, T=Table
Analysis sets: FAS=Full Analysis Set, PPS=Per-Protocol analysis Set, SAF=Safety analysis set,
PK=PK analysis set, QAS=QoL Analysis Set, OAS=Ophtalmologic analysis set

1 PATIENT DISPOSITION (SAP SECTION 15.1)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TDISP_F	T	Disposition of patients in studies AC-065A302 and AC-065A303	FAS
TDISPC_F	T	Number of patients by country and center	FAS
TANA_F	T	Overview of analysis sets	FAS
TEXC_F	T	Reasons for exclusion from analysis sets	FAS
TEXCLPP_F	T	Patients with data excluded in the per-protocol analysis of the primary endpoint and secondary endpoint change from baseline to Week 26 in 6MWD	FAS
TPDEV1_F	T	Protocol deviations in study AC-065A302 <i>categories:</i> <i>protocol deviation at study entry</i> <i>protocol deviation during study conduct (i.e. after randomization)</i> <i>protocol deviation after end of treatment</i>	FAS
TPDEV2_F	T	Protocol deviations in study AC-065A303 <i>categories:</i> <i>protocol deviation at study entry</i> <i>protocol deviation during study conduct (i.e. after enrollment)</i> <i>protocol deviation after end of treatment</i>	FAS, patients enrolled in AC-065A303
TPDEV1C_F	T	Protocol deviations by country in study AC-065A302 <i>categories:</i> <i>protocol deviation at study entry</i> <i>protocol deviation during study conduct (i.e. after randomization)</i> <i>protocol deviation after end of treatment</i>	FAS
TPDEV2C_F	T	Protocol deviations by country in study AC-065A303 <i>categories:</i> <i>protocol deviation at study entry</i> <i>protocol deviation during study conduct)(i.e. after enrollment)</i> <i>protocol deviation after end of treatment</i>	FAS, patients enrolled in AC-065A303
TPDEV1M_F	T	Major protocol deviations in study AC-065A302 <i>categories:</i> <i>protocol deviation at study entry</i> <i>protocol deviation during study conduct(i.e. after randomization)</i> <i>protocol deviation after end of treatment</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TPDEV2M_F	T	Major protocol deviations in study AC-065A303 <i>categories:</i> <i>protocol deviation at study entry</i> <i>protocol deviation during study conduct(i.e. after enrollment)</i> <i>protocol deviation after end of treatment</i>	FAS, patients enrolled in AC-065A303
TPDEVSIG_F	T	Significant protocol deviations in study AC-065A302 <i>categories:</i> <i>inclusion/exclusion criteria</i> <i>major significant GCP</i> <i>IMP dispensation</i>	FAS
TSWD_F	T	Reasons for screening failure in study AC-065A302	Patients screened
TPATFLOW_F	T	Patient flow up to Study Closure	SAF
LRAND_F	L	Randomization by center and bottle number allocated in study AC-065A302	FAS
LEXC_F	L	Reasons for excluding of patients from analysis sets	FAS
LPDEV1_F	L	Protocol deviations in study AC-065A302 <i>includes PV comments related to PV</i>	FAS
LPDEV2_F	L	Protocol deviations in study AC-065A303 <i>includes PV comments related to PV</i>	FAS
LSWD_SC	L	Reason for screening failure in study AC-065A302	Patients screened
LUNBL_F	L	Patients with treatment unblinded prior to database lock <i>Includes patient's outcome (MM event, death, SAE)</i>	FAS
LVDTH_F	L	Patients deceased or with vital status unknown at study closure <i>Patients who withdrew consent or who were lost to follow-up during Treatment Period are flagged</i>	FAS
LPVEXPA_P	L	Listing of protocol deviations that lead to exclusion of efficacy assessments for the per-protocol analysis	PPS

2 DEMOGRAPHICS (SAP SECTIONS 6.1 AND 16)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TDEM_F	T	Demographics at screening <i>sex, race, geographical region, age (categorized and continuous), weight (kg), height (cm), BMI (categorized and continuous)</i>	FAS
TDEM_OL	T	Demographics at screening	SAF subset of patients treated in AC-065A303
TCOUN_F	T	Summary of country at screening	FAS
TDEM_O	T	Demographics at screening <i>sex, race, geographical region, age (categorized and continuous), weight (kg), height (cm), BMI (categorized and continuous)</i>	OAS
TCOUN_O	T	Summary of country at screening	OAS
TDEM_W_F	T	Demographics at screening by modified NYHA/WHO functional class at Baseline	FAS
LDEM_F	L	Demographics at screening	FAS

3 BASELINE DISEASE CHARACTERISTICS (SAP SECTIONS 6.2, 16)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TBAS_F	T	Baseline disease characteristics <i>time from PAH diagnosis, etiology of PAH, modified NYHA/WHO functional class at Baseline, vital signs at Baseline, 6MWD at Baseline, Borg dyspnea index at Baseline</i>	FAS
TBAS_OL	T	Baseline disease characteristics in study AC-065A302	SAF subset of patients treated in AC-065A303
TBAS_W_F	T	Baseline disease characteristics by NYHA/WHO functional class at Baseline	FAS
TBASRH_F	T	Right heart catheterization (RHC) data from latest RHC performed prior to baseline	FAS
TBASRHG_F	T	Right heart catheterization (RHC) data from latest RHC performed prior to baseline by time of RHC <i>(for patients with RHC done <= 6 months prior to randomization versus > 6 months prior to randomization)</i>	FAS
TBSRH_W_F	T	Baseline right heart catheterization data by NYHA/WHO functional class at Baseline	FAS
TBASRH_OL	T	Right heart catheterization (RHC) data from latest RHC performed prior to baseline in study AC-065A302	SAF subset of patients treated in AC-065A303
TPAHD_F	T	Outcome of the blinded expert medical review of PAH baseline characteristics	FAS
LBAS_F	L	Baseline disease characteristics <i>(time from PAH diagnosis, etiology of PAH, modified NYHA/WHO functional class at Baseline, vital signs at Baseline, 6MWD at Baseline, Borg dyspnea index at Baseline),right heart catheterization data</i>	FAS
LBASD_F	L	Outcome of the blinded expert medical review of PAH baseline characteristics	FAS

4 PREVIOUS AND CONCOMITANT DISEASES AT BASELINE (SAP SECTION 16)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TPCDC_F	T	Previous and concomitant diseases at Baseline by SOC and preferred term	FAS
TPCDC_O	T	Previous and concomitant diseases at Baseline by SOC and preferred term	OAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TMHINT_F	T	Summary of medical history of specific interest	FAS
LPCD_F	L	Previous and concomitant diseases at screening	FAS

5 PREVIOUS AND CONCOMITANT MEDICATIONS (SAP SECTIONS 8 AND 23.5)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TCBC_F	T	Medications not for PAH concomitant at Baseline by class	FAS
TCNBF_O	T	PAH-non-specific medications concomitant at Baseline by frequency	OAS
TCNBC_F	T	PAH-non-specific medications concomitant at Baseline by class	FAS
TCBPAH_F	T	PAH specific medications concomitant at Baseline	FAS
TCBPAH_O	T	PAH specific medications concomitant at Baseline	OAS
TCBPAH_G_F	T	PAH specific medications concomitant at Baseline - by geographical region	FAS
TDCTBF_O	T	Concomitant medications not for PAH (started while on study drug) by frequency	OAS
TDCBC_F	T	Concomitant medications not for PAH (started while on study drug) by class	FAS
TDCBNF_F	T	Concomitant PAH non-specific medications (started while on study drug) by frequency	FAS
TDCBNF_O	T	Concomitant PAH non-specific medications (started while on study drug) by frequency	OAS
TDCBNC_F	T	Concomitant PAH non-specific medication (started while on study drug) by class	FAS
TDCPAHC_F	T	Concomitant PAH specific medications (started while on study drug)	FAS
TDCPAHC_O	T	Concomitant PAH specific medications (started while on study drug)	OAS
TMPAHC_F	T	PAH specific medication started after study drug discontinuation (in study AC-065A302 or AC-065A303)	FAS
LCONM_F	L	Previous and concomitant medications (including subsequent PAH medication)	FAS

6 EXPOSURE TO STUDY DRUG (SAP SECTIONS 7, 15.2)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TPDT2_S	T	Reason for premature discontinuation of study drug in study AC-065A302	SAF
TPDTD2_S	T	Reason for premature discontinuation of study drug in study AC-065A302 by last dose	SAF
TPDTR3_S	T	Reason for premature discontinuation of study drug in study AC-065A302 by time since randomization	SAF
TPDT3_S	T	Reason for premature discontinuation of study drug in study AC-065A303	SAF subset treated in study A303
TPDTD3_S	T	Reason for premature discontinuation of study drug in study AC-065A303 by last dose	SAF subset treated in study A303
TPDTETP_S	T	Reason for discontinuation of study drug in study AC-065A302 prior to Study Closure	SAF
FPDT2_S	F	Time from study drug start to premature discontinuation of study drug in study AC-065A302 - Kaplan-Meier estimates <i>Kaplan-Meier estimates with two-sided 95% CIs at 12, 24, 36 months</i>	SAF
TEXPO2_S	T	Duration of study treatment in AC-065A302 <i>duration intervals, cumulative duration</i>	SAF
FEXPO2_S	F	Duration of study treatment in AC-065A302 - inverse cumulative distribution function	SAF
TMTD2_S	T	Individual maintenance dose of selexipag in AC-065A302	SAF
TMTDWT2_S	T	Maximum and weighted-average dose of selexipag in the AC-065A302 Titration Period, Maintenance Period and Treatment period <i>Maximum and weighted average for placebo patients is "not applicable"</i>	SAF
TEXPO3_S	T	Duration of study treatment in AC-065A303 <i>duration intervals, cumulative duration</i>	SAF subset treated in study A303
FEXPO3_S	F	Duration of study treatment in AC-065A303 - inverse cumulative distribution function	SAF subset treated in study A303

Unique ID	Display	Title <i>additional description</i>	Analysis set
TMTD3_S	T	Individual maintenance dose of selexipag in AC-065A303	SAF subset treated in study A303
TMTDWT3_S	T	Maximum and weighted-average dose in the AC-065A303 Titration Period, Maintenance Period and Treatment Period	SAF subset treated in study A303
TMTD2PL_F	T	Individual maintenance dose of selexipag and placebo in AC-065A302	FAS
LEXPO_F	L	Duration of study treatment in AC-065A302 and 303 <i>start date, end date, dose and reasons for discontinuation</i>	FAS
LMTD_F	L	Individual maintenance dose, maximum dose and weighted-average dose of study drug in AC-065A302 and 303 <i>Including maximum and weighted average dose during titration and maintenance</i>	FAS

7 PRIMARY EFFICACY ENDPOINT (SAP SECTIONS 9 AND 17)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TMMTL_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Group-sequential main analysis <i>group-sequential analysis: log-rank test statistic, one-sided p-value compared to the nominal alpha according to the specified design, repeated confidence intervals for the hazard ratio, supplementary analysis: overall p-value, point estimate and confidence interval for the hazard ratio adjusted for the group-sequential design</i>	FAS
TMMT_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period - Kaplan-Meier estimates	FAS
FMMT_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier estimates up to Month 36 with two-sided 95% CIs at 12, 24, 36 months, log-rank test, point estimate and two-sided 99% CI for hazard ratio</i>	FAS
TMMTSUP_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Supportive analyses attempting to address potential informative censoring <i>Includes Method A: counting first events not confirmed by the CEC but with study drug discontinuation within 21 days after onset date of respective not confirmed event as events ; Method B: counting patients without a CEC-confirmed event but lost to follow-up in the Treatment Period as having an event at date of last visit in AC-065A302 ; Method C: counting signs of disease worsening at time of premature study drug discontinuation as events at date of last study drug intake in AC-065A302. unstratified and stratified log-rank tests and proportional hazards models.</i>	FAS
TMMTSU1P_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period - Supportive analysis including first events not confirmed by the CEC but with study drug discontinuation within 21 days after onset date of respective not confirmed event as events - Kaplan-Meier estimates	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
FMMTSU1P_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period - Supportive analysis including first events not confirmed by the CEC but with study drug discontinuation within 21 days after onset date of respective not confirmed event as events - Kaplan-Meier estimates <i>Kaplan-Meier estimates up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log-rank test and hazard ratio and two-sided 99% CI for hazard ratio</i>	FAS
TMMTSU2P_ F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Supportive analysis handling patients without a CEC-confirmed event but lost to follow-up in AC-065A302 Treatment Period as having an event at date of last visit - Kaplan-Meier estimates	FAS
FMMTSU2P_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Supportive analysis handling patients without a CEC-confirmed event but lost to follow-up in AC-065A302 Treatment Period as having an event at date of last visit - Kaplan-Meier estimates <i>Kaplan-Meier estimates up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log-rank test and hazard ratio with two-sided 99% CI for hazard ratio</i>	FAS
TMMTSU3P_ F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Supportive analysis handling signs of disease worsening at time of premature study drug discontinuation as event - Kaplan-Meier estimates	FAS
FMMTSU3P_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Supportive analysis handling signs of disease worsening at time of premature study drug discontinuation as event - Kaplan-Meier estimates <i>Kaplan-Meier estimates up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log-rank test and hazard ratio with two-sided 99% CI for hazard ratio</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TMMT670L_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Supportive analysis in the first 670 randomized patients up to the occurrence of 202 first CEC-confirmed morbidity/mortality events <i>unstratified and stratified log-rank tests and proportional hazards models; numbers represent the originally planned design prior to Study Protocol Amendment 5..</i>	FAS (subset of first 670 randomized patients)
TMMT670_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Supportive analysis in the first 670 randomized patients up to the occurrence of 202 first CEC-confirmed morbidity/mortality events - Kaplan-Meier estimates	FAS (subset of first 670 randomized patients)
FMMT670_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Supportive analysis in the first 670 randomized patients up to the occurrence of 202 first CEC-confirmed morbidity/mortality events - Kaplan-Meier estimates <i>Kaplan-Meier estimates up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log-rank test and hazard ratio with two-sided 99% CI for hazard ratio</i>	FAS (subset of first 670 randomized patients)
TMMTIL_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Unstratified and stratified analyses <i>unstratified and stratified log-rank tests and proportional hazards models.</i> <i>unstratified log-rank test and proportional hazards model</i> <i>stratified by geographical region</i> <i>stratified by PAH etiology</i> <i>stratified by modified NYHA / WHO functional class at Baseline (classes I/II versus classes III/IV)</i> <i>stratified by concomitant PAH medication (no/yes) at Baseline</i> <i>stratified by modified NYHA / WHO functional class at Baseline and concomitant PAH medication at Baseline</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TMMTWCO X_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Proportional hazard model adjusted for covariates at Baseline	FAS
TMMTI_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period - Kaplan-Meier estimates	FAS
FMMTI_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier estimates up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log-rank test and hazard ratio with two-sided 99% CI for hazard ratio</i>	FAS
TMMTICRG RAY_F	T	Competing risk analysis for Time from randomization to first CEC-confirmed morbidity / mortality event up to 7 days after last study drug intake in AC-065A302 treatment period Cumulative Incidence Function and Gray's Test	FAS
FMMTICRG RAYEV_F	F	Competing risk analysis for Time from randomization to first CEC-confirmed morbidity / mortality event up to 7 days after last study drug intake in AC-065A302 treatment period Cumulative Incidence Function - Gray's method, by event	FAS
FMMTICRG RAY_F	F	Competing risk analysis for Time from randomization to first CEC-confirmed morbidity / mortality event up to 7 days after last study drug intake in AC-065A302 treatment period Cumulative Incidence Function - Gray's method	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TMMTGRP_ F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Subgroup analyses <i>subgroups:</i> • <i>by geographical region</i> • <i>by PAH etiology</i> • <i>by modified NYHA/WHO functional class (classes I/II versus classes III/IV) at Baseline</i> • <i>by concomitant PAH medication (ERA, PDE5, ERA plus PDE5, prostacyclin/analogs, none) at Baseline</i> • <i>by race/ethnicity</i> • <i>by sex</i> • <i>by age category at screening</i> <i>p-values of log-rank tests, point estimates and 99% CIs for hazard ratios, proportional hazards model incorporating treatment-by-subgroup interaction term</i>	FAS
FMMTGRP_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period – forest plot for subgroup analyses <i>point estimates and 99% CIs for hazard ratios</i>	FAS
FMMTP_G_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Kaplan-Meier estimates by geographical region <i>Kaplan-Meier estimates up to Month 36 log-rank test and hazard ratio with two-sided 99% CI for hazard ratio</i>	FAS
FMMTP_ET_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Kaplan-Meier estimates by PAH etiology <i>Kaplan-Meier estimates up to Month 36 log-rank test and hazard ratio with two-sided 99% CI for hazard ratio</i>	FAS
FMMTP_W_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Kaplan-Meier estimates by modified NYHA/WHO functional class (classes I/II versus classes III/IV) at Baseline <i>Kaplan-Meier estimates up to Month 36 log-rank test and hazard ratio with two-sided 99% CI for hazard ratio</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
FMMTP_PH M_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Kaplan-Meier estimates by concomitant PAH medication at Baseline <i>Kaplan-Meier estimates up to Month 36 log-rank test and hazard ratio with two-sided 99% CI for hazard ratio</i>	FAS
FMMTP_R_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Kaplan-Meier estimates by race/ethnicity <i>Kaplan-Meier estimates up to Month 36 log-rank test and hazard ratio with two-sided 99% CI for hazard ratio</i>	FAS
FMMTP_SX_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Kaplan-Meier estimates by sex <i>Kaplan-Meier estimates up to Month 36 log-rank test and hazard ratio with two-sided 99% CI for hazard ratio</i>	FAS
FMMTP_AG _F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Kaplan-Meier estimates by age category at screening <i>Kaplan-Meier estimates up to Month 36 log-rank test and hazard ratio with two-sided 99% CI for hazard ratio</i>	FAS
TMMTCB1P _F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period <i>unstratified log-rank test and proportional hazards model</i>	FAS patients with typical or consistent PAH according to the blinded expert medical review
TMMTCBP_ F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period - Kaplan-Meier estimates	FAS (patients with typical or consistent PAH according to the blinded expert medical review)

Unique ID	Display	Title <i>additional description</i>	Analysis set
FMMTCBP_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment - Kaplan-Meier estimates <i>Kaplan-Meier estimates up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log-rank test and hazard ratio with 99% CI</i>	FAS (patients with typical or consistent PAH according to the blinded expert medical review)
TMMTCBP1_ F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period - Kaplan-Meier estimates	FAS (patients with typical PAH according to the blinded expert medical review)
FMMTCBP1_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment - Kaplan-Meier estimates <i>Kaplan-Meier estimates up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log-rank test and hazard ratio with 99% CI</i>	FAS (patients with typical PAH according to the blinded expert medical review)
TMMTLP_P	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period <i>unstratified log-rank test and proportional hazards model</i>	PPS
TMMTP_P	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period - Kaplan-Meier estimates	PPS
FMMTP_P	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log-rank test and hazard ratio with 99% CI</i>	PPS
TMMTINVI_ F	T	Time to first morbidity/mortality event reported by the investigator (irrespective of CEC confirmation) up to 7 days after last study drug intake in AC-065A302 Treatment Period <i>unstratified log-rank test and proportional hazards model</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
FMMTINVI_F	F	Time to first morbidity/mortality event reported by the investigator (irrespective of CEC confirmation) up to 7 days after last study drug intake in AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log-rank test and hazard ratio with 99% CI</i>	FAS
TMMTINVIK_M_F	T	Time to first morbidity/mortality event reported by the investigator (irrespective of CEC confirmation) up to 7 days after last study drug intake in AC-065A302 Treatment Period - Kaplan-Meier estimates	FAS
TMMTDPLP_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Supportive analysis ignoring CEC-confirmed "disease progression" event component when second 6MWT was not performed <i>unstratified and stratified log-rank tests and proportional hazards models</i>	FAS
FMMTDPLP_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Supportive analysis ignoring CEC-confirmed "disease progression" event component when second 6MWT was not performed Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log-rank test and hazard ratio with 99% CI</i>	FAS
TMMTDPLK_MP_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Supportive analysis ignoring CEC-confirmed "disease progression" event component when second 6MWT was not performed Kaplan-Meier estimates	FAS
TCECTZW_F	T	Type of first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Supportive analysis ignoring CEC-confirmed "disease progression" event component when second 6MWT was not performed	FAS
LMMT_F	L	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period <i>includes censored observations</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
LCECADJ_F	L	CEC adjudication of all morbidity/mortality events reported by the investigator <i>Includes CEC adjudication yes/no of the MM event, PTOP MM event, all components adjudication and onset date, need for consensus</i>	FAS
TCECT_F	T	Type of first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period	FAS
TCECTI_F	T	Type of first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period	FAS
TCECA_F	T	Event adjudication in old and new CEC system: agreement/disagreement	All morbidity/mortality events reported by the investigator and submitted in both CEC systems in study AC-065A302
TCECI_F	T	Agreement/disagreement between investigator and CEC (new CEC system) in assessing morbidity/mortality events	All morbidity/mortality events reported by the investigator in study AC-065A302
FMMTICAU G_F	F	Inversed censoring/event for Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months</i>	FAS
TMMTICAU G_F	T	Inversed censoring/event for Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period - Kaplan-Meier estimates	FAS
LCECI_F	L	Listing of morbidity/mortality events adjudication agreement/disagreement between investigator and old and new CEC system	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TCECVNT1_F	T	Summary of combined CEC-confirmed morbidity/mortality event components (in order of occurrence) up to 7 days after last study drug intake in the AC-065A302 Treatment Period.	FAS
TCECVNT_F	T	Summary of combined CEC-confirmed morbidity/mortality event components (in order of occurrence) up to 7 days after last study drug intake in the AC-065A302 Treatment Period.	FAS
TCECTCOM B_F	T	Summary of type of first CEC-confirmed morbidity/mortality up to 7 days after last study drug intake in AC-065A302 Treatment Period	FAS
TCECTCOM BAUG_F	T	Summary of type of first CEC-confirmed morbidity/mortality up to 7 days after last study drug intake in AC-065A302 Treatment Period	FAS
TCENR_F	T	Reason for censoring Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period	FAS

8 SECONDARY EFFICACY ENDPOINTS (SAP SECTIONS 10 AND 18)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TSEMP_LKP_F	T	Secondary efficacy endpoints main analyses applying hierarchical testing to account for multiplicity	FAS

8.1 Absolute change from Baseline at Week 26 in 6-Minute-Walk-Distance

Unique ID	Display	Title <i>additional description</i>	Analysis set
TWTS_F	T	Absolute change from Baseline to Week 26 in 6-Minute-Walk-Distance at trough Main imputation algorithm for missing data <i>including point estimate and two-sided 99% CI for location shift and point estimate for the probability to obtain a larger change for a patient treated with selexipag, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	FAS
TOXY_F	T	Supplemental oxygen for 6-Minute-Walk-Test at Week 26	FAS
TWTSANS_F	T	Non-parametric ANCOVA for absolute change from Baseline to Week 26 in 6-Minute-Walk-Distance at trough Main imputation algorithm for missing data Unstratified and stratified analyses <i>stratified by:</i> <i>geographical region</i> <i>PAH etiology</i> <i>modified NYHA / WHO functional class at Baseline (classes I/II versus classes III/IV)</i> <i>concomitant PAH medication (no/yes) at Baseline</i>	FAS
TWTSGR_F	T	Non-parametric ANCOVA for absolute change from Baseline to Week 26 in 6-Minute-Walk-Distance at trough Main imputation algorithm for missing data Subgroup analyses	FAS
TWTS_G_F	T	Absolute change from baseline to Week 26 in 6-Minute-Walk-Distance at trough Main imputation algorithm for missing data Subgroup analysis by geographical region <i>descriptive summary statistics including point estimate and two-sided 99% CI for location shift, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TWTS_ET_F	T	Absolute change from baseline to Week 26 in 6-Minute-Walk-Distance at trough Main imputation algorithm for missing data Subgroup analysis by PAH etiology <i>descriptive summary statistics including point estimate and two-sided 99% CI for location shift, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	FAS
TWTS_W_F	T	Absolute change from baseline to Week 26 in 6-Minute-Walk-Distance at trough Main imputation algorithm for missing data Subgroup analysis by modified NYHA/WHO functional class at Baseline <i>descriptive summary statistics including point estimate and two-sided 99% CI for location shift, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	FAS
TWTS_PHM_F	T	Absolute change from baseline to Week 26 in 6-Minute-Walk-Distance at trough Main imputation algorithm for missing data Subgroup analysis by concomitant PAH medication at Baseline <i>descriptive summary statistics including point estimate and two-sided 99% CI for location shift, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	FAS
TWTS_SX_F	T	Absolute change from baseline to Week 26 in 6-Minute-Walk-Distance at trough Main imputation algorithm for missing data Subgroup analysis by sex <i>descriptive summary statistics including point estimate and two-sided 99% CI for location shift, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	FAS
TWTS_R_F	T	Absolute change from baseline to Week 26 in 6-Minute-Walk-Distance at trough Main imputation algorithm for missing data Subgroup analysis by race/ethnicity <i>descriptive summary statistics including point estimate and two-sided 99% CI for location shift, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	FAS
TWTS_AG_F	T	Absolute change from baseline to Week 26 in 6-Minute-Walk-Distance at trough Main imputation algorithm for missing data Subgroup analysis by age categories at screening <i>descriptive summary statistics including point estimate and two-sided 99% CI for location shift, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TWTSCPH_F	T	Absolute change from Baseline to Week 26 in 6-Minute-Walk-Distance at trough Period Main imputation algorithm for missing data <i>including point estimate and two-sided 99% CI for location shift and point estimate for the probability to obtain a larger change for a patient treated with selexipag, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	FAS (patients with typical or consistent PAH according to the blinded expert medical review)
FWTSGR_F	F	Absolute change from Baseline to Week 26 in 6-Minute-Walk-Distance at trough – forest plot for subgroup analyses	FAS
TWTS1_F	T	Absolute change from Baseline to Week 26 in 6-Minute-Walk-Distance at trough Main imputation algorithm for missing data <i>including point estimate and two-sided 99% CI for location shift and point estimate for the probability to obtain a larger change for a patient treated with selexipag, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	FAS, excluding selexipag patients with 6MWT at Week 26 not performed at trough
TWTSA_F	T	Absolute change from Baseline to Week 26 in 6-Minute-Walk-Distance at trough Sensitivity imputation algorithm for missing data (only patients unable to walk at Week 26 are imputed) <i>including point estimate and two-sided 99% CI for location shift, point estimate for the probability to obtain a larger change for a patient treated with selexipag, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	FAS
TWTSB_F	T	Absolute change from Baseline to Week 26 in 6-Minute-Walk-Distance at trough Sensitivity imputation algorithm for missing data <i>including point estimate and two-sided 99% CI for location shift, point estimate for the probability to obtain a larger change for a patient treated with selexipag, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	FAS
TWTSC_F	T	Absolute change from Baseline to Week 26 in 6-Minute-Walk-Distance at trough Sensitivity imputation algorithm for missing data (using last observation carried forward) <i>including point estimate and two-sided 99% CI for location shift, point estimate for the probability to obtain a larger change for a patient treated with selexipag, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TWTS_P	T	Absolute change from Baseline to Week 26 in 6-Minute-Walk-Distance at trough Main imputation algorithm for missing data <i>including point estimate and two-sided 99% CI for location shift and point estimate for the probability to obtain a larger change for a patient treated with selexipag, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	PPS but excluding selexipag patients with 6MWT at Week 26 not performed at trough
LWTS_F	L	6-Minute-Walk-Distance and Borg Dyspnea Index <i>includes also 6MWTs not performed at trough and 6MWTs performed at unscheduled visits</i>	FAS
TWTSM_F	T	Reason for missing 6-Minute-Walk-Distance	FAS

8.2 Absence of worsening from Baseline in modified NYHA/WHO functional class at Week 26

Unique ID	Display	Title <i>additional description</i>	Analysis set
TWHO_F	T	Absence of worsening from Baseline in modified NYHA/WHO functional class at Week 26 Main imputation algorithm for missing data <i>descriptive frequency statistics: overall and by NYHA/WHO functional class at Baseline, Cochran-Mantel-Haenszel test and Breslow-Day test for common odds ratio</i>	FAS excluding patients with Baseline FC IV
TWHOHS_F	T	Absence of worsening from Baseline in modified NYHA/WHO functional class at Week 26 Cochran-Mantel-Haenszel test and common odds ratios unstratified and stratified analyses Main imputation algorithm for missing data <i>stratified by:</i> <i>geographical region</i> <i>PAH etiology</i> <i>concomitant PAH medication (no/yes) at Baseline</i>	FAS excluding patients with Baseline FC IV
TWHOS_F	T	Absence of worsening from Baseline in modified NYHA/WHO functional class at Week 26 No imputation for missing data <i>descriptive frequency statistics: overall and by NYHA/WHO functional class at Baseline, Cochran-Mantel-Haenszel test and Breslow-Day test for common odds ratio</i>	FAS excluding patients with Baseline FC IV
TWHO_P	T	Absence of worsening from Baseline in modified NYHA/WHO functional class at Week 26 Main imputation algorithm for missing data <i>descriptive frequency statistics: overall and by NYHA/WHO functional class at Baseline, Cochran-Mantel-Haenszel test and Breslow-Day test for common odds ratio</i>	PPS but excluding patients with Baseline FC IV
LWHO_F	L	Modified NYHA/WHO functional class <i>includes functional class assessment at unscheduled visits</i>	FAS
TWHOM_F	T	Reason for missing modified NYHA/WHO functional class	FAS excluding patients with Baseline FC IV

8.3 Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period

Unique ID	Display	Title <i>additional description</i>	Analysis set
TDHPHP1_F	T	Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period <i>unstratified and stratified log-rank tests and proportional hazards models</i> <i>unstratified log-rank test and proportional hazards model</i> <i>stratified by geographical region</i> <i>stratified by PAH etiology</i> <i>stratified by modified NYHA / WHO functional class at Baseline (classes I/II versus classes III/IV)</i> <i>stratified by concomitant PAH medication (no/yes) at Baseline</i>	FAS
TDHPHP_F	T	Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates	FAS
FDHPHP_F	F	Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier estimates up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log-rank test and hazard ratio with 99% CI</i>	FAS
TDHPCB1P_F	T	Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period <i>unstratified log-rank test and proportional hazards model</i>	FAS, patients with typical or consistent PAH according to the blinded expert medical review
TDHPCBP_F	T	Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates	FAS, patients with typical or consistent PAH according to the blinded expert medical review

Unique ID	Display	Title <i>additional description</i>	Analysis set
FDHPCBP_F	F	Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier estimates up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log-rank test and hazard ratio with 99% CI</i>	FAS, patients with typical or consistent PAH according to the blinded expert medical review
TDHPCD1P_P	T	Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period <i>unstratified log-rank test and proportional hazards model</i>	PPS
TDHPCDP_P	T	Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates	PPS
FDHPCDP_P	F	Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log-rank test and hazard ratio with 99% CI</i>	PPS
FDHPHGR_F	F	Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period - forest plot for subgroup analysis	FAS
LDHPHP_F	L	Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period <i>includes censored observations; events with onset date in PTOP are flagged</i>	FAS
TCENPHP_F	T	Reason for censoring Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302	FAS

8.4 Time to death up to Study Closure

Unique ID	Display	Title <i>additional description</i>	Analysis set
TTDSTI1_F	T	Time to death up to Study Closure Unstratified and stratified analyses <i>unstratified and stratified log-rank test and proportional hazards model</i> <i>stratified by:</i> • <i>geographical region</i> • <i>PAH etiology</i> • <i>modified NYHA / WHO functional class at Baseline (classes I/II versus classes III/IV)</i> • <i>concomitant PAH medication (no/yes) at Baseline</i> <i>stratified log-rank test and proportional hazards model</i>	FAS
TTDSTI_F	T	Time to death up to Study Closure - Kaplan-Meier estimates	FAS
FTDSTI_F	F	Time to death up to Study Closure - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 42 with two-sided 95% CI at 12, 24, 36 months, unstratified log-rank test and hazard ratio</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TTDSTPH1P_F	T	Time to death up to Study Closure <i>unstratified log-rank test and proportional hazards model</i>	FAS, patients with typical or consistent PAH according to the blinded expert medical review
TTDSTPHP_F	T	Time to death up to Study Closure - Kaplan-Meier estimates	FAS, patients with typical or consistent PAH according to the blinded expert medical review
FTDSTPHP_F	F	Time to death up to Study Closure - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 42 with two-sided 95% CI at 12, 24, 36 months, unstratified log-rank test and hazard ratio with 99% CI</i>	FAS, patients with typical or consistent PAH according to the blinded expert medical review
TTDSTPHP1_F	T	Time to death up to Study Closure - Kaplan-Meier estimates	FAS, patients with typical PAH according to the blinded expert medical review
FTDSTPHP1_F	F	Time to death up to Study Closure - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 42 with two-sided 95% CI at 12, 24, 36 months, unstratified log-rank test and hazard ratio with 99% CI</i>	FAS, patients with typical PAH according to the blinded expert medical review
LTDP_F	L	Time to death up to Study Closure <i>includes censored observations, outcome of CEC adjudication 'PAH related' yes/no</i>	FAS
LDEATHA_F	L	Listing of all deaths <i>Includes causes of death (original, coded term and outcome of CEC adjudication 'PAH related' yes/no)</i>	FAS

8.5 Absolute change from Baseline to Week 26 in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score

Unique ID	Display	Title <i>additional description</i>	Analysis set
TQSBR_Q	T	Absolute change from Baseline to Week 26 in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score Imputation for missing data <i>including point estimate and two-sided 99% CI for location shift and point estimate for the probability to obtain a lower change for a patient treated with selexipag, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	QAS
TQSBRANS_Q	T	Non-parametric ANCOVA for absolute change from Baseline to Week 26 in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score Imputation for missing data Unstratified and stratified analyses <i>stratified by:</i> <i>modified NYHA / WHO functional class at Baseline (classes I/II versus classes III/IV)</i> <i>concomitant PAH medication (no/yes) at Baseline</i>	QAS
LQS_F	L	CAMPHOR questionnaire	FAS
LQSA_F	L	CAMPHOR questionnaire - Appendix	FAS

8.6 Absolute change from Baseline to Week 26 in CAMPHOR 'Symptoms' score

Unique ID	Display	Title <i>additional description</i>	Analysis set
TQSSY_Q	T	Absolute change from Baseline to Week 26 in CAMPHOR 'Symptoms' score Imputation for missing data <i>including point estimate and two-sided 99% CI for location shift and point estimate for the probability to obtain a lower change for a patient treated with selexipag, one-sided Wilcoxon-Mann-Whitney test statistic and p-value</i>	QAS
TQSSYANS_Q	T	Non-parametric ANCOVA for absolute change from Baseline to Week 26 in CAMPHOR 'Symptoms' score Unstratified and stratified analyses Imputation for missing data <i>stratified by:</i> <i>modified NYHA / WHO functional class at Baseline (classes I/II versus classes III/IV)</i> <i>concomitant PAH medication (no/yes) at Baseline</i>	QAS

9 EXPLORATORY EFFICACY ENDPOINTS (SAP SECTIONS 11 AND 19)

9.1 Exploratory efficacy endpoints related to morbidity/mortality

Unique ID	Display	Title <i>additional description</i>	Analysis set
TMMT1STP_ F	T	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure - Kaplan-Meier estimates	FAS
TMMT1STI_ F	T	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure <i>unstratified and stratified log-rank tests and proportional hazards models, one-sided p-value, point estimate and two-sided 95% CI for hazard ratio</i> <i>stratified by:</i> • <i>geographical region</i> • <i>PAH etiology</i> • <i>modified NYHA / WHO functional class at Baseline (classes I/II versus classes III/IV)</i> • <i>concomitant PAH medication (no/yes) at Baseline</i> • <i>modified NYHA / WHO functional class at Baseline and concomitant PAH</i>	FAS
FMMT1STI_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 42 with two-sided 95% CI at 12, 24, 36 months log rank test and hazard ratio with 95% CI</i>	FAS
TMMT1STIV P_F	T	Time to first morbidity/mortality event (excluding “disease progression”) reported by the investigator (irrespective of CEC confirmation) up Study closure <i>Unstratified log-rank test and proportional hazards model (point estimates and 95% CIs for hazard ratio)</i>	FAS
FMMT1STIV P_F	F	Time to first morbidity/mortality event (excluding “disease progression”) reported by the investigator (irrespective of CEC confirmation) up to Study closure - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 42 with two-sided 95% CI at 12, 24, 36 months log rank test and hazard ratio with 95% CI</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TMMT1ST2P_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure <i>unstratified log-rank test and proportional hazards model</i>	FAS, patients with typical or consistent PAH according to the blinded expert medical review
FMMT1ST2P_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 42 with two-sided 95% CI at 12, 24, 36 months , log rank test and hazard ratio with 95% CI</i>	FAS, patients with typical or consistent PAH according to the blinded expert medical review
TCECTSCP_F	T	Type of first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to Study Closure	FAS
LCEC1STP_F	L	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding 'disease progression') up to Study Closure <i>Include event with onset date during PTOP flagged, censored observations</i>	FAS
TMMT2P_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates	FAS
TMMT2STI_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period Unstratified analysis <i>unstratified log-rank statistic, one-sided p-value, point estimate and two-sided 95% CI for hazard ratio</i>	FAS
FMMT2STI_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log rank test and hazard ratio with 95% CI</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TCECTDPP_ F	T	Type of first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period	FAS
TMMT2CBP_ _F	T	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period <i>unstratified log-rank test and proportional hazards model</i>	FAS, patients with typical or consistent PAH according to the blinded expert medical review
FMMT2CBP_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months</i> , log rank test and hazard ratio with 95% CI	FAS, patients with typical or consistent PAH according to the blinded expert medical review
LMMT2P_F	L	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period <i>includes censored observations</i>	FAS
TMMT3STP_ F	T	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and “initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH”) up to Study Closure - Kaplan-Meier estimates	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TMMT3STIP_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding "disease progression" and "initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH") up to Study Closure Unstratified and stratified analyses <i>unstratified and stratified log-rank tests and proportional hazards models</i> <i>stratified by:</i> <i>geographical region</i> <i>PAH etiology</i> <i>modified NYHA / WHO functional class at Baseline (classes I/II versus classes III/IV)</i> <i>concomitant PAH medication (no/yes) at Baseline</i> <i>modified NYHA / WHO functional class at Baseline and concomitant PAH medication at Baseline</i> <i>unstratified log-rank statistic, one-sided p-value, point estimate and two-sided 95% CI for hazard ratio</i>	FAS
FMMT3STIP_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding "disease progression" and "initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH") up to Study Closure - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 42 with two-sided 95% CI at 12, 24, 36 months, log rank test and hazard ratio with 95% CI</i>	FAS
TMMT3IP_F	T	Time to first morbidity/mortality event (excluding "disease progression" and "initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH") reported by the investigator (irrespective of CEC confirmation) up to Study closure <i>Unstratified log-rank test and proportional hazards model (point estimates and 95% CIs for hazard ratio)</i>	FAS
FMMT3IP_F	F	Time to first morbidity/mortality event (excluding "disease progression" and "initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH") reported by the investigator (irrespective of CEC confirmation) up to Study closure - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 42 with two-sided 95% CI at 12, 24, 36 months, log rank test and hazard ratio with 95% CI</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TMMT3ICBP_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and “initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH”) up to Study Closure <i>unstratified log-rank test and proportional hazards model</i>	FAS, patients with typical or consistent PAH according to the blinded expert medical review
FMMT3ICBP_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and “initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH”) up to Study Closure - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 42 with two-sided 95% CI at 12, 24, 36 months</i> , log rank test and hazard ratio with 95% CI	FAS, patients with typical or consistent PAH according to the blinded expert medical review
LMMT3STP_F	L	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and “initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH”) up to Study Closure <i>includes censored observations; events with onset date in PTOp are flagged</i>	FAS
TCEC3STP_F	T	Type of first CEC-confirmed morbidity/mortality event (excluding “disease progression” and “initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH”) up to Study Closure	FAS
TMMT4P_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and “initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates	FAS
TMMT4STI_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding “disease progression” and “initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH”) up to 7 days after last study drug intake in the AC-065A302 Treatment Period Unstratified analysis <i>unstratified log-rank tests and proportional hazards models</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
FMMT4STI_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding "disease progression" and "initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH") up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log rank test and hazard ratio with 95% CI</i>	FAS
TCECT4P_F	T	Type of first CEC-confirmed morbidity/mortality event (excluding "disease progression" and "initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH") up to 7 days after last study drug intake in the AC-065A302 Treatment Period	FAS
TMMT4INP_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding "disease progression" and "initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH") up to 7 days after last study drug intake in the AC-065A302 Treatment <i>unstratified log-rank test and proportional hazards model</i>	FAS, patients with typical or consistent PAH according to the blinded expert medical review
FMMT4INP_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding "disease progression" and "initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH") up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months</i> , log rank test and hazard ratio with 95% CI	FAS, patients with typical or consistent PAH according to the blinded expert medical review
LMMT4P_F	L	Time from randomization to first CEC-confirmed morbidity/mortality event (excluding "disease progression" and "initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH") up to 7 days after last study drug intake in the AC-065A302 Treatment Period <i>includes censored observations</i>	FAS
TPHD1P_F	T	Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period Unstratified analysis <i>unstratified log-rank statistic, one-sided p-value, point estimate and two-sided 95% CI for hazard ratio</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
TPHDP_F	T	Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates	FAS
FPHDP_F	F	Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log rank test and hazard ratio with 95% CI</i>	FAS
TPHD1P1_F	T	Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period <i>unstratified log-rank test and proportional hazards model</i>	FAS, patients with typical or consistent PAH according to the blinded expert medical review
FPHDP1_F	F	Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log rank test and hazard ratio with 95% CI</i>	FAS, patients with typical or consistent PAH according to the blinded expert medical review
LPHDP_F	L	Time from randomization to CEC-confirmed death due to PAH up to 7 days after last study drug intake in the AC-065A302 Treatment Period <i>includes censored observations</i>	FAS
TDHPHST1P_F	T	Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study Closure Unstratified analysis <i>unstratified log-rank statistic, one-sided p-value, point estimate and two-sided 95% CI for hazard ratio</i>	FAS
TDHPHSTP_F	T	Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study Closure - Kaplan-Meier estimates	FAS
FDHPHSTP_F	F	Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study Closure - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log rank test and hazard ratio with 95% CI</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
LDHPHSTP_F	L	Time from randomization to CEC-confirmed death due to PAH or CEC-confirmed first hospitalization due to PAH worsening up to Study Closure <i>includes censored observations; events with onset date in PTOp are flagged</i>	FAS
TMMTST1P_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to Study Closure Unstratified analysis <i>unstratified log-rank statistic, one-sided p-value, point estimate and two-sided 95% CI for hazard ratio</i>	FAS
TMMTSTPP_F	T	Time from randomization to first CEC-confirmed morbidity/mortality event up to Study Closure - Kaplan-Meier estimates	FAS
FMMTSTPP_F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to Study Closure - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 42 with two-sided 95% CI at 12, 24, 36 months, log rank test and hazard ratio with 95% CI</i>	FAS
TCECTDPSP_F	T	Type of first CEC-confirmed morbidity/mortality event up to Study Closure	FAS
LMMTSTP_F	L	Time from randomization to first CEC-confirmed morbidity/mortality event up to Study Closure <i>includes censored observations, events with onset date in PTOp are flagged</i>	FAS
TPHDST1P_F	T	Time from randomization to CEC-confirmed death due to PAH up to Study Closure Unstratified analyses <i>unstratified log-rank statistic, one-sided p-value, point estimate and two-sided 95% CI for hazard ratio</i>	FAS
TPHDSTP_F	T	Time from randomization to CEC-confirmed death due to PAH up to Study Closure - Kaplan-Meier estimates	FAS
FPHDSTP_F	F	Time from randomization to CEC-confirmed death due to PAH up to Study Closure - Kaplan-Meier estimates <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months, log rank test and hazard ratio with 95% CI</i>	FAS
LPHDSTP_F	L	Time from randomization to CEC-confirmed death due to PAH up to Study Closure <i>includes censored observations, events with onset date in PTOp are flagged</i>	FAS

9.2 Exploratory efficacy endpoints related to 6MWD (SAP section 11.9 and 19.10)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TWTS2_F	T	Absolute change from Baseline to regular visits in 6MWD at trough <i>descriptive statistics up to Month 36</i>	FAS
FWTS2_F	F	Absolute change from Baseline to regular visits in 6MWD at trough <i>boxplots - horizontal axis: weeks/months up to Month 36</i>	FAS
TWTSEOS_F	T	Absolute change from Baseline in 6MWD to EOS visit <i>descriptive summary statistics</i>	FAS

9.3 Exploratory efficacy endpoints related to NYHA/WHO functional class (SAP section 11.10 and 19.10)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TWHO1_F	T	Absence of worsening from Baseline in modified NYHA/WHO functional class at regular visits <i>descriptive frequency statistics: overall and by NYHA/WHO functional class at Baseline, up to Month 36</i>	FAS but excluding patients with baseline FC IV
FWHO1_F	F	Absence of worsening from Baseline in modified NYHA/WHO functional class at regular visits <i>point estimates for probability of absence of worsening and two-sided 95% confidence intervals - horizontal axis: weeks/months up to Month 36</i>	FAS but excluding patients with baseline FC IV
TWHO1SH_F	T	Shift table from baseline to each regular post-baseline visit for modified NYHA/WHO functional class <i>up to Month 36</i>	FAS
TWHO2SH_F	T	Shift table from baseline to worst post-baseline for modified NYHA/WHO functional class	FAS
TWHO3SH_F	T	Change from baseline in modified NYHA/WHO functional class at regular visits <i>Categories: improvement / no change / worsening with 95% CI, up to Month 36</i>	FAS
TWHOEOS_F	T	Absence of worsening from Baseline in modified NYHA/WHO functional class at EOS visit <i>descriptive frequency statistics: overall and by NYHA/WHO functional class at Baseline</i>	FAS (patients with baseline FC IV excluded)

9.4 Exploratory efficacy endpoints related to Borg dyspnea index (SAP section 11.11 and 19.9)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TBORG1_F	T	Borg dyspnea index at regular visits <i>descriptive statistics up to Month 36</i>	FAS
FBORG1_F	F	Borg dyspnea index at regular visits <i>boxplots - horizontal axis: weeks/months, up to Month 36</i>	FAS
TBORGEO5_F	T	Borg dyspnea index at EOS visit <i>descriptive summary statistics</i>	FAS

9.5 Exploratory efficacy endpoints related to CAMPHOR (SAP section 11.13 and 19.10)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TQSB1_Q	T	Absolute change from Baseline to regular visits in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score <i>descriptive statistics up to Month 24</i>	QAS
FQSB1_Q	F	Absolute change from Baseline to regular visits in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score <i>boxplots - horizontal axis: weeks/month, up to Month 24</i>	QAS
TQSCS_Q	T	Absolute change from Baseline to EOS visit in sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' score <i>Descriptive statistics up to Month 24</i>	QAS
TQSSY1_Q	T	Absolute change from Baseline to regular visits in CAMPHOR 'Symptoms' score <i>descriptive statistics</i>	QAS
FQSSY1_Q	F	Absolute change from Baseline to regular visits in CAMPHOR 'Symptoms' score <i>boxplots - horizontal axis: weeks/month up to Month 24</i>	QAS
TQSSYSB_Q	T	Absolute change from Baseline to EOS visit in CAMPHOR 'Symptoms' score <i>descriptive statistics</i>	QAS

9.6 Exploratory efficacy endpoints related to plasma NT pro-brain natriuretic peptide (SAP section 11.12 and 19.10)

Unique ID	Display	Title <i>Additional description</i>	Analysis set
TBNP_F	T	Absolute change from Baseline to regular visits in plasma NT pro-BNP <i>descriptive statistics up to Month 36</i>	FAS
FBNP_F	F	Absolute change from Baseline to regular visits in plasma NT pro-BNP <i>boxplots - horizontal axis: weeks/months up to Month 36</i>	FAS
TBNPEOS_F	T	Absolute change in plasma NT pro-BNP from baseline to EOS visit	FAS

10 EXPLORATORY ANALYSIS OF DOSE-RESPONSE RELATIONSHIP (SAP SECTION 20)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TMMDSE1P_ F	T	Relationship between IMD and time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period <i>unstratified proportional hazards models with</i> <i>selexipag IMD in AC-065A302 as single continuous covariate</i> <i>selexipag IMD in AC-065A302 as single categorical covariate (IMD categories: 0 mcg (Placebo), 200 to 500 mcg, 600 to 1100 mcg, 1200 to 1600 mcg)</i> <i>point estimates and two-sided 95% CIs for hazard ratios relative to 0 mcg(Placebo)</i> <i>Log rank test with selexipag IMD in AC-065A302 as single categorical covariate</i>	FAS, excluding patients randomized to selexipag with IMD = 0 or "other"
FMMDSE1P_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period by selexipag individual maintenance dose <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months, point estimates and two-sided 95% CIs for hazard ratios relative to 0 mcg, log rank test</i> <i>IMD categories: 0 mcg (Placebo), 200 to 500 mcg, 600 to 1100 mcg, 1200 to 1600 mcg</i>	FAS, excluding patients randomized to selexipag with IMD = 0 or "other"
FMMDSEA_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period by selexipag individual maintenance dose <i>All Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months on our graph, IMD categories: 0 mcg (Placebo), 200 to 500 mcg, 600 to 1100 mcg, 1200 to 1600 mcg</i>	FAS, excluding patients randomized to selexipag with IMD = 0 or "other"

Unique ID	Display	Title <i>additional description</i>	Analysis set
TMMDSE2P_ F	T	Relationship between IMD and time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Subgroup analysis: patients with versus without selexipag dose reductions or study drug discontinuation because of Prostacyclin-like associated AEs <i>unstratified proportional hazards models with selexipag IMD in AC-065A302 as single continuous covariate separately</i> <i>for patients with selexipag dose reductions or study drug discontinuation because of prostacyclin like associated AEs</i> <i>for patients without selexipag dose reductions or study drug discontinuation because of prostacyclin like associated AEs</i> <i>both subgroups compared to all patients randomized to placebo: point estimates and two-sided 95% CIs for hazard ratio</i> <i>log rank test and unstratified proportional hazards models with selexipag IMD in AC-065A302 as single categorical covariate separately</i> <i>for patients with selexipag dose reductions or study drug discontinuation because of prostacyclin like associated AEs</i> <i>for patients without selexipag dose reductions or study drug discontinuation because of prostacyclin like associated AEs</i> <i>both subgroups compared to all patients randomized to placebo: point estimates and two-sided 95% CIs for hazard ratio</i>	FAS, excluding patients randomized to selexipag with IMD = 0 or "other"

Unique ID	Display	Title <i>additional description</i>	Analysis set
FMMDSE2P_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period by selexipag individual maintenance dose Subgroup analysis: patients with versus without selexipag dose reductions or study drug discontinuation because of Prostacyclin-like associated AEs <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months, point estimates and two-sided 95% CIs for hazard ratios relative to 0 mcg, log rank test</i> <i>for patients with selexipag dose reductions or study drug discontinuation because of prostacyclin like associated AEs</i> <i>for patients without selexipag dose reductions or study drug discontinuation because of prostacyclin like associated AEs</i> <i>for patients randomized to placebo</i> <i>IMD categories: 0 mcg(Placebo), 200 to 500 mcg, 600 to 1100 mcg, 1200 to 1600 mcg</i>	FAS, excluding patients randomized to selexipag with IMD = 0 or "other"
TMMDSE3P_ F	T	Relationship between individual maintenance dose and time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period Subgroup analysis: patients with versus without Prostacyclin-like associated AEs <i>unstratified proportional hazards models with selexipag IMD in AC-065A302 as single continuous covariate separately</i> <i>for selexipag patients with prostacyclin like associated AEs</i> <i>for selexipag patients without prostacyclin like associated AEs</i> <i>both subgroups compared to all patients randomized to placebo: point estimates and two-sided 95% CIs for hazard ratio</i> <i>log rank test and unstratified proportional hazards models with selexipag IMD in AC-065A302 as single categorical covariate separately</i> <i>for selexipag patients with prostacyclin like associated AEs</i> <i>for selexipag patients without prostacyclin like associated AEs</i> <i>both subgroups compared to all patients randomized to placebo: point estimates and two-sided 95% CIs for hazard ratio</i>	FAS, excluding patients randomized to selexipag with IMD = 0 or "other"

Unique ID	Display	Title <i>additional description</i>	Analysis set
FMMDSE3P_ F	F	Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period by selexipag individual maintenance dose Subgroup analysis: patients with versus without Prostacyclin-like associated AEs <i>Kaplan-Meier curves up to Month 36 with two-sided 95% CI at 12, 24, 36 months, point estimates and two-sided 95% CIs for hazard ratios relative to 0 mcg, log rank test</i> <i>for selexipag patients with prostacyclin like associated AEs</i> <i>for selexipag patients without prostacyclin like associated AEs</i> <i>for patients randomized to placebo</i> <i>IMD categories: 0 mcg (Placebo), 200 to 500 mcg, 600 to 1100 mcg, 1200 to 1600 mcg</i>	FAS, excluding patients randomized to selexipag with IMD = 0 or "other"
TWTSDSE1_ F	T	Relationship between categorical IMD and absolute change from Baseline to Week 26 in 6MWD at trough Main imputation algorithm for missing data <i>non-parametric ANCOVA</i> <i>selexipag IMD in AC-065A302 as continuous covariate in addition to Baseline 6MWD</i> <i>selexipag IMD in AC-065A302 as categorical covariate (IMD categories: 0 mcg (Placebo), 200 to 500 mcg, 600 to 1100 mcg, 1200 to 1600 mcg) in addition to Baseline 6MWD</i>	FAS, excluding patients randomized to selexipag with IMD = 0 or "other"
TWTSDSE2_ F	T	Absolute change from Baseline to Week 26 in 6MWD at trough by categorical selexipag IMD in AC-065A302 Main imputation algorithm for missing data <i>descriptive statistics</i>	FAS, excluding patients randomized to selexipag with IMD = 0 or "other"

Unique ID	Display	Title <i>additional description</i>	Analysis set
TWTSDSE3_ F	T	Relationship between IMD and absolute change from Baseline to Week 26 in 6MWD at trough Subgroup analysis: for patients with versus without selexipag dose reduction or study drug discontinuation because of Prostacyclin-like associated AEs Main imputation algorithm for missing data <i>non-parametric ANCOVAs with selexipag IMD in AC-065A302 as continuous covariate (in addition to Baseline 6MWD) separately</i> <i>for patients with selexipag dose reductions or study drug discontinuation because of prostacyclin like associated AEs</i> <i>for patients without selexipag dose reductions or study drug discontinuation because of prostacyclin like associated AEs</i> <i>both subgroups compared to all patients randomized to placebo</i> <i>non-parametric ANCOVAs with selexipag IMD in AC-065A302 as categorical covariate (in addition to Baseline 6MWD) separately</i> <i>for patients with selexipag dose reductions or study drug discontinuation because of prostacyclin like associated AEs</i> <i>for patients without selexipag dose reductions or study drug discontinuation because of prostacyclin like associated AEs</i> <i>both subgroups compared to all patients randomized to placebo</i>	FAS, excluding patients randomized to selexipag with IMD = 0 or "other"
TWTSDSE6_ F	T	Absolute change from Baseline to Week 26 in 6MWD at trough by categorical selexipag IMD in AC-065A302 Subgroup analysis: for patients with versus without selexipag dose reduction or study drug discontinuation because of Prostacyclin-like associated AEs Main imputation algorithm for missing data <i>descriptive statistics</i>	FAS, excluding patients randomized to selexipag with IMD = 0 or "other"

Unique ID	Display	Title <i>additional description</i>	Analysis set
TWTSDSE5_ F	T	Relationship between IMD and absolute change from Baseline to Week 26 in 6MWD at trough Subgroup analysis: for patients with versus without Prostacyclin-like associated AEs Main imputation algorithm for missing data <i>non-parametric ANCOVAs with selexipag IMD in AC-065A302 as continuous covariate (in addition to Baseline 6MWD) separately</i> <i>for selexipag patients with prostacyclin like associated AEs</i> <i>for selexipag patients with prostacyclin like associated AEs</i> <i>both subgroups compared to all patients randomized to placebo</i> <i>non-parametric ANCOVAs with selexipag IMD in AC-065A302 as categorical covariate (in addition to Baseline 6MWD) separately</i> <i>for selexipag patients with prostacyclin like associated AEs</i> <i>for selexipag patients with prostacyclin like associated AEs</i> <i>both subgroups compared to all patients randomized to placebo</i>	FAS, excluding patients randomized to selexipag with IMD = 0 or "other"
TWTSDSE7_ F	T	Absolute change from Baseline to Week 26 in 6MWD at trough by categorical selexipag IMD in AC-065A302 Subgroup analysis: for patients with versus without Prostacyclin-like associated AEs Main imputation algorithm for missing data <i>descriptive statistics</i>	FAS, excluding patients randomized to selexipag with IMD = 0 or "other"

11 PHARMACOECONOMIC ENDPOINT (SAP SECTION 12 AND 21)

11.1 Annualized number of hospitalizations (for all causes) up to the EOS visit

Unique ID	Display	Title <i>additional description</i>	Analysis set
THSPS_F	T	Annualized number of hospitalizations (for all causes) up to the EOS visit Main analysis <i>results of the negative binomial model: p-value of two-sided Wald-type test; point estimate and two-sided 99% CI for relative reduction in mean annualized hospitalization rate , descriptive statistics</i>	FAS

11.2 Annualized number of PAH-related hospitalizations up to the EOS visit

Unique ID	Display	Title <i>additional description</i>	Analysis set
THSPA_H_F	T	Annualized number of PAH-related hospitalizations up to the EOS visit <i>results of the negative binomial model: p-value of two-sided Wald-type test; point estimate and two-sided 99% CI for relative reduction in mean annualized rate for PAH-related hospitalizations, descriptive statistics</i>	FAS

11.3 Annualized number of days spent in hospital (for all causes) up to the EOS visit

Unique ID	Display	Title <i>additional description</i>	Analysis set
TADH_F	T	Annualized number of days spent in hospital (for all causes) up to the EOS visit <i>p-value of non-parametric one-sided Wilcoxon-Mann-Whitney test, descriptive statistics</i>	FAS
FADH_F	F	Number of days spent in hospital (for all causes) up to the EOS visit <i>By treatment group</i>	FAS

11.4 Annualized number of days spent in hospital for PAH-related causes up to the EOS visit

Unique ID	Display	Title <i>additional description</i>	Analysis set
TADHPA_H_F	T	Annualized number of days spent in hospital for PAH-related causes up to the EOS visit <i>p-value of non-parametric one-sided Wilcoxon-Mann-Whitney test, descriptive statistics</i>	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
FADHPAH_F	F	Number of days spent in hospital for PAH-related causes up to the EOS visit <i>By treatment group</i>	FAS

12 PHARMACOKINETIC ENDPOINT (SAP SECTION 22)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TPLASM_PK	T	Plasma trough concentrations of ACT-293987 (selexipag) and ACT-33679 per time point and by last dose prior to PK sampling <i>95% CI for the geometric mean based on log-transformed data and presented back-transformed to the original scale</i>	PK
LPLASM_PK	L	Plasma trough concentrations of ACT-293987 (selexipag) and ACT-33679 <i>Includes last selexipag dose prior to PK sampling, PK sampling date/time</i>	PK

13 SAFETY AND TOLERABILITY ENDPOINTS (SAP SECTIONS 14 AND 23)

13.1 Adverse events (SAP section 23.1)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TAESF2_S	T	Treatment-emergent AEs in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TAESC2_S	T	Treatment-emergent AEs in study AC-065A302 sorted by SOC (alphabetical order) and PT incidence in the selexipag group within the SOC	SAF
TAESC2D_S	T	Treatment-emergent AEs in study AC-065A302 sorted by difference in incidence between selexipag and placebo	SAF
TAESF3_S	T	Treatment-emergent AEs in study AC-065A303 sorted by PT incidence	SAF subset treated in study AC-065A303
TAESC3_S	T	Treatment-emergent AEs in study AC-065A303 sorted by SOC (alphabetical order) and PT incidence within the SOC	SAF subset treated in study AC-065A303
TAESC23_S	T	Treatment-emergent AEs in studies AC-065A302 and AC-065A303 – intra-patient comparison sorted by SOC (alphabetical order) and PT incidence in AC-065A302 selexipag group within the SOC	SAF subset treated in study AC-065A303
TAESIC2_S	T	Treatment-emergent AEs in study AC-065A302 – maximum intensity sorted by PT incidence in the selexipag group	SAF
TAESIC3_S	T	Treatment-emergent AEs in study AC-065A303 – maximum intensity sorted by PT incidence	SAF subset treated in study AC-065A303
TAESIF23_S	T	Treatment-emergent AEs in studies AC-065A302 and AC-065A303 – intra-patient comparison of maximum intensity sorted by PT incidence in AC-065A302 selexipag group	SAF subset treated in study AC-065A303
TAEREL2_S	T	Treatment-emergent AEs in study AC-065A302 reported by the investigator as related to study treatment sorted by SOC (alphabetical order) and PT incidence in the selexipag group within the SOC	SAF
TAEREL3_S	T	Treatment-emergent AEs in study AC-065A303 reported by the investigator as related to study treatment sorted by SOC (alphabetical order) and PT incidence within the SOC	SAF subset treated in study AC-065A303

Unique ID	Display	Title <i>additional description</i>	Analysis set
TAESF2IMD_S	T	Treatment-emergent AEs in study AC-065A302 by IMD categories <i>Sorted by highest IMD category</i>	SAF
TAESF3IMD_S	T	Treatment-emergent AEs in study AC-065A302 by IMD categories <i>Sorted by highest IMD category</i>	SAF subset treated in study AC-065A303
TNSAEC2_S	T	Non-serious treatment-emergent AEs in study AC-065A302 sorted by SOC (alphabetical order) and PT incidence in the selexipag group within the SOC <i>PTs in descending order by frequency in the selexipag group down to 5%; only for clintrials.gov, not for CSR</i>	SAF
TNSAEC3_S	T	Non-serious treatment-emergent AEs in study AC-065A303 sorted by SOC (alphabetical order) and PT incidence within the SOC <i>PTs in descending order by frequency down to 5%; only for clintrials.gov, not for CSR</i>	SAF subset treated in study AC-065A303
TAEDF2_S	T	Treatment-emergent AEs leading to discontinuation of study drug in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TAEDC2_S	T	Treatment-emergent AEs leading to discontinuation of study drug in study AC-065A302 sorted by SOC (alphabetical order) and PT incidence in the selexipag group within the SOC	SAF
TAEDF3_S	T	Treatment-emergent AEs leading to discontinuation of study drug in study AC-065A303 sorted by PT incidence <i>Presented overall and by treatment received in AC-065A302</i>	SAF subset treated in study AC-065A303
TAEDC3_S	T	Treatment-emergent AEs leading to discontinuation of study drug in study AC-065A303 sorted by SOC (alphabetical order) and PT incidence within the SOC <i>Presented overall and by treatment received in AC-065A302</i>	SAF subset treated in study AC-065A303
TAEDR1_S	T	Treatment-emergent AEs in study AC-065A302 with onset date up to Week 12 or up to the first time study drug dose is reduced or discontinued - by selexipag dose <i>Lowest to highest dose</i>	SAF
TAEDR1A_S	T	Treatment-emergent AEs in study AC-065A302 with onset date up to Week 12 leading to dose reduction or to discontinuation of study drug sorted by PT incidence in the selexipag group	SAF
TAEDR2_S	T	Treatment-emergent AEs in study AC-065A303 with onset date up to Week 12 or up to the first time study drug dose is reduced - by selexipag dose	SAF

Unique ID	Display	Title <i>additional description</i>	Analysis set
TAEDR2A_S	T	Treatment-emergent AEs in study AC-065A303 with onset date up to Week 12 leading to dose reduction or to permanent discontinuation of study drug sorted by PT incidence in the selexipag group	SAF
TSAEF2_S	T	Treatment-emergent SAEs in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TSAEC2_S	T	Treatment-emergent SAEs in study AC-065A302 sorted by SOC (alphabetical order) and PT incidence within the SOC	SAF
TSAEF3_S	T	Treatment-emergent SAEs in study AC-065A303 sorted by PT incidence	SAF subset treated in study AC-065A303
TSAEC3_S	T	Treatment-emergent SAEs in study AC-065A303 sorted by SOC (alphabetical order) and PT incidence within the SOC	SAF subset treated in study AC-065A303
TSAEC23_S	T	Treatment-emergent SAEs in studies AC-065A302 and AC-065A303 – intra-patient comparison sorted by SOC (alphabetical order) and PT incidence in AC-065A302 selexipag group within the SOC	SAF subset treated in study AC-065A303
TSAEOD2_S	T	SAEs with fatal outcome in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TSAEF3O2_S	T	Treatment-emergent SAEs with fatal outcome in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TSAEF3O3_S	T	Treatment-emergent SAEs with fatal outcome in study AC-065A303 sorted by PT incidence	SAF subset treated in study AC-065A303
FAESI_S	F	Treatment-emergent AEs of special interest in study AC-065A302: Graphical display of the relative risk <i>Overall relative risk for each AE of special interest category, order by higher selexipag RR</i>	
TAES_EYE1_S	T	Treatment-emergent AEs of special interest “eye disorders” in study AC-065A302 sorted by PT incidence in the selexipag group <i>for the "combined occurrence":</i> • <i>point estimate and two-sided 95% CI for relative risk</i> • <i>point estimate and two-sided 95% CI for the hazard ratio from the Andersen-Gill model for recurrent events</i>	SAF

Unique ID	Display	Title <i>additional description</i>	Analysis set
FAES_EYE1_S	F	Treatment-emergent AEs of special interest “eye disorders” in study AC-065A302 - Graphical display of the relative risk <i>sorted by relative risk more frequent in selexipag</i>	SAF
TAES_EYE2_O	T	Treatment-emergent AEs of special interest eye disorders” in study AC-065A302 “sorted by PT incidence in the selexipag group <i>for the "combined occurrence":</i> point estimate and two-sided 95% CI for relative risk	OAS
TAES_EYEA_S	T	Treatment-emergent AEs of special interest “eye disorders” in study AC-065A302 sorted by PT incidence in the selexipag group by age at screening <i>Age categories: 18-40, 41-60, >60</i>	SAF
TAES_EYED_S	T	Treatment-emergent AEs of special interest “eye disorders” in study AC-065A302 leading to discontinuation of study drug in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TAES_EYES_S	T	Treatment-emergent serious AEs of special interest “eye disorders” in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TAES_EYEF_S	T	Treatment-emergent AEs of special interest “eye disorders” in study AC-065A302 with fatal outcome in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
LAES_EYE2_S	L	Listing of concomitant medication ongoing at the time of the AE of special interest “eye disorders” in study AC-065A302 <i>includes PT and ATC as well as start/end dates for AE of special interest "eye disorders" and concomitant medication(s)</i>	SAF
TAES_HEM1_S	T	Treatment-emergent AEs of special interest “hemorrhage” in study AC-065A302 sorted by PT incidence in the selexipag group <i>for the "combined occurrence":</i> - point estimate and two-sided 95% CI for relative risk - point estimate and two-sided 95% CI for the hazard ratio from the Andersen-Gill model for recurrent events	SAF
FAES_HEM1_S	F	Treatment-emergent AEs of special interest “hemorrhage” in study AC-065A302- Graphical display of the relative risk <i>Two graphs: one sorted by relative risk more frequent in selexipag (for PTs included in the AE of special interest) and one sorted by relative risk more frequent in placebo</i>	SAF

Unique ID	Display	Title <i>additional description</i>	Analysis set
TAES_HEM2_S	T	Treatment-emergent AEs of special interest “hemorrhage” in study AC-065A302 sorted by PT incidence in the selexipag group - by PAH etiology <i>for the "combined occurrence":</i> point estimate and two-sided 95% CI for relative risk	SAF
TAES_HEM3_S	T	Treatment-emergent AEs of special interest “hemorrhage” in study AC-065A302 by time period with/without confounding factor(s) <i>Footnote: confounding factors include treatment with antithrombotic agents, non-steroidal anti-inflammatory drugs, corticosteroids or medical history of “hemorrhage” or etiology of PAH associated with connective tissue disease.</i>	SAF
TAES_HEMD_S	T	Treatment-emergent AEs of special interest “hemorrhage” in study AC-065A302 leading to discontinuation of study drug in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TAES_HEMS_S	T	Treatment-emergent serious AEs of special interest “hemorrhage” in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TAES_HEMF_S	T	Treatment-emergent AEs of special interest “hemorrhage” in study AC-065A302 with fatal outcome in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TAES_HEMSEV_S	T	Treatment-emergent AEs of special interest “hemorrhage” in study AC-065A302– maximum intensity sorted by PT incidence in the selexipag group	SAF
TAES_HEM4_S	T	Treatment-emergent AEs of special interest “hemorrhage” in study AC-065A302 by time period with/without confounding medications(s) <i>Footnote: confounding medications include treatment with antithrombotic agents, non-steroidal anti-inflammatory drugs or corticosteroids.</i>	SAF
LAES_HEM1_S	L	Listing of concomitant medication ongoing at the time of the AE of special interest “hemorrhage” in study AC-065A302 <i>includes PT and ATC as well as start/end dates for AE of special interest "hemorrhage" and concomitant medication(s)</i>	SAF

Unique ID	Display	Title <i>additional description</i>	Analysis set
TAES_HT1_S	T	Treatment-emergent AEs of special interest “hypotension” in study AC-065A302 sorted by PT incidence in the selexipag group <i>for the "combined occurrence":</i> - point estimate and two-sided 95% CI for relative risk - point estimate and two-sided 95% CI for the hazard ratio from the Andersen-Gill model for recurrent events	SAF
FAES_HT1_S	F	Treatment-emergent AEs of special interest “hypotension” in study AC-065A302 - Graphical display of the relative risk <i>Two graphs: one sorted by relative risk more frequent in selexipag (for PTs included in the AE of special interest) and one sorted by relative risk more frequent in placebo</i>	SAF
TAES_HT2_S	T	Treatment-emergent AEs of special interest “hypotension” in study AC-065A302 by time period with/without confounding factor(s) <i>Footnote: confounding factors include treatment with PDE5-Is, ERAs, Riociguat, anti-hypertensive drugs, diuretics or a medical history of “hypotension” or low blood pressure at baseline (defined a SBP < 90 mmHg or DBP < 50 mmHg)</i>	SAF
TAES_HTD_S	T	Treatment-emergent AEs of special interest “hypotension” in study AC-065A302 leading to discontinuation of study drug in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TAES_HTI_S	T	Treatment-emergent serious AEs of special interest in study AC-065A302: “hypotension” sorted by PT incidence in the selexipag group	SAF
TAES_HTF_S	T	Treatment-emergent AEs of special interest “hypotension” in study AC-065A302 with fatal outcome in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TAES_HT3_S	T	Treatment-emergent AEs of special interest “hypotension” in study AC-065A302 by time period with/without confounding medications(s) <i>Footnote: confounding factors include treatment with PDE5-Is, ERAs, Riociguat, anti-hypertensive drugs or diuretics</i>	SAF
LAES_HT1_S	L	Listing of concomitant medication ongoing at the time of the AE of special interest “hypotension” in study AC-065A302 <i>includes PT and ATC as well as start/end dates for AE of special interest "hypotension" and concomitant medication(s)</i>	SAF

Unique ID	Display	Title <i>additional description</i>	Analysis set
TAEIPRA_S	T	Treatment-emergent prostacyclin like associated AEs in study AC-065A302 – separately for Titration Period and Maintenance Period	SAF, patients treated in both Titration and Maintenance periods
TAES_AHG1_S	T	Treatment-emergent AEs denoting "anemia or hemoglobin decrease" in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TAES_AHG1_D_S	T	Treatment-emergent AEs denoting "anemia or hemoglobin decrease" in study AC-065A302 leading to discontinuation of study drug in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TAES_AHG1_S_S	T	Treatment-emergent serious AEs denoting "anemia or hemoglobin decrease" in study AC-065A302 sorted by PT incidence in the selexipag group	SAF
TAES_AHG2_S	T	Treatment-emergent AEs denoting "anemia or hemoglobin decrease" in study AC-065A302 by time period with/without confounding medications(s) <i>Footnote: confounding factors include treatment with ERAs or antithrombotic agents</i>	SAF
TAES_AHG3_S	T	Treatment-emergent AEs denoting "anemia or hemoglobin decrease" in study AC-065A302 by time period with/without ERA(s)	SAF
TAES_AHG4_S	T	Treatment-emergent AEs denoting "anemia or hemoglobin decrease" in study AC-065A302 by time period with/without antitrombotic agents	SAF
TAES_AHG5_S	T	Treatment-emergent AEs denoting "anemia or hemoglobin decrease" in study AC-065A302 for patients with/without medical history denoting "anemia or hemoglobin decrease".	SAF
Adverse events listings			
LAES_F	L	Adverse events	FAS
LSAE_F	L	Serious adverse events	FAS
LAESWC_F	L	Adverse events ongoing at study discontinuation in patients who withdrew consent	FAS
LDEATH_F	L	Adverse event with fatal outcome	FAS
LAESD1_F	L	Adverse event leading to discontinuation of study drug in study AC-065A302	FAS
LAESD2_F	L	Adverse event leading to discontinuation of study drug in study AC-065A303	FAS
LAESINT_F	L	Adverse event of special interest in study AC-065A302	FAS
LSAES1_F	L	Serious adverse events occurring before study drug start date in study AC-065A302	FAS

Unique ID	Display	Title <i>additional description</i>	Analysis set
LSAES1A_F	L	Serious adverse events occurring after 7 from last study drug intake in AC-065A302 and before study drug start date in study AC-065A303 (if applicable)	FAS
LSAES2_F	L	Serious adverse events occurring after 3 from last study drug intake in AC-065A303	FAS

13.2 ECG data (SAP section 23.2)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TECG_S	T	ECG variables at scheduled visits in study AC-065A302 <i>Up to Month 36</i>	SAF
TECG12_S	T	ECG variables at Month 12 in study AC-065A302 <i>pre-dose and post-dose assessments</i>	SAF
TECGCH_S	T	Absolute change in ECG variables from Baseline to scheduled visits in study AC-065A302 <i>Up to Month 36</i>	SAF
TECGCH12_S	T	Absolute change in ECG variables from pre-dose to post-dose at Month 12 in study AC-065A302	SAF
TECGAB_S	T	Treatment-emergent qualitative ECG abnormalities (sorted by incidence) in study AC-065A302	SAF
TQTC_S	T	Treatment-emergent QTcF prolongation in study AC-065A302	SAF
TQTCSH_S	T	Shift table for change from baseline to highest treatment-emergent QTcF prolongation in study AC-065A302	SAF
FECG_S	F	Absolute change in ECG variables from Baseline to scheduled visits in study AC-065A302- boxplot <i>Up to Month 36</i>	SAF
FECG1_S	F	ECG variables at scheduled visits in study AC-065A302- boxplot <i>Up to Month 36</i>	SAF
LECG_F	L	ECG data in study AC-065A302	FAS
LQTC_F	L	ECG data for patients with at least one treatment emergent QTcF prolongation	FAS

13.3 Laboratory data (SAP section 23.3)

Unique ID	Display	Title <i>additional description</i>	Analysis set
THEM2_S	T	Hematology tests at regular visits in study AC-065A302 <i>Overall and separately by factors, as per table 11 of the SAP includes EOS visit, up to Month 36</i>	SAF
FHEM2_S	F	Hematology tests at regular visits in study AC-065A302 - boxplot <i>Overall and separately by factors, as per table 11 of the SAP, up to Month 36</i>	SAF
THEM3_S	T	Hematology tests at regular visits in study AC-065A303 (<i>Overall and separately by factors, as per table 11 of the SAP includes EOS visit, up to Month 36</i>	SAF subset treated in study AC-065A303
THEMAB2_S	T	Hematology tests: treatment-emergent (marked/alert) abnormalities in study AC-065A302 <i>(except white blood cell differentials)</i>	SAF
THEMAB3_S	T	Hematology tests: treatment-emergent (marked/alert) abnormalities in study AC-065A303 <i>(except white blood cell differentials)</i>	SAF subset treated in study AC-065A303
THEMABI_S	T	Hematology tests: treatment-emergent (marked/alert) abnormalities in studies AC-065A302 and AC-065A303 - intra-patient comparison <i>(except white blood cell differentials)</i>	SAF subset treated in study AC-065A303
THEMCH2_S	T	Hematology tests: absolute change from Baseline at regular visits in study AC-065A302 <i>Overall includes EOS visit, up to Month 36</i>	SAF
FHEMCH2_S	F	Hematology tests: absolute change from Baseline at regular visits in study AC-065A302 - boxplot <i>Overall up to Month 36</i>	SAF
THEMCH3_S	T	Hematology tests: absolute change from baseline at regular visits in study AC-065A303 <i>Overall includes EOS visit, up to Month 36</i>	SAF subset treated in study A303
TCHE2_S	T	Chemistry tests at regular visits in study AC-065A302 <i>Overall and separately by factors, as per table 11 of the SAP includes EOS visit, up to Month 36</i>	SAF
FCHE2_S	F	Chemistry tests at regular visits in study AC-065A302 - boxplot <i>Overall and separately by factors, as per table 11 of the SAP, up to Month 36</i>	SAF

Unique ID	Display	Title <i>additional description</i>	Analysis set
TCHE3_S	T	Chemistry tests at regular visits in study AC-065A303 <i>Overall and separately by factors, as per table 11 of the SAP includes EOS visit, up to Month 36</i>	SAF subset treated in study A303
TCHEAB2_S	T	Chemistry tests: treatment-emergent (marked / alert) abnormalities in study AC-065A302	SAF
TCHEAB3_S	T	Chemistry tests: treatment-emergent (marked / alert) abnormalities in study AC-065A303	SAF subset treated in study A303
TCHEABI_S	T	Chemistry tests: treatment-emergent (marked / alert) abnormalities in studies AC-065A302 and AC-065A303 - intra-patient comparison	SAF subset treated in study A303
TCHECH2_S	T	Chemistry tests: absolute change from baseline at regular visits in study AC-065A302 <i>Overall includes EOS visit, up to Month 36</i>	SAF
FCHECH2_S	F	Chemistry tests: absolute change from baseline at regular visits in study AC-065A302 boxplot <i>Overall up to Month 36</i>	SAF
TCHECH3_S	T	Chemistry tests: absolute change from baseline at regular visits in study AC-065A303 <i>Overall includes EOS visit, up to Month 36</i>	SAF subset treated in study A303
TTHY_S	T	Thyroid markers at regular visits in study AC-065A302 <i>separately by factors, as per table 11 of the SAP includes EOS visit, up to Month 36</i>	SAF
FTHY_S	F	Thyroid markers at regular visits in study AC-065A302-boxplot <i>Overall and separately by factors, as per table 11 of the SAP, up to Month 36</i>	SAF
TTHYCH_S	T	Thyroid markers: absolute change from Baseline at regular visits in study AC-065A302 <i>Overall , up to Month 36</i>	SAF
FTHYCH_S	F	Thyroid markers: absolute change from Baseline at regular visits in study AC-065A302 boxplot <i>Overall up to Month 36</i>	SAF
TBTM_S	T	Bone turnover markers at regular visits in study AC-065A302 <i>Overall and separately by factors, as per table 11 of the SAP includes EOS visit, up to Month 36</i>	SAF

Unique ID	Display	Title <i>additional description</i>	Analysis set
FBTM_S	F	Bone turnover markers at regular visits in study AC-065A302 - boxplot <i>Overall and separately by factors, as per table 11 of the SAP, up to Month 36</i>	SAF
TBTMCH_S	T	Bone turnover markers: absolute change from Baseline at regular visits in study AC-065A302 <i>Overall includes EOS visit, up to Month 36</i>	SAF
FBTMCH_S	F	Bone turnover markers: absolute change from Baseline at regular visits in study AC-065A302 - boxplot <i>Overall up to Month 36</i>	SAF
FEDISH2_S	F	eDISH plot of treatment-emergent peak values for total bilirubin versus peak values for ALT in study AC-065A302	SAF
FEDISH3_S	F	eDISH plot of treatment-emergent peak values for total bilirubin versus peak values for ALT in study AC-065A303	SAF subset treated in study A303
LHYS_F	L	Possible Hy's Law cases	FAS
LLAB_F	L	Laboratory test results	FAS
LABN_F	L	Marked laboratory abnormalities	FAS
LHGBMA_F	L	Patients with treatment-emergent marked laboratory abnormalities LL or LLL in hemoglobin in study AC-065A302 <i>(listing includes the hemoglobin values at baseline and at screening, the lowest and the last hemoglobin value observed during the treatment-emergent period in AC-065A302, and whether patient had concomitant (at Baseline or during treatment) "Antithrombotics agents" (as defined by the SDG), ERAs, had a medical history denoting "anemia or hemoglobin decrease" (as defined in section 6.3 of the SAP) and had a treatment-emergent AE denoting "anemia or hemoglobin decrease" (as defined in section 14.2.8 of the SAP) in AC-065A302)</i>	FAS
LWBCMA_F	L	Patients with treatment-emergent marked laboratory abnormalities LL or LLL in leukocytes in study AC-065A302 <i>(listing includes includes the leukocytes values at baseline and at screening, the lowest and the last leukocytes value observed during the treatment-emergent period in AC-065A302, and whether patient had concomitant (at Baseline or during treatment) "Immunosuppressant" (Therapeutic class))</i>	FAS

13.4 Vital signs and body weight (SAP Section 23.4)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TVIS2_S	T	Vital signs and body weight at scheduled visits in study AC-065A302 <i>includes EOS visit, up to Month 36</i>	SAF
FVIS2_S	F	Vital signs and body weight at scheduled visits in study AC-065A302 - boxplot <i>up to Month 36</i>	SAF
TVIS3_S	T	Vital signs and body weight at scheduled visits in study AC-065A303 <i>includes EOS visit, up to Month 36</i>	SAF subset treated in study A303
TVISCH2_S	T	Vital signs and body weight: absolute change from Baseline to scheduled visits in study AC-065A302 <i>includes EOS visit, up to Month 36</i>	SAF
FVISCH2_S	F	Vital signs and body weight: absolute change from Baseline to scheduled visits in study AC-065A302 - boxplot <i>up to Month 36</i>	SAF
TVISCH3_S	T	Vital signs and body weight: absolute change from baseline to scheduled visits in study AC-065A303 <i>includes EOS visit, up to Month 36</i>	SAF subset treated in study A303
TBP2_S	T	Treatment-emergent low blood pressure in study AC-065A302	SAF
TBP3_S	T	Treatment-emergent low blood pressure in study AC-065A303	SAF subset treated in study A303
TBPI_S	T	Treatment-emergent low blood pressure in studies AC-065A302 and AC-065A303 - intra-patient comparison	SAF subset treated in study A303
LVIS_F	L	Vital signs and body weight	FAS

13.5 Ophthalmologic sub-study (SAP Section 23.6)

Unique ID	Display	Title <i>additional description</i>	Analysis set
TOPHF_O	T	Baseline and post-baseline findings in study AC-065A302	OAS
TOPHF1_O	T	Change from baseline findings in study AC-065A302	OAS
TOPHF2_O	T	Change from baseline in qualitative severity of retinal arterial tortuosity	OAS
LOPH_O	L	Ophthalmological assessments	FAS