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Study design and rationale for the Olpasiran trials of Cardiovascular Events And lipoproteiN(a) reduction-DOSE finding study (OCEAN(a)-DOSE)☆

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Abstract

Background Data support lipoprotein(a) (Lp[Lp(a)]) being a risk factor for atherosclerotic cardiovascular disease (ASCVD). Olpasiran is a small interfering RNA molecule that markedly reduces Lp(a) production in hepatocytes.

Study Design The Olpasiran trials of Cardiovascular Events And lipoproteiN(a) reduction-DOSE finding study is a multicenter, randomized, double-blind, placebo-controlled dose-finding study in 281 subjects with established ASCVD and Lp(a) > 150 nmol/L. Patients were randomly allocated to one of 4 active subcutaneous doses of olpasiran (10 mg q12 weeks, 75 mg q12 weeks, 225 mg q 12 weeks, or 225 mg q24 weeks) or matched placebo. The primary objective is to evaluate the effects of olpasiran dosed every 12 weeks compared with placebo on the percent change in Lp(a) from baseline at 36 weeks. Enrollment is now complete and follow-up is ongoing.

Conclusions OCEAN(a)-DOSE trial is assessing the Lp(a)-lowering efficacy and safety of olpasiran. These data will be used to determine optimal dosing and design for a cardiovascular outcomes trial. (Am Heart J 2022;251:61–69.)

Background

Despite advances in preventing and managing cardiovascular (CV) disease, substantial residual risk remains. The identification of additional treatable risk factors is therefore critical to further reduce CV morbidity and mortality. Apolipoprotein(a) [apo(a)] was first identified from the low-density lipoprotein (LDL) fraction of human serum by geneticist Kare Berg in 1963.[1] A little more than a decade later; he described the relationship between Lipoprotein(a) [Lp(a)] and the risk of coronary heart disease (CHD). (Lp(a)) consists of an apolipoprotein B (apoB)-containing-containing lipoprotein that is similar to LDL but bound to apo(a) via the apoB-100 protein. The plasma concentration of Lp(a) is primarily genetically determined (estimated at 70-≥90%),[2] and its expression is controlled by the apo(a) gene (*LPA*).[3] Numerous epidemiologic studies over the past 3 decades have reported an association between higher plasma Lp(a) concentrations and risk of atherosclerotic CV disease (ASCVD), particularly CHD.[4-7] Moreover, an emerging number of genome-wide association and Mendelian randomization studies support a causal role for Lp(a) in atherogenesis and progression of calcific valvular aortic stenosis.[8-12]

Although Lp(a) is a presumed causal risk factor for ASCVD,[13] no pharmacological therapies are available that provide a large reduction of Lp(a) in plasma. Olpasiran is a small interfering (siRNA) molecule that interrupts the expression of the *LPA* gene by degrading the messenger RNA (mRNA) that encodes the apo(a) protein, thereby preventing its translation and subsequent assembly of the Lp(a) particle in the hepatocyte (Figure 1). Olpasiran is targeted to the liver via an N-acetylgalactosamine moiety that binds to the asialoglycoprotein receptor on the hepatic cell surface. Once inside the hepatocyte, the antisense strand of olpasiran is loaded into an RNA-induced silencing complex (RISC) while the sense strand is degraded. The loaded RISC then binds to *apo(a)* mRNA

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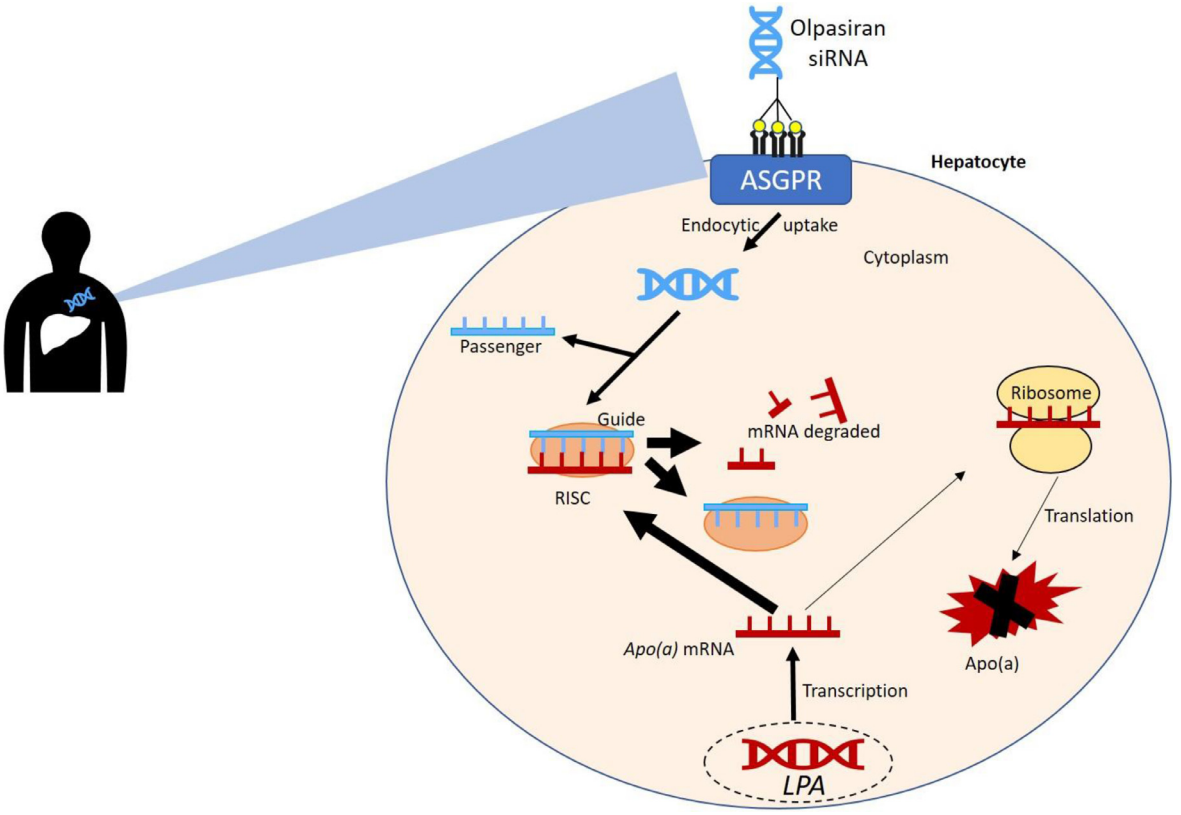
Figure 1



Mechanism of action for olpasiran. Olpasiran is a small-interfering RNA that prevents assembly of Lp(a) by preventing translation of the apo(a) protein in the hepatocyte, thereby leading to a marked reduction in Lp(a) in the circulation. Apo(a), apolipoprotein(a); ASGPR, asialoglycoprotein receptor; GalNAc, N-Acetylgalactosamine; LPA, lipoprotein(A); mRNA, messenger RNA; RISC, RNA-induced silencing complex; RNA, ribonucleic acid; siRNA, small interfering RNA.

via the complementary antisense strand sequence of olpasiran and degrades it through RISC-associated argonaute proteins. Following its cleavage, the RISC complex dissociates and can target additional mRNA for silencing, thereby allowing for a prolonged duration of effect.[14] Efficacy data collected from transgenic mice and cynomolgus monkeys suggest that a sustained reduction of >80% in plasma Lp(a) can be achieved with olpasiran. In phase 1 testing in adults with elevated Lp(a), a single dose of olpasiran reduced Lp(a) in a dose-dependent manner with doses of ≥9 mg reducing Lp(a) by >90% with a duration of effect that persisted for 3 to 6 months. To date, there are no identified safety concerns for olpasiran.[15]

This manuscript describes the rationale and design of the phase 2 OCEAN(a)-DOSE trial [Olpasiran trials of Cardiovascular Events And LipoproteiN(a) reduction-DOSE Finding Study] to test the efficacy, safety and tolerability of olpasiran.

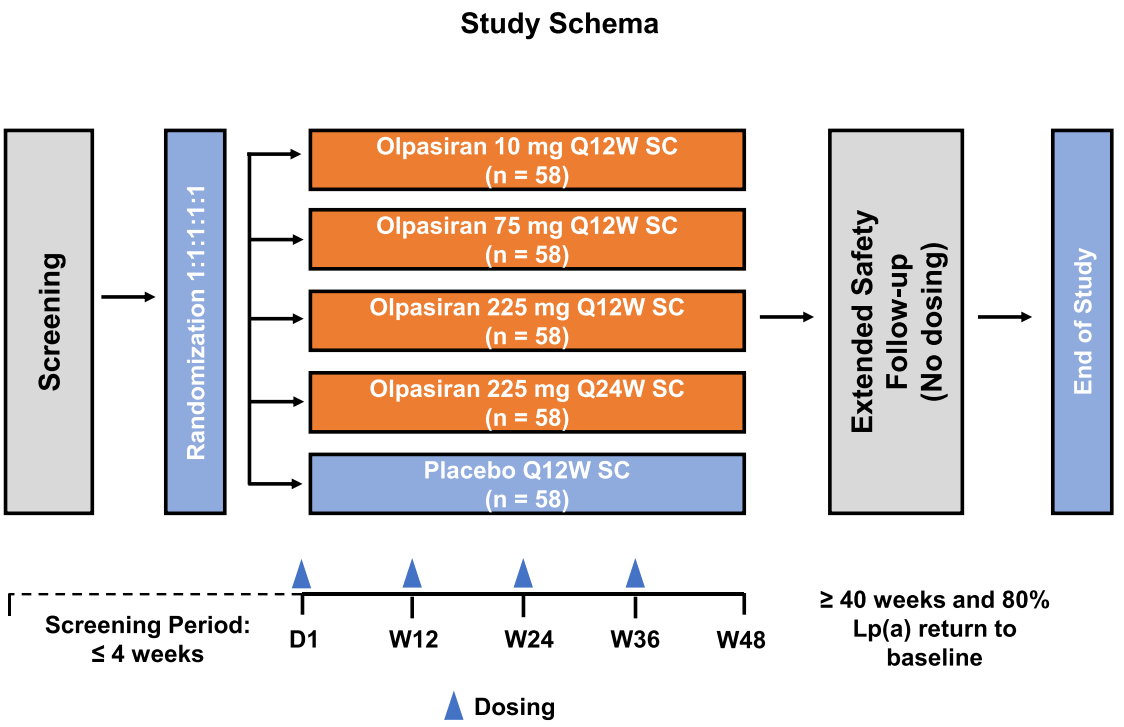
Study design

The OCEAN(a)-DOSE trial is an ongoing multicenter, randomized, double-blind, placebo-controlled dose finding study of olpasiran in individuals with established ASCVD and elevated Lp(a) (Figure 2). The treatment phase duration is 48 weeks, after which time participants are being followed for an extended safety follow-up without further dosing with the investigational product for ≥ 40 weeks, and until Lp(a) returns to 80% of baseline, whichever is later. The primary objective is to evaluate olpasiran administered subcutaneously every 12 weeks compared with placebo on percent change from baseline in Lp(a) after 36 weeks of treatment.

Study population

The OCEAN(a) DOSE trial enrolled 281 subjects from July 10, 2020, until April 26, 2021. Study participants were between the ages of 18-80 years and had an Lp(a)

Figure 2



Study schema for OCEAN(a)-DOSE- trial. OCEAN(a)-DOSE, Olpasiran trials of cardiovascular events and lipoprotein(a) reduction-DOSE finding study.

concentration of >150 nmol/L (corresponding to ~60 mg/dL) at the time of screening. Patients were required to have a history of ASCVD, including established CHD, peripheral arterial disease or atherosclerotic cerebrovascular disease. Patients were excluded from participation if they had severe renal dysfunction (estimated glomerular filtration rate < 30 mL/min/1.73 m^2), history or clinical evidence of active liver disease, New York Heart Association class III or IV heart failure or known left ventricular ejection fraction < 30%, history of major adverse CV events in the prior 6 months or planned coronary or carotid revascularization. A complete listing of the inclusion and exclusion criteria is provided in Tables I and II.

Treatment protocol and study assessments

Patients were randomly allocated in a 1:1:1:1:1 ratio to one of four active doses of olpasiran (10 mg every 12 weeks, 75 mg every 12 weeks, 225 mg every 12 weeks or 225 mg every 24 weeks) or matched placebo every 12 weeks administered as a subcutaneous injection (Figure 2). Randomized allocation of study treatment was performed via a central computerized system with stratification of randomization by screening Lp(a) concentration (≤ vs >200 nmol/L) and geographic region (Japan vs rest of world).

The study treatment period is 48 weeks, with doses administered at day 1, week 12, week 24, and week 36. After week 48, there is an extended safety follow-up without further dosing with investigational product for at least 40 weeks and until Lp(a) returns to ≥80% of baseline, whichever is later. Patients on lipid-lowering therapy were asked to be on a stable dose for ≥4 weeks before and during screening. Changes in lipid-lowering therapy were not to be made after randomization unless medically indicated. All other therapy for the management of the patient's ASCVD is at the discretion of the responsible medical staff and is to be commensurate with contemporary local treatment guidelines and practices.

Following a screening visit, patients are to return for in-person study visits at day 1, day 2, week 4, then every 4 weeks during the treatment phase. At each study visit, adverse events, concomitant medications, fasting lipids

Table I. Inclusion criteria

- Subject has provided informed consent prior to initiation of any study specific activities/procedures.
- Age 18-80 y
- Fasting Lp(a) > 150 nmol/L during screening by central laboratory (approximately corresponds to > 60 mg/dL [note that molarity determines eligibility])
  - Atherosclerotic cardiovascular disease based on 1 of the following:
  - History of coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)
  - Diagnosis of coronary artery disease with or without prior myocardial infarction
  - Diagnosis of atherosclerotic cerebrovascular disease
  - Diagnosis of peripheral arterial disease
- For subjects receiving lipid-lowering therapy (not required to participate in this study), lipid-lowering therapy, including statin dose, must remain stable per local guidelines for ≥ 4 wk prior to and during screening

and Lp(a) concentration are assessed. A complete assessment, including a physical exam and study drug administration, are to occur every 12 weeks. Any subject who discontinues the study drug is asked to continue to attend scheduled in-person visits whenever possible.

Study endpoints

The trial's primary endpoint is percent change from baseline in Lp(a) at week 36 in the intention-to-treat study population, including all randomized subjects who received at least 1 dose of investigational product regardless of whether they stopped study drug during follow-up. No imputations will be made for missing values. The trial's secondary endpoints are percent change from baseline in Lp(a) at week 48, percent change from baseline in low-density lipoprotein cholesterol (LDL-C) at week 36 and week 48, and percent change from baseline in apoB at week 36 and 48. Pharmacokinetic parameters will also be evaluated. A complete list of pre-specified endpoints is included in Table III.

An independent clinical endpoint committee (CEC) chaired by the TIMI Study Group is adjudicating causes of death and all investigator-reported cases of cardiac ischemic events, cerebrovascular events, revascularization (coronary and noncoronary) and acute limb ischemia. All CEC members are blinded to treatment assignment.

Statistical considerations

Sample size

Assuming a standard deviation of 30%, a 5% drop-out rate, and with Bonferroni multiplicity adjustment to control family-wise type 1 error rate at 0.05, a minimum of 48 subjects per arm is required to provide at least 90% power to detect a treatment difference of 25% between active and placebo arm in the percent change of Lp(a) from baseline. Assuming a 5% rate of withdrawal of consent, at least 48 subjects per arm provides a 95% confidence of detecting 1 case of an adverse event at an incidence of 1 in 60.

Study organization

The OCEAN(a)-DOSE trial is a collaborative effort between the TIMI Study Group (an Academic Research Organization based at Brigham and Women's Hospital and Harvard Medical School) and Amgen, the trial Sponsor. A joint leadership team consisting of members of the TIMI Study Group and Amgen oversees all aspects of the trial (see Appendix). The trial is being conducted at 35 investigative sites in 7 countries across North America (USA, Canada), Europe (Iceland, Netherlands, Denmark), Australia and Japan. Amgen is providing site management and monitoring services worldwide.

The trial database is stored at Amgen and is protected by internal firewalls. The randomization code is stored separately from the trial database and the study team. The TIMI Study Group will receive an independent copy of the complete database once the study is finished.

The authors are solely responsible for the drafting and editing the paper and its final contents. The trial adheres fully to the ethical principles of the Declaration of Helsinki, the specifications of the International Conference on Harmonization, and Good Clinical Practice, including approval by an independent Ethics Committee or Institutional Review Board and the requirement for each subject's written informed consent. The trial registration number at www.clinicaltrials.gov is NCT04270760. Qualified researchers may request data from Amgen clinical studies: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparencypractices/clinical-trial-data-sharing-request/.

Baseline characteristics

The enrollment of 281 participants in the study is now complete. In aggregate, the mean (SD) age of the population is 61.9 (9.5) years and 32.0% are female. Overall, 91.1% of subjects have coronary artery disease, 20.3% have cerebrovascular disease and 10.7% have peripheral arterial disease (PAD). In addition, 17.8% have a history of type 2 diabetes mellitus and 17.4% have familial hypercholesterolemia. At baseline, 88.3% were on statin therapy (including 61.2% on high-intensity statin therapy), 52.0% were on ezetimibe, and 23.1% on a monoclonal antibody proprotein convertase subtilisin/kexin

Table II. Exclusion criteria

Subjects are excluded from the study if any of the following criteria apply:

Disease related

- Severe renal dysfunction, defined as an estimated glomerular filtration rate < 30 mL/min/1.73 m^2 during screening
- History or clinical evidence of active liver disease or hepatic dysfunction, defined as aspartate aminotransferase or alanine aminotransferase > 3 × upper limit of normal (ULN), or total bilirubin > 2 × ULN during screening
- Inherited or other bleeding disorders
- Recent major cardiovascular event (myocardial infarction, unstable angina, PCI, CABG, or stroke) within 6 mo prior to day 1
- Planned cardiac surgery, PCI or carotid stenting, or planned major noncardiac surgery during the study period

Other medical conditions

- Malignancy (except nonmelanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 5 y prior to day 1
- Moderate to severe heart failure (New York Heart Association Functional Classification III or IV at day 1) or last known left ventricular ejection fraction < 30%
- Uncontrolled cardiac arrhythmia defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia that are not controlled by medications, in the past 3 mo prior to day 1
- Uncontrolled hypertension at day 1, defined as an average systolic blood pressure of ≥ 160 mmHg or an average diastolic blood pressure of ≥ 100 mmHg at rest after a minimum of 3 measurements
- Fasting triglycerides ≥ 400 mg/dL (4.5 mmol/L) during screening
- Type 1 diabetes or poorly controlled (HbA1c ≥ 8.5%) type 2 diabetes mellitus as determined by central laboratory at screening
- Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction, or a chronic disease or infection (eg, HIV) that is not currently stable and appropriately managed in the judgment of the investigator at day 1

Prior/concomitant therapy

- Previously received treatment with antisense oligonucleotides, siRNA therapies (eg, inclisiran), or any experimental therapy targeting Lp(a)
- Currently undergoing lipid apheresis or < 3 mo since last apheresis treatment at day 1
- Subject has taken a cholesterol ester transfer protein inhibitor (eg, anacetrapib, dalcetrapib, evacetrapib) or lomitapide in the last 12 mo prior to day 1
- Currently receiving, or < 3 mo at day 1 since receiving > 200 mg/d Niacin

Prior/concurrent clinical study experience

- Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.
- Use of any herbal medicines, vitamins or supplements known to affect lipid metabolism (eg, fish oil > 4000 mg/d, red yeast rice extract), within 30 d prior to day 1

Other exclusions

- Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 90 d after the last dose of investigational product.
- Female subjects of childbearing potential unwilling to use a highly effective method of contraception during treatment and for an additional 90 d after the last dose of investigational product.
- Female subjects of childbearing potential with a positive serum pregnancy test assessed at screening or positive urine pregnancy test on day 1.
- Subject has known sensitivity to any of the products to be administered during dosing.
- Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge.
- History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; HbA1c, hemoglobin A1c; HIV, human immunodeficiency virus; Lp(a), lipoprotein(a); siRNA, small interfering RNA.

Table III. Study endpoints

Primary	• Percent change in Lp(a) from baseline at week 36
Secondary	• Percentage change from baseline in: - Lp(a) at week 48 - LDL-C at week 36 and week 48 - ApoB at week 36 and week 48
Safety	• Treatment emergent adverse events • Clinically significant safety laboratory values and vital signs at each scheduled visit
Select exploratory	• Adjudicated events • Change from baseline in PROMIS Global Health measures at each scheduled visit • Change from baseline at week 48 in: - high sensitivity (hs) C-reactive protein (CRP) - hs-interleukin 6 (IL-6) • Percent change from baseline at each scheduled visit, except weeks 36 and 48, in: - Lp(a) - LDL-C - ApoB • Achievement at each scheduled visit of the following: - Lp(a) < 125 nmol/L - Lp(a) < 100 nmol/L - Lp(a) < 75 nmol/L - Lp(a) < 50 nmol/L For the olpasiran SC Q24W group: • Percent change from baseline at each scheduled visit, in: - Lp(a) - LDL-C - ApoB • Achievement at each scheduled visit of the following: - Lp(a) < 125 nmol/L - Lp(a) < 100 nmol/L - Lp(a) < 75 nmol/L - Lp(a) < 50 nmol/L

type 9 (PCSK9) inhibitor. In addition, 61.2% of participants were on high-intensity (dose expected to reduce LDL-C by greater or equal to 50%) lipid-lowering therapy. The median baseline Lp(a) concentration is 260.3 nmol/L (interquartile range 198.1-352.4) and median LDL-C is 67.5 mg/dL (interquartile range 50.5-83.5). Baseline characteristics are displayed in Table IV.

Discussion

Despite progress in its management and prevention, there remains significant morbidity and mortality from CV disease, including those patients with well-managed LDL-C. Although several avenues of investigation support the role of Lp(a) as a causal risk factor in AS,[2] clinical trials of therapeutics that directly target Lp(a) and lower its concentration are required to definitively demonstrate the mechanistic link between Lp(a) and atherogenesis.

To that end, the physiological function of Lp(a) is unclear, but Lp(a) has been shown to have a pathogenic role in atherosclerosis and thrombosis formation.[16] Lp(a) is a major carrier of oxidized phospholipids in human plasma, which are believed to promote atherogenesis by crossing the vascular endothelium and promoting atherosclerosis through chemotaxis and propagation of inflammation.[17,18] Lp(a) also shares a high degree of homology with plasminogen and may modulate the coagulation cascade through its interaction with plasminogen and the fibrinolytic system.[19] In the setting of plaque rupture, Lp(a) is hypothesized to exert prothrombotic effects by inhibiting plasminogen activation.

Although several organizations now support the measurement of Lp(a) in adults, Lp(a) currently remains infrequently measured in routine clinical practice. Notably, the 2018 American Heart Association/American College of Cardiology/Multisociety guideline on the management of blood cholesterol has now identified an elevated Lp(a) as a "risk-enhancer" that may influence decisions regarding lipid-lowering therapy.[20] However, there remains disagreement about the threshold that should be used to define an abnormal level.[10-13] In part, this stems from substantial differences in assays, variability in baseline distribution by race and ancestry, and differences in other patient characteristics and disease states that may influence Lp(a) distribution in the population.[2] In a large national databank, the proportion of patients with an "elevated" Lp(a) $\geq$ 150 nmol/L ($\sim$70 mg/dL) was higher in those with established ASCVD (20.3%) than in those without (12.2%).[14] Pooled patient data from many observational studies suggest that the relationship between Lp(a) and CV risk is broadly continuous and log-linear, therefore disputing the concept that there is a clear threshold

Table IV. Baseline characteristics of the study population in aggregate

	Randomized population ($N = 281$)
Age, mean (SD)	61.9 (9.5)
Women	90 (32.0%)
White race	248 (88.3%)
BMI (kg/m^2), mean (SD)	28.1 (4.6)
Cardiovascular risk factors	
Family history of premature coronary heart disease	100 (35.6%)
Familial hypercholesterolemia	49 (17.4%)
Type 2 diabetes	50 (17.8%)
Hypertension	184 (65.5%)
Current smoker	17 (6.0%)
History of CV disease	
Coronary artery disease	256 (91.1%)
Cerebrovascular disease	57 (20.3%)
Peripheral arterial disease	30 (10.7%)
Aortic stenosis	9 (3.2%)
Lipid-lowering therapy	
Statin	248 (88.3%)
High-intensity statin*	172 (61.2%)
Ezetimibe	148 (52.7%)
PCSK9 monoclonal antibody	65 (23.1%)
Baseline laboratory values, median (IQR)	
Total cholesterol (mg/dL)	141.5 (120, 165.5)
LDL-C (mg/dL)†	67.5 (50.5, 83.5)
Triglycerides (mg/dL)	96.5 (73, 124.5)
High-density lipoprotein cholesterol (HDL-C) (mg/dL)	52.5 (42.5, 64.0)
Lp(a) (nmol/L)	260.3 (198.1, 352.4)

CV, cardiovascular; LDL-C, low-density lipoprotein-C; Lp(a), lipoprotein(a).

*Dose expected to reduce LDL-C by greater or equal to 50%. Data cutoff date of August 16, 2021.

†When the calculated LDL-C is <40 mg/dL or triglycerides are >400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C and calculated very low-density lipoprotein cholesterol (VLDL-C) will be replaced with ultracentrifugation VLDL-C from the same blood sample, if available.

in patient risk above a specific value.[15] Early consensus documents defined a threshold above 50 mg/dl as an "elevated" level reflecting the 80th percentile in a Northern European population.[3] Several assays exist to measure Lp(a) using either its mass or molar concentration. Due to a highly variable number of LPA kringle-IV type 2 repeats on apo(a),[16] direct conversion between mass and molar concentration is not possible. The variable number of kringle-IV repeats can also lead mass assays to underestimate or overestimate the "true" atherogenic Lp(a) concentration in the presence of small or large isoforms, respectively. As such, assays that quantify the molar concentration are increasingly endorsed since these adequately account for isoform size.[10,11,17] Although efforts are being made to harmonize assays,[18] results of published studies have sometimes yielded heterogeneous results.[2]

Although Lp(a) is a presumed CV risk factor, it remains unknown how large of a reduction in Lp(a) may be required to translate into a meaningful clinical benefit. Estimates derived from Mendelian randomization studies suggest that an absolute reduction in Lp(a) of 60 to 100 mg/dL (~125-215 nmol/L) may be required to derive comparable clinical benefit to a 1 mM (38.67 mg/dL) reduction in LDL-C.[19,20] To date, no pharmacological therapies are available that lead to a large decrease in Lp(a) concentration. Available treatments also have variable effects on other lipid subfractions, so the direct benefit of Lp(a) lowering remains unclear. Lipoprotein apheresis can lead to a marked decrease of Lp(a), in addition to its effects on lowering of LDL-C, but Lp(a) levels return to baseline within a couple of weeks, thereby necessitating frequent use of this more invasive procedure. Small clinical trial data suggest that lowering Lp(a) by lipoprotein apheresis may reduce the risk of CV events, but more extensive studies would be needed to confirm these observations.[21,22] Niacin has been shown to reduce Lp(a) by up to 30% to 40% in a dose-dependent manner, but niacin also influences other lipids in tandem and has not been proven to have clinical benefit.[23] Despite their effects on LDL-C lowering, statins do not reduce Lp(a) concentration and may raise its concentration.[2] The PCSK9 monoclonal antibody inhibitors have been shown to reduce Lp(a) by a median of 25% to 30%. Although some studies suggest that at least some of their benefit may be mediated by Lp(a) lowering, firm conclusions cannot be drawn due to their substantial effects on LDL-C lowering.[24-26,5]

Aside from olpasiran, other drugs that directly target Lp(a) are in clinical development.[27] Pelacarsen is an an-

tisense oligonucleotide that binds to its target complementary RNA sequence via base pairing, thereby leading to degradation of the *apo(a)* mRNA strand and reduced Lp(a) production. Pelacarsen lowers Lp(a) by 80% at a dose of 20 mg subcutaneously administered once per week or 72% at a dose of 60 mg once monthly in patients with established CV disease and a screening Lp(a) $\geq$ 60 mg/dL ($\sim$150 nM).[28,7] The efficacy and safety of pelacarsen is now being evaluated in phase 3 testing (NCT04023552) in patients with a prior history of myocardial infarction (MI), ischemic stroke or symptomatic PAD and who have an Lp(a) concentration $\geq$ 70 mg/dL. A dose of 80 mg administered once monthly subcutaneously is being evaluated, which was not studied in phase 2 testing.

In contrast to an antisense oligonucleotide, siRNA therapeutics are double-stranded RNA molecules that dissociate once inside the cell, and the antisense strand is inserted into the RISC. The antisense strand binds to its homologous target mRNA sequence leading to its degradation. Its stability bound to the RISC complex, an advantage of siRNA is its prolonged pharmacodynamic effect as its action against target mRNA strands can be repeated, thereby requiring less frequent dosing. Aside from olpasiran, another siRNA that interferes with Lp(a) production, SLN-360, has now completed phase 1 testing (NCT04606602).[29]

In summary, the current phase 2 dose-ranging study of olpasiran builds upon the phase 1 experience that demonstrated that a single dose of olpasiran reduced Lp(a) by > 90% at doses $\geq$ 9 mg with effects persisting on average 3 to 6 months. The prolonged mechanism of action for olpasiran is related to its incorporation into the RISC inside the hepatocyte, which increases its stability and allows for the cleavage of repeated *apo(a)* mRNA molecules through hybridization to the olpasiran antisense strand. Based on phase 1 data, olpasiran appears to be a promising avenue toward achieving both pronounced and prolonged effects toward the systemic lowering of Lp(a). As such, the OCEAN(a)-DOSE trial will provide critical new insights into the pharmacokinetic and pharmacodynamic properties of olpasiran, as well as key insights into possible dosing for phase 3 testing.

J. Antonio G. López, Beat Knusel, Huei Wang, You Wu, Helina Kassahun are employees of and shareholders of Amgen.

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Conflict of interest

Dr. Sabatine: Research grant support through Brigham and Women's Hospital from: Amgen; Anthos Therapeutics; AstraZeneca; Daiichi-Sankyo; Eisai; Intarcia; Ionis; Medicines Company; MedImmune; Merck; Novartis; Pfizer. Consulting for: Althera; Amgen; Anthos Therapeutics; AstraZeneca; Beren Therapeutics; Bristol-Myers Squibb; DalCor; Dr. Reddy's Laboratories; Fibrogen; Intarcia; Merck; Moderna; Novo Nordisk; Silence Therapeutics. Additionally, Dr. Sabatine is a member of the TIMI Study Group, which has also received institutional research grant support through Brigham and Women's Hospital from: Abbott, ARCA Biopharma, Inc., Janssen Research and Development, LLC, Siemens Healthcare Diagnostics, Inc., Softcell Medical Limited, Regeneron, Roche, and Zora Biosciences.

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Appendix

TIMI Study Group Study Team Members

- Marc S Sabatine MD MPH; Study Chair
- Michelle L O'Donoghue MD MPH; Principal Investigator
- M. Polly Fish; Director of Operations
- Steven Ahern; Project Manager
- Stephen Wiviott MD; Chair, Clinical Events Committee
- Cheryl Lowe RN; Director, Clinical Events Committee
- Elaine Gershman; Senior Project Manager, Clinical Events Committee
- Baris Gencer MD; TIMI fellow (former)

Amgen Study Team Members

- Mei Di MD MS Global Safety Senior Medical Scientist, Research and Development: Study Conduct
- Natasha Hambley BSc, Director Global Clinical Program Management; Research and Development; Study Conduct
- Helina Kassahun MD, Executive Director and Global Development Lead, Global Development; Study Design
- Beat Knusel PhD, Clinical Research Director, Global Development; Study Design
- Kathryn Jones BA, Senior Manager Global Clinical Program Management, Research and Development; Study Conduct
- J. Antonio G. López MD, Clinical Research Medical Director, Global Development; Study Conduct
- Huei Wang PhD, Director Biostatistics, Research and Development; Study Design
- You Wu PhD, Biostatistics Senior Manager, Research and Development; Study Conduct

Event Types Undergoing Adjudication by an Independent Clinical Events Committee

Cardiovascular CEC

- All death events
- Cardiac ischemic events (myocardial infarction, hospitalization for unstable angina)
- Arterial revascularizations (coronary and noncoronary)
- Hospitalization for heart failure
- Major adverse limb events (acute limb ischemia, major amputation)

Neurology CEC

- Cerebrovascular events (stroke, transient ischemic attack [TIA])

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