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Pooled Safety Results Through 1 Year of 2 Phase III Trials of Guselkumab in Patients With Psoriatic Arthritis

Proton Rahman[1], Christopher T. Ritchlin[2], Philip S. Helliwell[3], Wolf-Henning Boehncke[4], Philip J. Mease[5], Alice B. Gottlieb[6], Shelly Kafka[7], Alexa P. Kollmeier[8], Elizabeth C. Hsia[9], Xie L. Xu[8], May Shawi[10], Shihong Sheng[11], Prasheen Agarwal[11], Bei Zhou[11], Paraneedharan Ramachandran[11], Yanli Zhuang[11], and Iain B. McInnes[12]

ABSTRACT. ***Objective.*** Evaluate the safety of guselkumab (monoclonal antibody targeting interleukin [IL]-23p19) in patients with psoriatic arthritis (PsA) through 1 year (1Y) of the phase III DISCOVER-1 and DISCOVER-2 trials.

Methods. Patients with active PsA (n = 1120; biologic-naïve except 118 patients treated with tumor necrosis factor inhibitors in DISCOVER-1) were randomized to subcutaneous guselkumab 100 mg every 4 weeks (Q4W) or at Week 0, Week 4, then every 8 weeks (Q8W); or placebo. At Week 24, patients in the placebo group switched to guselkumab 100 mg Q4W. Treatment continued through 1Y and 2 years for DISCOVER-1 and DISCOVER-2, respectively. In this pooled analysis, patients with ≥ 1 adverse event (AE) through 1Y were standardized for 100 patient-years [100 PYs] of follow-up.

Results. Through Week 24, adverse events (AEs) were consistent between patients treated with placebo and guselkumab (Q4W + Q8W). AEs were 142.8/100 PYs and 150.6/100 PYs, serious AEs were 7.1/100 PYs and 4.4/100 PYs, and AEs leading to study agent discontinuation were 4.1/100 PYs and 3.8/100 PYs, respectively. Through 1Y in patients treated with guselkumab, no uveitis, active tuberculosis, opportunistic infections, or inflammatory bowel disease were observed, and low rates of malignancy and major adverse cardiovascular (CV) events were observed. Injection-site reactions occurred in 1.7%, and antibodies to guselkumab in 4.5% of patients treated with guselkumab through 1Y; the vast majority of antibodies to guselkumab were nonneutralizing. Serum hepatic transaminase elevations (more common with Q4W than Q8W dosing) and decreased neutrophil counts were generally mild, transient, and did not require treatment discontinuation, with minimal change from Week 24 to 1Y.

Conclusion. Guselkumab 100 mg Q4W and Q8W were well tolerated in patients with PsA, with no new safety concerns through 1Y of the phase III DISCOVER trials. Guselkumab safety through 1Y in patients with PsA is consistent with that established in patients with psoriasis who were treated with guselkumab. [ClinicalTrials.gov: NCT03162796 and NCT03158285]

Key Indexing Terms: adverse effects, biologics, psoriatic arthritis, safety, tolerability

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[1]P. Rahman, MD, Memorial University of Newfoundland, St. John's, Newfoundland, Canada; [2]C.T. Ritchlin, MD, MPH, University of Rochester, Rochester, New York, USA; [3]P.S. Helliwell, PhD, University of Leeds, Leeds, UK; [4]W.H. Boehncke, MD, Geneva University Hospitals, Geneva, Switzerland; [5]P.J. Mease, MD, Swedish Medical Center/Providence St Joseph Health and University of Washington School of Medicine, Seattle, Washington, USA; [6]A.B. Gottlieb, MD, PhD, Icahn Medical School at Mount Sinai, New York, New York, USA; [7]S. Kafka, MD, Janssen Scientific Affairs, Horsham, Pennsylvania, USA; [8]A.P. Kollmeier, MD, X.L. Xu, PhD, Janssen Research & Development, San Diego, California, USA; [9]E.C. Hsia, MD, Janssen Research & Development, Spring House, Pennsylvania, USA, and University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA; [10]M. Shawi, PhD, Immunology Global Medical Affairs, Janssen Pharmaceutical Companies of Johnson & Johnson, Horsham, Pennsylvania, USA; [11]S. Sheng, PhD, P. Agarwal, PhD, B. Zhou, PhD, P. Ramachandran, MD, MPH, Y. Zhuang, PhD, Janssen Research & Development, Spring House, Pennsylvania, USA; [12]I.B. McInnes, MD, PhD, University of Glasgow, Glasgow, UK.

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Guselkumab is a novel human monoclonal antibody that binds to the p19 subunit of interleukin (IL)-23 with high affinity. Guselkumab prevents binding of IL-23 to the IL-23 receptor and inhibits release of proinflammatory cytokines.[1,2] IL-23 has been implicated in the pathogenesis of autoimmune diseases, including psoriasis (PsO), psoriatic arthritis (PsA), and inflammatory bowel disease (IBD).[3,4,5] IL-23 is an important driver of Th17 cell differentiation and survival and an upstream regulator of IL-17A, a central proinflammatory effector cytokine in PsO pathogenesis.[5,6,7] Guselkumab is the first IL-23p19-subunit inhibitor approved to treat moderate-to-severe PsO and active PsA.[1,8,9,10,11]

PsA is a seronegative, chronic, inflammatory arthropathy that occurs in approximately 30% of patients with PsO.[12] IL-23 can also induce IL-22 (a cytokine important in enthesitis and excess bone formation) and elicit joint damage, in part by IL-17A and tumor necrosis factor (TNF) induction. Two phase III studies, DISCOVER-1 and DISCOVER-2, demonstrated that guselkumab is efficacious in treating the signs and symptoms of active PsA and inhibiting structural damage progression,[9,10] with sustained response rates and low levels of radiographic progression seen through 1 year.[13,14]

As most patients with PsA who receive biologics will require continual therapy to maintain control of their disease, understanding the safety of long-term treatment with cumulative exposure, particularly for a new mechanism of action for the disease, is critical. The treatment of rheumatologic conditions with biologic agents may be associated with long-term adverse effects, most commonly serious infections, particularly with anti-TNF agents.[15,16] Other less common serious adverse effects are associated with biologic therapies and may be specific to a select target.[17]

The long-term safety results through 4 years of 2 pivotal phase III studies, VOYAGE-1 and VOYAGE-2, of guselkumab 100 mg every 8 weeks (Q8W) in patients with PsO have been published.[8,11,18,19,20] Safety results from DISCOVER-1 and DISCOVER-2 have been reported separately through the placebo-controlled periods[9,10] and also through 1 year.[13,14] Here, we report the pooled safety results of guselkumab 100 mg every 4 weeks (Q4W) and Q8W in patients with PsA, including time-adjusted incidences of adverse events (AEs) and AEs of special interest, as well as clinical laboratory results, through 1 year of DISCOVER-1 and DISCOVER-2.

METHODS

Study design. DISCOVER-1[9] and DISCOVER-2[10] were randomized, double-blind, phase III trials of guselkumab in patients with active PsA who had inadequate responses to standard therapies (Figure 1). Patients were randomized 1:1:1 to receive subcutaneous (SC) guselkumab 100 mg at Week 0, then Q4W; guselkumab 100 mg at Weeks 0, 4, then Q8W; or placebo Q4W (Figure 1). Stable doses of nonsteroidal antiinflammatory drugs (NSAIDs), oral corticosteroids, and selected nonbiologic disease-modifying antirheumatic drugs (DMARDs) were permitted. At Week 16, early escape to initiation or increase of allowed concomitant PsA medications was available to patients with < 5% improvement in both tender and swollen joint counts. At Week 24, patients receiving placebo crossed over to receive guselkumab 100 mg Q4W. In DISCOVER-1, treatment continued through Week 48 with a final follow-up safety visit at Week 60; treatment continued through Week 100 of DISCOVER-2, with a final follow-up safety visit at Week 112 (data through 1 yr are included in these analyses). Upon premature discontinuation of treatment, patients had a final safety visit approximately 12 weeks after the last study agent administration.

The trials were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practices. Protocols were approved by ethics committees at each site (Sterling institutional review board approval numbers [US sites]: 5959C and 5910C), and all patients provided written informed consent. The trials are registered at ClinicalTrials.gov: NCT03162796 and NCT03158285.

Patients. Detailed inclusion and exclusion criteria for DISCOVER-1 and DISCOVER-2 have been reported.[9,10] Briefly, enrolled patients were adults with active PsA despite previous therapy with DMARDs, apremilast, and/or NSAIDs. Patients had been diagnosed with PsA for at least 6 months and met the Classification Criteria for Psoriatic Arthritis. In DISCOVER-1, patients were required to have ≥ 3 swollen joints, ≥ 3 tender joints, and C-reactive protein (CRP) ≥ 0.3 mg/dL. In DISCOVER-2, patients were required to have ≥ 5 swollen joints, ≥ 5 tender joints, and CRP ≥ 0.6 mg/dL. Patients were biologic-naïve with the exception of approximately 30% of patients in DISCOVER-1 who had previously received 1 or 2 anti-TNF agents. Exclusion criteria included other inflammatory diseases such as rheumatoid arthritis; specified infections including active tuberculosis (TB); most malignancies within 5 years of screening; and any prior use of Janus kinase inhibitors, or phototherapy or systemic immunosuppressants within 4 weeks of study agent administration.

Safety assessments. Tolerability of guselkumab (through Week 60 in DISCOVER-1 and Week 52 of DISCOVER-2) was evaluated based on reports of AEs, clinical laboratory investigations (abnormalities classified by National Cancer Institute Common Terminology Criteria for AEs [NCI-CTCAE] grade), physical examinations, vital signs, concomitant medication use, and screening for TB. The AEs of interest included malignancies, active TB, opportunistic infections, major adverse CV events (MACE, defined as CV death, nonfatal myocardial infarction, or nonfatal stroke), clinical laboratory abnormalities, and injection-site reactions. Serum samples were collected at regular intervals through Week 52 of both studies and were analyzed for the presence of antibodies to guselkumab using a validated immunoassay method.

Statistical methods. The descriptive summaries of posthoc safety data reported pooled data across DISCOVER-1 and DISCOVER-2. All patients who received at least 1 dose of study medication were included in the safety assessments, with AEs summarized by actual treatment received. As exposure time to guselkumab varied in different treatment groups as a result of the placebo crossover study design, the number of patients with AEs are reported on the basis of 100 patient-years (PYs) of follow-up. The numbers of AEs through 1 year were also standardized per 100 PYs.

RESULTS

Patients. A total of 1123 patients were enrolled in DISCOVER-1 and DISCOVER-2; of these, 3 patients discontinued before receiving any study treatment. Thus, the pooled population of patients from the 2 studies included 1120 treated patients: 381

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Address correspondence to Dr. P. Rahman, 154 LeMarchant Road, St. Clare's Mercy Hospital, St. John's, NL A1C 5B8, Canada. Email: prahman@mun.ca.

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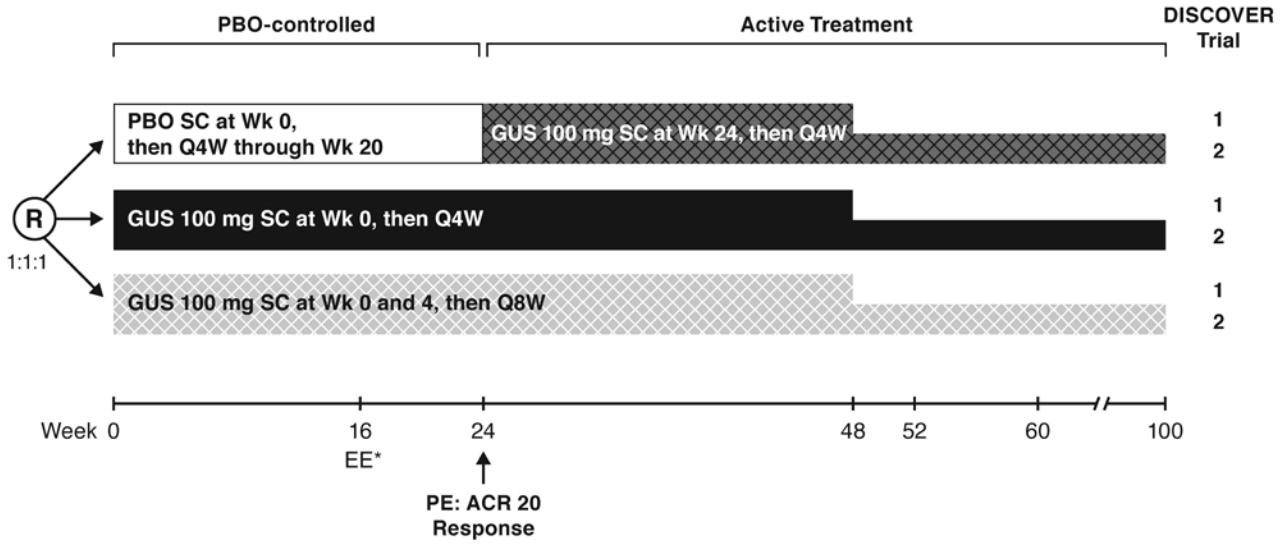

Figure 1. DISCOVER 1 and DISCOVER 2 Study Designs. * Patients were eligible to initiate/increase background medications if they had < 5% improvement from baseline in both tender and swollen joint counts at Week 16. ACR20: American College of Rheumatology criteria 20% improvement; EE: early escape; GUS: guselkumab; PBO: placebo; PE: primary endpoint; Q4W: every 4 weeks; Q8W: every 8 weeks; R: randomization; SC: subcutaneous; Wk: week.

from DISCOVER-1[9] and 739 from DISCOVER-2.[10] Patients had an approximate mean age of 47 years and mean PsA duration of 6 years at study outset. Consistent with each study's entrance criteria, patients entered the trials with active PsA (Table 1). Baseline characteristics were generally similar between the studies[9,10] with the exception of patients in DISCOVER-1 having a longer disease duration, and patients in the DISCOVER-2 trial having higher CRP and numerically higher numbers of swollen and tender joints and greater extent or severity of skin disease assessed using the Psoriasis Area Severity Index.

Detailed patient disposition through 1 year has been reported.[9,10,13,14] Through Week 24, 3.8% (14/373) of patients in the guselkumab Q4W group, 3.2% (12/375) in the guselkumab Q8W group, and 5.4% (20/372) in the placebo group

Table 1. Pooled baseline characteristics from the DISCOVER-1 and DISCOVER-2 trials.

	Placebo	GUS 100 mg Q4W	GUS 100 mg Q8W	GUS Combined[a]
Patients, n	372	373	375	748
Age, yrs	47.2 (11.5)	46.5 (11.5)	46.2 (11.9)	46.3 (11.7)
Sex, male, n (%)	178 (48)	208 (56)	197 (53)	405 (54)
BMI, kg/m^2	29.2 (6.1)	29.4 (5.8)	29.1 (6.3)	29.2 (6.0)
PsA disease duration, yrs	6.3 (6.4)	5.9 (6.1)	5.6 (5.7)	5.7 (5.9)
Swollen joint count (0–66)	11.5 (7.0)	11.4 (7.5)	11.4 (7.7)	11.4 (7.6)
Tender joint count (0–68)	21.0 (13.5)	20.8 (13.6)	19.9 (12.8)	20.4 (13.2)
CRP, mg/dL, median (IQR)	0.9 (0.5–2.4)	0.9 (0.5–1.9)	1.0 (0.5–2.3)	0.9 (0.5–2.2)
HAQ-DI	1.3 (0.6)	1.2 (0.6)	1.3 (0.6)	1.2 (0.6)
BSA affected by PsO, %	15.4 (18.9)	17.1 (19.7)	15.7 (20.0)	16.4 (19.9)
PASI (0–72)	8.8 (9.5)	10.4 (11.2)	9.2 (11.1)	9.8 (11.1)
IGA, VAS (0–10 cm)				
≥ 2, n (%)	301 (81)	311 (83)	295 (79)	606 (81)
Previous anti-TNF use[b], n (%)	39 (10)	38 (10)	41 (11)	79 (11)
Medication use at baseline, n (%)				
MTX	227 (61)	218 (58)	209 (56)	427 (57)
Oral corticosteroids	69 (19)	62 (17)	68 (18)	130 (17)
NSAIDs	245 (66)	240 (64)	236 (63)	476 (64)

Results presented are mean (SD), unless otherwise indicated. [a] Combined GUS Q4W and Q8W treatment groups. [b] All patients with previous anti-TNF use were in the DISCOVER-1 trial. BSA: body surface area; CRP: C-reactive protein; GUS: guselkumab; HAQ-DI: Health Assessment Questionnaire–Disability Index; IGA: investigator global assessment of psoriasis (cleared = 0, minimal = 1, mild = 2, moderate = 3, severe = 4); MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drug; PASI: Psoriasis Area And Severity Index; PsA: psoriatic arthritis; PsO: psoriasis; Q4W: every 4 weeks; Q8W: every 8 weeks; TNF: tumor necrosis factor; VAS: visual analog scale.

discontinued the study agent. AEs leading to study agent discontinuation occurred in 1.9%, 1.3%, and 1.6% of patients, respectively, in the guselkumab Q4W, guselkumab Q8W, and placebo groups.

Among patients continuing treatment at Week 24, 2.2% (8/359) of patients in the guselkumab Q4W group, 3.7% (13/363) in the guselkumab Q8W group, and 4.8% (17/352) of patients who crossed over from placebo to guselkumab Q4W at Week 24 discontinued the study agent through 1 year. AEs leading to study agent discontinuation occurred in 0.3%, 0.6%, and 1.7% patients, respectively, in the guselkumab Q4W, guselkumab Q8W, and placebo to guselkumab crossover groups.

AEs during the placebo-controlled period through Week 24. Through Week 24, the numbers of patients with ≥ 1 AE per 100 PYs (95% CI) were 153.7 (132.3–177.7) for guselkumab 100 mg Q4W, 147.7 (127.0–170.7) for guselkumab 100 mg Q8W, and 142.8 (122.5–165.6) for placebo. The numbers of patients experiencing serious AEs (SAEs; 4.4 and 7.1/100 PYs), AEs leading to discontinuation of study agent (3.8 and 4.1/100 PYs), infections (49.5 and 49.9/100 PYs), and serious infections (1.2 and 1.7/100 PYs) were similar in patients treated with the combined guselkumab and placebo regimens, respectively (Table 2). Results were consistent when assessing the numbers of events/100 PYs (Supplementary Table 1, available with the online version of this article). The most common infections were nasopharyngitis (combined guselkumab Q4W and Q8W groups, n = 45 [6.0%]; placebo, n = 17 [4.6%]), upper respiratory tract infection (n = 38 [5.1%]; placebo, n = 17 [4.6%]), and bronchitis (n = 17 [2.3%]; placebo, n = 4 [1.1%]).

AEs reported with guselkumab through 1 year. At 1 year, time-adjusted incidences of AEs and SAEs remained stable in both guselkumab treatment groups. Among patients treated with placebo who crossed over to guselkumab 100 mg Q4W at Week 24, time-adjusted incidences of AEs were generally comparable to those of patients originally randomized to either dose regimen of guselkumab and treated for 1 year (Table 2). Infections were the most common class of AEs through 1 year, with nasopharyngitis, upper respiratory infections, and bronchitis occurring in 8.4%, 7.1%, and 3.4% of the 1100 patients treated with guselkumab, respectively, including those who crossed over from placebo at Week 24. As through Week 24, results through 1 year were consistent when assessing the numbers of events/100 PYs (Supplementary Table 1, available with the online version of this article).

AEs of interest. Two patients treated with placebo died through Week 24 (cardiac failure, pneumonia)[9,10]; no patients treated with guselkumab died through 1 year.[13,14] Serious infections were

Table 2. Number of patients with AEs per 100 PYs.

	Week 0 to Week 24				1 Year[a]			
	GUS 100 mg Placebo[b]	GUS 100 mg Q4W	GUS 100 mg Q8W	Placebo to Combined[c]	GUS 100 mg GUS Q4W[d]	GUS 100 mg Q4W	GUS 100 mg Q8W	Combined[c]
Patients, n	372	373	375	748	352	373	375	1100
Average duration of follow-up, weeks	24.2	24.1	24.1	24.1	30.3	53.8	53.5	46.2
Median PYs of follow-up	0.5	0.5	0.5	0.5	0.5	1.0	1.0	1.0
Patients with ≥ 1 AE								
Total PYs of follow-up	123	119	123	242	155	209	212	576
Patients/100 PYs (95% CI)	142.8 (122.5–165.6)	153.7 (132.3–177.7)	147.7 (127.0–170.7)	150.6 (135.6–166.9)	91.5 (77.1–107.9)	115.4 (101.3–130.9)	114.3 (100.3–129.6)	108.6 (100.2–117.4)
SAEs								
Total PYs of follow-up	170	170	171	341	200	377	374	951
Patients/100 PYs (95% CI)	7.1 (3.7–12.3)	4.7 (2.0–9.3)	4.1 (1.6–8.4)	4.4 (2.5–7.3)	7.0 (3.8–11.8)	4.0 (2.2–6.6)	4.8 (2.9–7.6)	4.9 (3.6–6.6)
Patients with ≥ 1 infection								
Total PYs of follow-up	154	153	157	309	182	306	308	796
Patients/100 PYs (95% CI)	49.9 (39.4–62.4)	52.4 (41.6–65.2)	46.6 (36.5–58.6)	49.5 (41.9–57.9)	39.1 (30.5–49.3)	37.9 (31.3–45.4)	40.6 (33.8–48.4)	39.2 (35.0–43.8)
Patients with ≥ 1 serious infection								
Total PYs of follow-up	172	172	173	345	202	383	382	968
Patients/100 PYs (95% CI)	1.7 (0.4–5.1)	1.8 (0.4–5.1)	0.6 (0.0–3.2)	1.2 (0.3–3.0)	2.5 (0.8–5.8)	0.8 (0.2–2.3)	1.3 (0.4–3.1)	1.3 (0.7–2.3)
Discontinuations due to AEs								
Total PYs of follow-up	171	170	172	342	203	382	382	967
Patients/100 PYs (95% CI)	4.1 (1.6–8.4)	4.7 (2.0–9.3)	2.9 (1.0–6.8)	3.8 (2.0–6.5)	3.5 (1.4–7.1)	2.6 (1.3–4.8)	2.1 (0.9–4.1)	2.6 (1.7–3.8)

[a] Through Week 60 for DISCOVER-1 and Week 52 for DISCOVER-2. [b] For patients in the PBO group who crossed over to GUS Q4W, only data prior to first administration of GUS are included in this group. [c] Combined patients treated with GUS Q4W and Q8W (including patients crossed over from PBO for 1-year results). [d] For patients in the PBO group who crossed over to GUS Q4W, only data on and after first administration of GUS were included in this group. AE: adverse event; GUS: guselkumab; PBO: placebo; PY: patient-year; Q4W: every 4 weeks; Q8W: every 8 weeks; SAE: serious adverse event.

uncommon across treatment groups (Table 2), with no cases of active TB or opportunistic infections reported through 1 year. One case of nonserious oral thrush was reported in a patient treated with guselkumab with a history of asthma and concomitant inhaled corticosteroid use.[14] One case each of IBD and iridocyclitis occurred in a patient treated with placebo.

Malignancies occurred in 4 patients and have been previously reported in detail. One patient receiving placebo was diagnosed with renal cell carcinoma,[10] and another patient who crossed over from placebo to guselkumab 100 mg Q4W at Week 24 had squamous cell skin carcinoma and malignant melanoma (both reported at Week 36).[14] Among patients receiving guselkumab 100 mg Q8W, one was diagnosed with multiple myeloma 15 days after the first guselkumab injection,[9] and another (with a preexisting skin lesion of pigmented macule) was diagnosed with melanoma in situ.[13] No increase in malignancy was observed from Week 24 to 1 year (Table 3). The MACE events that occurred in 2 patients prior to Week 24 (i.e., the aforementioned event of cardiac failure in a patient receiving placebo[9] and ischemic stroke in 1 patient receiving guselkumab 100 mg Q4W[10]) were also previously reported. The latter patient had hypertension, hyperlipidemia, and diabetes at baseline.

The incidence of injection-site reactions through Week 24 was low in both guselkumab treatment groups (1.1% and 1.3% in the Q4W and Q8W groups, respectively; Table 3). Through 1 year, the rate of injection-site reactions remained low (2.4% and 1.6% in the Q4W and Q8W groups, respectively). Most injection-site reactions were mild, and the most common reaction was erythema. Two moderate injection-site reactions occurred in patients receiving guselkumab 100 mg Q4W, and both led to discontinuation of study treatment.[13]

Laboratory investigations. Results of laboratory investigations within the individual studies have been previously reported through 1 year.[9,10,13,14] During the placebo-controlled periods of the DISCOVER trials, elevations in serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) appeared to be more common with guselkumab than placebo. Pooled incidences of hepatic aminotransferase elevations through 1 year of treatment with either regimen of guselkumab were generally consistent with those through Week 24, considering the additional duration of follow-up (Table 4). The majority of these elevations were NCI-CTCAE Grade 1. No patients treated with guselkumab experienced Grade 4 ALT or AST elevations through 1 year. Whereas Grade 2 and 3 elevations were more common in the Q4W group compared with the Q8W group, most were transient and did not result in discontinuation (see exceptions in the following section), and none was associated with increases in bilirubin > 2 times the upper limit of normal. Confounding factors were present in the majority of patients with Grade 2 or 3 elevations in hepatic transaminases, such as an underlying medical condition, obesity, concomitant alcohol use, latent TB treatment, or concomitant treatment with DMARDs or NSAIDs that are associated with liver injury.

Through 1 year, Grade 1 or higher elevated ALT levels were slightly more common in pooled patients with baseline use of methotrexate (MTX; guselkumab Q4W: 38.7%, guselkumab Q8W: 39.0%), compared with pooled patients without baseline use of MTX (Q4W: 35.9%, Q8W: 32.5%; Table 4). Grade 1 or higher increased AST levels were also slightly more common in patients with baseline use of MTX (Q4W: 30.1%; Q8W: 27.1%) compared with patients without use of baseline MTX (Q4W: 25.6%; Q8W: 25.3%).

Four patients receiving guselkumab 100 mg Q4W discontinued treatment as a result of hepatobiliary AEs or elevated transaminases.[13] Three of the patients were also receiving isoniazid; 2 had drug (isoniazid)-induced liver injury, and the third patient had elevated transaminase levels with active alcohol use, with hepatology evaluation revealing chronic pancreatitis, chronic cholecystitis, and fatty liver disease. Isoniazid was discontinued in these patients, and transaminase levels declined in all 3. The patient who was not receiving isoniazid had acute hepatitis B; of note, the patient's family history included hepatitis B–positive status of the spouse.

Table 3. Adverse events of interest.

	Week 0 to Week 24				1 Year[a]			
	Placebo[b]	GUS 100 mg Q4W	GUS 100 mg Q8W	GUS 100 mg Combined[c]	Placebo to GUS Q4W[d]	GUS 100 mg Q4W	GUS 100 mg Q8W	GUS 100 mg Combined[c]
Patients, n	372	373	375	748	352	373	375	1100
Death	2 (0.5)	0	0	0	0	0	0	0
Malignancy	1 (0.3)	0	2 (0.5)	2 (0.3)	1 (0.3)	0	2 (0.5)	3 (0.3)
MACE	1 (0.3)	1 (0.3)	0	1 (0.1)	0	1 (0.3)	0	1 (0.1)
OIs	0	0	0	0	0	0	0	0
TB	0	0	0	0	0	0	0	0
IBD	1 (0.3)	0	0	0	0	0	0	0
Injection-site reaction	1 (0.3)	4 (1.1)	5 (1.3)	9 (1.2)	4 (1.1)	9 (2.4)	6 (1.6)	19 (1.7)

Data presented as n (%) unless otherwise indicated. [a] Through Week 60 for DISCOVER-1 and Week 52 for DISCOVER-2. [b] For patients in the PBO group who crossed over to GUS Q4W, only data prior to first administration of GUS are included in this group. [c] Combined patients treated with GUS Q4W and Q8W (including patients who crossed over from PBO for 1-year results). [d] For patients in the PBO group who crossed over to GUS Q4W, only data on and after first administration of GUS were included in this group. GUS: guselkumab; IBD: inflammatory bowel disease; MACE: major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke); OI: opportunistic infection; PBO: placebo; Q4W: every 4 weeks; Q8W: every 8 weeks; TB: tuberculosis.

Table 4. Proportions of patients with clinical laboratory abnormalities according to NCI-CTCAE grade.

	Week 0 to Week 24				1 Year[a]				
	PBO[b]	GUS 100 mg Q4W	GUS 100 mg Q8W	GUS 100 mg Combined[c]	PBO to GUS Q4W[d]	GUS 100 mg Q4W	GUS 100 mg Q8W	GUS 100 mg Q4W Combined[c]	GUS 100 mg Combined[c]
ALT increased[f]									
n	370	371	373	744	351	371	373	722	1095
Grade 1	111 (30.0)	130 (35.0)	105 (28.2)	235 (31.6)	90 (25.6)	153 (41.2)	125 (33.5)	243 (33.7)	368 (33.6)
Grade 2	5 (1.4)	10 (2.7)	4 (1.1)	14 (1.9)	7 (2.0)	17 (4.6)	6 (1.6)	24 (3.3)	30 (2.7)
Grade 3	2 (0.5)	4 (1.1)	3 (0.8)	7 (0.9)	0	4 (1.1)	4 (1.1)	4 (0.6)	8 (0.7)
Grade 4	1 (0.3)	0	0	0	0	0	0	0	0
ALT increased, baseline MTX[f]									
n	225	216	207	423	213	216	207	429	636
Grade 1	78 (34.7)	82 (38.0)	66 (31.9)	148 (35.0)	57 (26.8)	92 (42.6)	74 (35.7)	149 (34.7)	223 (35.1)
Grade 2	5 (2.2)	7 (3.2)	3 (1.4)	10 (2.4)	5 (2.3)	10 (4.6)	4 (1.9)	15 (3.5)	19 (3.0)
Grade 3	1 (0.4)	2 (0.9)	2 (1.0)	4 (0.9)	0	2 (0.9)	3 (1.4)	2 (0.5)	5 (0.8)
Grade 4	0	0	0	0	0	0	0	0	0
ALT increased, no baseline MTX[f]									
n	145	155	166	321	138	155	166	293	459
Grade 1	33 (22.8)	48 (31.0)	39 (23.5)	87 (27.1)	33 (23.9)	61 (39.4)	51 (30.7)	94 (32.1)	145 (31.6)
Grade 2	0	3 (1.9)	1 (0.6)	4 (1.2)	2 (1.4)	7 (4.5)	2 (1.2)	9 (3.1)	11 (2.4)
Grade 3	1 (0.7)	2 (1.3)	1 (0.6)	3 (0.9)	0	2 (1.3)	1 (0.6)	2 (0.7)	3 (0.7)
Grade 4	1 (0.7)	0	0	0	0	0	0	0	0
AST increased[f]									
n	370	371	373	744	351	371	373	722	1095
Grade 1	74 (20.0)	80 (21.6)	70 (18.8)	150 (20.2)	74 (21.1)	103 (27.8)	85 (22.8)	177 (24.5)	262 (23.9)
Grade 2	2 (0.5)	6 (1.6)	6 (1.6)	12 (1.6)	6 (1.7)	14 (3.8)	11 (2.9)	20 (2.8)	31 (2.8)
Grade 3	4 (1.1)	6 (1.6)	2 (0.5)	8 (1.1)	1 (0.3)	6 (1.6)	2 (0.5)	7 (1.0)	9 (0.8)
Grade 4	0	0	0	0	0	0	0	0	0
AST increased, baseline MTX[f]									
n	225	216	207	423	213	216	207	429	636
Grade 1	54 (24.0)	56 (25.9)	41 (19.8)	97 (22.9)	46 (21.6)	68 (31.5)	50 (24.2)	114 (26.6)	164 (25.8)
Grade 2	1 (0.4)	4 (1.9)	3 (1.4)	7 (1.7)	4 (1.9)	9 (4.2)	5 (2.4)	13 (3.0)	18 (2.8)
Grade 3	1 (0.4)	2 (0.9)	1 (0.5)	3 (0.7)	0	2 (0.9)	1 (0.5)	2 (0.5)	3 (0.5)
Grade 4	0	0	0	0	0	0	0	0	0
AST increased, no baseline MTX[f]									
n	145	155	166	321	138	155	166	293	459
Grade 1	20 (13.8)	24 (15.5)	29 (17.5)	53 (16.5)	28 (20.3)	35 (22.6)	35 (21.1)	63 (21.5)	98 (21.4)
Grade 2	1 (0.7)	2(1.3)	3 (1.8)	5 (1.6)	2 (1.4)	5 (3.2)	6 (3.6)	7 (2.4)	13 (2.8)
Grade 3	3 (2.1)	4 (2.6)	1 (0.6)	5 (1.6)	1 (0.7)	4 (2.6)	1 (0.6)	5 (1.7)	6 (1.3)
Grade 4	0	0	0	0	0	0	0	0	0
Neutrophil count decreased[f]									
n	370	371	373	744	351	371	373	722	1095
Grade 1	12 (3.2)	22 (5.9)	21 (5.6)	43 (5.8)	15 (4.3)	29 (7.8)	36 (9.7)	44 (6.1)	80 (7.3)
Grade 2	3 (0.8)	6 (1.6)	6 (1.6)	12 (1.6)	3 (0.9)	12 (3.2)	10 (2.7)	15 (2.1)	25 (2.3)
Grade 3	1 (0.3)	0	0	0	2 (0.6)	1 (0.3)	2 (0.5)	3 (0.4)	5 (0.5)
Grade 4	0	1 (0.3)	0	1 (0.1)	0	1 (0.3)	0	1 (0.1)	1 (0.1)

Data presented as n (%) unless otherwise indicated. [a] Through week 60 for DISCOVER-1 and week 52 for DISCOVER-2. [b] For patients in the PBO group who crossed over to GUS Q4W, only data prior to the first administration of GUS are included in this group. [c] Combined patients treated with GUS Q4W and Q8W (including patients who crossed over from PBO for 1-year results). [d] For patients in the PBO group who crossed over to GUS Q4W, only data on and after first administration of GUS were included in this group. [e] Combined patients treated with GUS Q4W (including patients who crossed over from PBO). [f] NCI-CTCAE grades. ALT: alanine aminotransferase; AST: aspartate aminotransferase; GUS: guselkumab; MTX: methotrexate; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PBO: placebo; Q4W: every 4 weeks; Q8W: every 8 weeks.

Decreased neutrophil counts were slightly more common in patients treated with guselkumab than those treated with placebo, with no increase seen from Week 24 to 1 year (Table 4). Most cases were NCI-CTCAE Grade 1; those Grade 2 or greater were reversible and did not result in treatment discontinuation. The decreased neutrophil counts were not associated with infection, except for 1 patient who experienced mild nasopharyngitis that lasted 5 days after a decreased neutrophil count of Grade 2 was observed.

Immunogenicity. Antibodies to guselkumab were detected in the serum of 4.5% (49/1094) of pooled patients treated with guselkumab with appropriate samples through Week 52 of the

Table 5. Proportions of GUS-treated patients with antibodies to GUS.

	Through Week 24			Through Week 52			
	GUS 100 mg Q4W	GUS 100 mg Q8W	GUS 100 mg Combined[a]	PBO to GUS Q4W[b]	GUS 100 mg Q4W	GUS 100 mg Q8W	GUS 100 mg Combined[a]
n/N (%)[c]	9/371 (2.4)	6/373 (1.6)	15/744 (2.0)	14/350 (4.0)	17/371 (4.6)	18/373 (4.8)	49/1094 (4.5)

[a] Included all patients who received at least 1 dose of GUS. [b] Included patients in the PBO group who crossed over to GUS Q4W at Week 24. [c] Presence of antibodies to GUS in serum samples of GUS-treated patients was assessed using a validated immunoassay method. Denominator is patients with appropriate samples. GUS: guselkumab; PBO: placebo; Q4W: every 4 weeks; Q8W: every 8 weeks.

DISCOVER trials, with similar incidence between guselkumab dosing regimens (Table 5). No association was noted between the development of antibodies to guselkumab and the occurrence of injection-site reactions, albeit the number of positive patients was small. Through Week 52, 10.2% (5/49) of patients with aantibodies to guselkumab (0.5% of all patients treated with guselkumab) had neutralizing antibodies (data not shown).

DISCUSSION

Herein, we report the pooled safety results through 1 year in 1120 patients from DISCOVER-1 and DISCOVER-2, the placebo-controlled, phase III studies of SC guselkumab 100 mg Q4W or Q8W conducted in patients with active PsA. Findings were consistent with those previously reported for each trial through Week 24[9,10] and through 1 year,[13,14] as well as with the long-term safety results through 4 years of guselkumab treatment in the VOYAGE-1 and VOYAGE-2 trials conducted in patients with moderate-to-severe PsO.[19,20] Through Week 24, time-adjusted rates (per 100 PYs) of AEs, SAEs, infections, serious infections, and discontinuations as the result of an AE were similar across the placebo and guselkumab treatment groups. Through 1 year, the rates for these AE categories remained stable. In addition, no patients treated with guselkumab developed uveitis, active TB, an opportunistic infection (noting 1 case of nonserious oral thrush), or IBD through 1 year. As well, incidences of malignancy and MACE were similar across treatment groups through Week 24, with no increase through 1 year. Two deaths occurred through 1 year, both in patients receiving placebo. Injection-site reactions were uncommon, as was the development of neutralizing antibodies to guselkumab. Elevated serum hepatic transaminases and decreased neutrophil counts were generally mild and transient through 1 year.

Biologics have provided a highly effective alternative for treating the signs and symptoms of PsA and PsO, including anti-TNF agents and monoclonal antibodies targeting IL-12/23, IL-17, and IL-23. The safety profiles of anti-TNF agents and ustekinumab, a monoclonal antibody targeting IL-12/23, are well established,[16,21] with IL-17 antibodies accruing longer-term data more recently. While generally not associated with chronic organ damage, biologics can have significant AEs.[17,22]

Concerns associated with anti-TNF therapies include an increased risk of serious infections, particularly TB and opportunistic infections, new-onset or worsening of heart failure, hypersensitivity reactions, and malignancy.[23] Prescribing information for the IL-12/23 inhibitor ustekinumab includes warnings and precautions for infections, malignancy, and hypersensitivity reactions.[24] However, long-term registry data in PsO suggest the risk of serious infection with ustekinumab may be lower than with anti-TNF agents.[25] IL-17 antibodies are associated with a risk of infection, hypersensitivity, and new-onset or exacerbation of IBD.[26,27] Agents targeting IL-23p19 represent the newest class of biologics approved for PsA. The prescribing information for guselkumab cautions on infection and hypersensitivity.[1] Prescribing information for ustekinumab and anti-IL-17 and -IL-23 agents approved for PsA all recommend TB testing and prophylaxis.[1,24,26,27]

Longer-term clinical data and registries have further clarified the actual risk of these AEs.[25,28] For example, the increased risk of TB (new-onset TB and reactivation of latent TB infection [LTBI]) with anti-TNF agents is well established and derives from the pivotal role of TNF in maintaining granuloma integrity.[29] TB screening and treatment of LTBI are recommended before initiating therapy with any biologic approved for PsA, implying an increased risk associated with treatment. However, associations with active TB and LTBI are generally less common with other biologic classes for immune-mediated diseases than with anti-TNF agents.[30,31,32,33] No cases of new-onset TB or reactivation of LTBI occurred through 1 year of the DISCOVER-1 and DISCOVER-2 trials. This is consistent with the pivotal phase III PsO trials of guselkumab that included an active comparator arm, adalimumab.[8,11] In the PsO trials, among patients who had LTBI and received prophylactic treatment, no cases of active TB were reported in any treatment group. Among patients with no TB at baseline, no new cases of active TB developed in patients treated with either guselkumab or placebo, whereas 2 patients with PsO treated with adalimumab developed active TB.[34] While further long-term safety data are awaited, choice of biologic treatment for PsA, particularly in TB endemic regions, should include consideration of the current data on TB reactivation.

In the phase III studies of anti–IL-17 antibodies for PsA, increased rates of mucocutaneous *Candida* infections, rarely serious, occurred in the active treatment arms,[35,36,37] continued during longer treatment periods,[38,39] and are consistent with the PsO phase III studies.[40,41,42,43] The increased rate is likely attributable to the role of IL-17 in host defense against fungal infections, particularly at mucosal sites.[44] In contrast, in DISCOVER-1 and DISCOVER-2, no opportunistic infections occurred through 1 year (noting 1 case of nonserious oral thrush). New-onset or exacerbation of IBD has also been reported in clinical trials

of anti–IL-17 antibodies. Clinical trials for IL-17 blockade to treat Crohn disease were either unsuccessful or stopped early as a result of exacerbation of disease.[45,46] In clinical trials of a monoclonal antibody against IL-17A for PsO or PsA, cases of new-onset or exacerbation of IBD have been reported.[38,47,48] In the ECLIPSE study, which compared guselkumab with secukinumab in patients with PsO, 3 (1%) patients in the secukinumab group compared with none in the guselkumab group reported an event of Crohn disease through Week 56.[18] In the current pooled analysis of the phase III guselkumab PsA studies of 1120 patients through 1 year, no cases of IBD were reported among patients treated with guselkumab.

Elevations in hepatic aminotransferases appeared to be more common among patients treated with guselkumab (higher with Q4W than Q8W dosing) than patients treated with placebo. The elevations were generally of low toxicity grade, transient, and not associated with clinically significant increases in bilirubin. Elevations of Grade 2 or 3 were mostly associated with confounding factors such as prior and/or concomitant use of medications associated with liver injury. In general, increases in ALT and AST were more common in patients with baseline MTX use. Decreased neutrophil counts were also somewhat more common with guselkumab compared with placebo, although most were of low toxicity grade, transient, and not associated with infection.

Injection-site reactions were uncommon through 1 year, occurring in fewer than 2% of patients treated with guselkumab. While nearly all were mild, the 2 moderate injection-site reactions led to discontinuation of guselkumab. The overall incidence of antibodies to guselkumab remained low (4.5%) through Week 52, with no apparent association between their development and the occurrence of injection-site reactions. Of the antibodies detected, 10% were neutralizing antibodies. However, because the number of patients who were positive for antibodies to guselkumab was small, no definitive conclusions about the influence of antibodies on pharmacokinetics or pharmacodynamics of guselkumab can be drawn.

This pooled analysis is limited by a 1-year follow-up time. However, the upcoming 2-year results from DISCOVER-2 will provide longer-term safety results. In addition, the studies were not powered to detect rare events.

In conclusion, the results of this pooled safety analysis of the DISCOVER-1 and DISCOVER-2 trials indicate that guselkumab 100 mg, given either Q4W or Q8W, was generally well tolerated in this population of patients with active PsA. Further, the guselkumab safety profile in patients with PsA through 1 year is consistent with that in patients with PsO who received up to 5 years of guselkumab.[49]

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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