Pooled Safety Results Through One Year of Two Phase-3 Trials of Guselkumab in Patients with Psoriatic Arthritis

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ABSTRACT

Objective. Evaluate safety of guselkumab (monoclonal antibody targeting IL-23p19) in psoriatic arthritis (PsA) patients through 1year (1Y) of the Phase-3 DISCOVER-1&2 trials.

Methods. Patients with active PsA (N=1120; biologic-naïve except the118 TNFi-treated DISCOVER-1 patients) were randomized to subcutaneous guselkumab 100 mg every 4 weeks (Q4W) or at Week 0, Week4, then Q8W; or placebo. At Week24, placebo patients switched to guselkumab 100 mg Q4W. Treatment continued through 1Y and 2Y for DISCOVER-1&2, respectively. In this pooled analysis, patients with ≥1 adverse event (AE) through 1Y were standardized for 100 patient-years of follow-up [100PY]).

Results. Through Week24, AEs were consistent between placebo- and guselkumab (Q4W+Q8W)-treated patients: AEs 143/100PY and 151/100PY; serious AEs 7.1/100PY and 4.4/100PY; AEs leading to study agent discontinuation 4.1/100PY and 3.8/100PY, respectively. Through 1Y, no active tuberculosis, opportunistic infections, or inflammatory bowel disease, and low rates of malignancy and major adverse cardiovascular events, were observed in guselkumab-treated patients. Injection-site reactions occurred in 1–2%, and antibodies to guselkumab in 4.5% of guselkumab-treated patients through 1Y; the vast majority of antibodies to guselkumab were non-neutralizing. Serum hepatic transaminase elevations (more common with Q4W than Q8W) and decreased neutrophil counts were generally mild, transient, and did not require treatment discontinuation, with minimal change from Week24 to 1Y.

Conclusion. Guselkumab 100 mg Q4W and Q8W were well tolerated in PsA patients, with no new safety concerns through 1Y of the Phase-3 DISCOVER trials. Guselkumab safety through 1Y in PsA patients is consistent with that established in guselkumab-treated psoriasis patients.

(Trials registered at ClinicalTrials.gov: NCT03162796, NCT03158285)

INTRODUCTION

Guselkumab (Janssen Biotech, Inc., Horsham, PA, USA) 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, psoriatic arthritis (PsA), and inflammatory bowel disease (IBD (3-5). 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 psoriasis pathogenesis (5-7). Guselkumab is the first IL-23p19 subunit inhibitor approved to treat of moderate-to-severe psoriasis and active PsA (1, 8-11).

PsA is a seronegative, chronic, inflammatory arthropathy that occurs in approximately 30% of patients with psoriasis (12). IL-23 can also induce IL-22 (a cytokine important in enthesitis and excess bone formation) and elicit joint damage, in part via IL-17A and tumor necrosis factor (TNF) induction. Two Phase 3 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 two pivotal Phase 3 studies, VOYAGE-1 and VOYAGE-2, of guselkumab 100 mg every 8 weeks (Q8W) in patients with psoriasis have been published (8, 11, 18-20). 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 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.

MATERIALS AND METHODS

Study Design. DISCOVER-1 (9), and DISCOVER-2 (10), were randomized, double-blind, Phase 3 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 non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, and selected non-biologic disease-modifying anti-rheumatic 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 year 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 IRB approval numbers (US sites): 5959C and 5910C), and all patients provided written informed consent. The trials are registered at ClinicalTrials.gov: NCT03162796, 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 Classification Criteria for Psoriatic Arthritis (CASPAR). 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 ~30% of patients in DISCOVER-1 who had previously received one or two 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 prior use of Janus kinase inhibitors, or (within 4 weeks of study-agent administration) phototherapy or systemic immunosuppressants.

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 cardiovascular events (MACE, cardiovascular death, non-fatal myocardial infarction, or non-fatal 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 post-hoc 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 due to the placebo crossover study design, the number of patients with AEs are reported on the basis of 100 patient-years of follow-up (PY). The numbers of AEs through 1 year were also standardized per 100PY.

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 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/tender joints and greater extent/severity of skin disease assessed using the Psoriasis Area Severity Index (PASI).

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 guselkumab Q8W group, and 5.4% (20/372) in the placebo group discontinued 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 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→guselkumab crossover groups.

Adverse events during the placebo-controlled period through Week 24. Through Week 24, the numbers of patients with ≥1 AE per 100 PY (95% confidence intervals) 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. Serious AEs (SAEs; 4.4 and 7.1/100PY), AEs leading to discontinuation of study agent (3.8 and 4.1/100PY), infections (49.5 and 49.9/100PY), and serious infections (1.2 and 1.7/100PY) occurred with similar frequency in combined guselkumab- and placebo-treated patients (Table 2). Results were consistent when assessing the

numbers of events/100PY (Supplemental Table 1). 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 (combined guselkumab, n=38 [5.1%]; placebo, n=17 [4.6%]), and bronchitis (combined guselkumab, n=17 [2.3%]; placebo, n=4 [1.1%]).

Adverse events reported with guselkumab through 1 year. At 1 year, time-adjusted incidences of AEs and SAEs remained stable in both guselkumab treatment groups. Among placebo patients 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 and infestations 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 guselkumab-treated patients, 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/100PY (Supplemental Table 1).

Adverse events of interest. Two placebo-treated patients died through Week 24 (cardiac failure, pneumonia) (9, 10); no guselkumab-treated patient died through 1 year (13, 14). Serious infections were uncommon across treatment groups (Table 2), with no uveitis, active TB, or opportunistic infection reported through 1-year. One case of nonserious oral thrush was reported in a guselkumab-treated patient with a history of asthma and concomitant inhaled corticosteroid use (14). One case each of IBD and iridocyclitis occurred in a placebo-treated patient.

Malignancies occurred in four 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 pre-existing 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 two patients prior to Week 24, i.e., the aforementioned event of cardiac failure in a patient receiving placebo (9) and ischemic stroke in one 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, Table 3). 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 guselkumab-treated patients experienced Grade 4 ALT or AST elevations through 1 year. While Grade 2/3 ALT/AST elevations were more common in the Q4W group compared with the Q8W group, most were transient and did not result in discontinuation (see exceptions below), and none was associated with increases in bilirubin >2 x the upper limit of normal. Confounding factors were present in the majority of patients with Grade 2 to 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 due to hepatobiliary AEs or elevated transaminases (13). Three of the patients were also receiving isoniazid; two 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 three. 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.

Decreased neutrophil counts were slightly more common in guselkumab- than placebo-treated patients, with no increase seen from Week 24 at 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 one 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 guselkumab-treated patients with appropriate samples through Week 52 of the 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 antibodies to guselkumab, and 0.5% of all guselkumab-treated patients, had neutralizing antibodies.

DISCUSSION

Herein, we report the pooled safety results through 1 year in 1120 patients from DISCOVER-1 and DISCOVER-2, the placebo-controlled, Phase 3 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 psoriasis (19, 20). Through Week 24, time-adjusted rates (per 100 PY) of AEs, serious AEs, infections, serious infections, and discontinuations due to 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 guselkumab-treated patient developed, uveitis, active TB, an opportunistic infection (noting one case of non-serious 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 psoriasis, 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, the monoclonal antibody to 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 psoriasis 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/LTBI are generally less common with other biologic classes for immune-mediated diseases than with anti-TNF agents (30-33). 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 3 psoriasis trials of guselkumab that included an active comparator arm, adalimumab (8, 11). In the psoriasis 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 either guselkumab- or placebo-treated patients, while two adalimumab-treated psoriasis patients 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 3 studies of anti-IL-17 antibodies for PsA, increased rates of mucocutaneous *Candida* infections, rarely serious, occurred in the active treatment arms (35-37), continued during longer treatment periods (38, 39), and are consistent with the psoriasis Phase 3 studies (40-43). 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 (one case of non-serious 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's disease were either unsuccessful or stopped early due to exacerbation of disease (45, 46). In clinical trials of a monoclonal antibody against IL-17A for psoriasis 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 psoriasis patients, 3 (1%) patients in the secukinumab group compared with none in the guselkumab group reported an event of Crohn's disease through Week 56 (18). In the current pooled analysis of the Phase 3 guselkumab PsA studies of 1120 patients through 1 year, no cases of IBD were reported among guselkumab-treated patients.

Elevations in hepatic aminotransferases appeared to be more common among guselkumab- (higher with Q4W than Q8W dosing) than placebo-treated patients. 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 guselkumab-treated patients. While nearly all were mild, the two 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 -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 comparable to that in psoriasis patients who received up to 5 years of guselkumab (49).

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

Characteristic[a]	Placebo	Guselkumab 100 mg Q4W	Guselkumab 100 mg Q8W	Guselkumab Combined[b]
Patients, N	372	373	375	748
Age, years	47.2 (11.5)	46.5 (11.5)	46.2 (11.9)	46.3 (11.7)
Gender, 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, years	6.3 (6.4)	5.9 (6.1)	5.6 (5.7)	5.7 (5.9)
Number swollen joints (0-66)	11.5 (7.0)	11.4 (7.5)	11.4 (7.7)	11.4 (7.6)
Number tender joints (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)
PsO % BSA	15.4 (18.9)	17.1 (19.7)	15.7 (20.0)	16.4 (19.9)
PASI, (0-72) score	8.8 (9.5)	10.4 (11.2)	9.2 (11.1)	9.8 (11.1)
IGA Score, VAS (0-10 cm):				
≥ 2, n (%)	301 (81)	311 (83)	295 (79)	606 (81)
Previous anti-TNF use[c], n (%)	39 (10)	38 (10)	41 (11)	79 (11)
Medication use at baseline, n (%)				
Methotrexate	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)

[a]Results presented are mean (SD), unless otherwise noted. [b]Combined guselkumab Q4W and Q8W treatment groups. [c]All patients with previous anti-TNF use were in the DISCOVER-1 trial. BMI, body mass index; BSA, body surface area; CRP, C-reactive protein; HAQ-DI, health assessment questionnaire-disability index; IGA, investigators global assessment of psoriasis (cleared=0, minimal=1, mild=2, moderate=3, severe=4); IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; 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

Table 2. Number of patients with adverse events per 100 patient-years

	Week 0 - Week 24					1 Year[a]		
		Guselkumab 100 mg			Placebo→ Guselkumab Q4W[d]	Guselkumab 100 mg		
	Placebo[b]	Q4W	Q8W	Combined[c]		Q4W	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 patient-years of follow-up	0.5	0.5	0.5	0.5	0.5	1.0	1.0	1.0
Patients with ≥1 AE								
Total PY of follow-up	123	119	123	242	155	209	212	576
Patients/100 patient-years (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 PY of follow-up	170	170	171	341	200	377	374	951
Patients/100 patient-years (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 PY of follow-up	154	153	157	309	182	306	308	796
Patients/100 patient-years (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 PY of follow-up	172	172	173	345	202	383	382	968
Patients/100 patient-years (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 PY of follow-up	171	170	172	342	203	382	382	967
Patients/100 patient-years (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 placebo group who crossed over to guselkumab Q4W, only data prior to first administration of guselkumab are included in this group. [c]Combined patients treated with guselkumab Q4W and Q8W (including patients crossed over from placebo for 1-year results). [d]For patients in the placebo group who crossed over to guselkumab Q4W, only data on and after first administration of guselkumab were included in this group.

AE, adverse event; CI, confidence interval; PY, patient year; Q4W, every 4 weeks; Q8W, every 8 weeks; SAE, serious adverse event

Table 3. Adverse events of interest

	Week 0 - Week 24					1 Year[a]		
		Guselkumab 100 mg			Placebo→ Guselkumab Q4W[d]	Guselkumab 100 mg		
	Placebo[b]	Q4W	Q8W	Combined[c]		Q4W	Q8W	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)
Opportunistic infections	0	0	0	0	0	0	0	0
Tuberculosis	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 noted. [a]Through Week 60 for DISCOVER-1 and Week 52 for DISCOVER-2. [b]For patients in the placebo group who crossed over to guselkumab Q4W, only data prior to first administration of guselkumab are included in this group. [c]Combined patients treated with guselkumab Q4W and Q8W (including patients who crossed over from placebo at Week 24). [d]For patients in the placebo group who crossed over to guselkumab Q4W, only data on and after first administration of guselkumab were included in this group.
IBD, inflammatory bowel disease; MACE, major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke); Q4W, every 4 weeks; Q8W, every 8 weeks

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

	Week 0 - Week 24					1 Year[a]			
		Guselkumab 100 mg			Placebo→ Guselkumab Q4W[d]	Guselkumab 100 mg			
	Placebo[b]	Q4W	Q8W	Combined[c]		Q4W	Q8W	Q4W Combined[e]	All 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 noted. [a]Through Week 60 for DISCOVER-1 and Week 52 for DISCOVER-2. [b]For patients in the placebo group who crossed over to guselkumab Q4W, only data prior to the first administration of guselkumab are included in this group. [c]Combined patients treated with guselkumab Q4W and Q8W (including patients who crossed over from placebo at Week 24). [d]For patients in the placebo group who crossed over to guselkumab Q4W, only data on and after first administration of guselkumab were included in this group. [e]Combined patients treated with guselkumab Q4W (including patients who crossed over from placebo at Week 24). [f]NCI-CTCAE Grades. ALT, alanine aminotransferase; AST, aspartate aminotransferase; MTX, methotrexate; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; Q4W, every 4 weeks; Q8W, every 8 weeks

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

	Through Week 24			Through Week 52			
	Guselkumab 100 mg			Placebo→ Guselkumab	Guselkumab 100 mg		
	Q4W	Q8W	Combined[a]	Q4W[b]	Q4W	Q8W	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 one dose of guselkumab. [b]Included patients in the placebo group who crossed over to guselkumab Q4W at Week 24. [c]Presence of antibodies to guselkumab in serum samples of guselkumab-treated patients was assessed using a validated immunoassay method. Denominator is patients with appropriate samples.
Q4W, every 4 weeks; Q8W, every 8 weeks

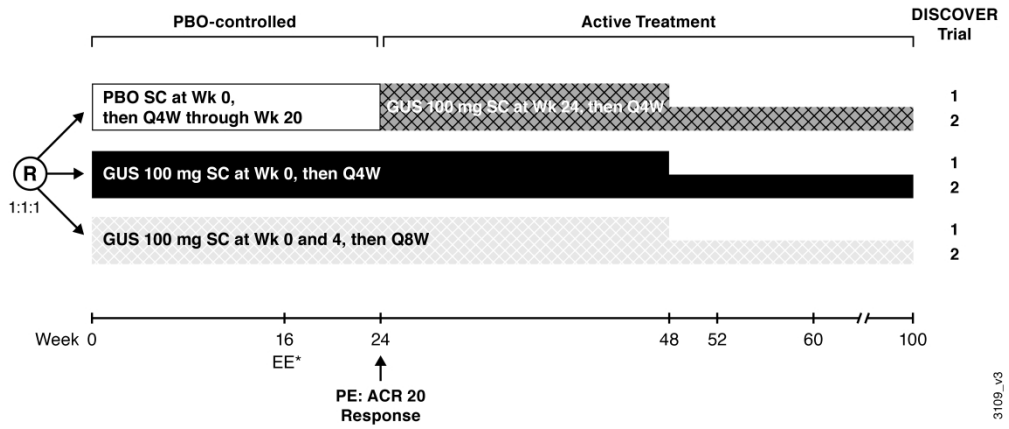

Figure 1. DISCOVER 1 and DISCOVER 2 Study Designs. * EE=early escape (patients were eligible to initiate/increase background medications if they had <5% improvement from baseline in both tender and swollen joint counts at Week 16). ACR 20, ≥ 20% improvement in the American College of Rheumatology criteria;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