Running title: GUS safety in PsA by TNFi experience

Safety of guselkumab with and without prior TNF-α inhibitor treatment: Pooled results across four studies in patients with psoriatic arthritis

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ABSTRACT

Objective: Assess pooled safety results through the end of the Phase 2/3 studies of guselkumab (≤2 years) in tumor necrosis factor-α inhibitor (TNFi) -naïve and -experienced patients with psoriatic arthritis (PsA).

Methods: Data were pooled from the Phase 2 and DISCOVER-1 (TNFi-naïve/experienced), DISCOVER-2 (TNFi-naïve), and COSMOS (TNFi-experienced) studies. Patients with active PsA were randomized to guselkumab 100 mg every 4 or 8 weeks (Q4W+Q8W=Combined Guselkumab) or placebo with crossover to guselkumab Q4W or Q8W at Week 24. Time-adjusted adverse event (AE) rates (events/100 patient-years [PY]) and clinical laboratory findings were assessed during the placebo-controlled period and through end of study.

Results: Of 1554 randomized patients (n=373 [guselkumab Q4W], 664 [guselkumab Q8W], and 517 [placebo]), 1138 (73.23%) were TNFi-naive and 416 (26.76%) were TNFi-experienced. Respective AE rates through Week 24 were 220.8/100PY (TNFi-naïve) and 251.6/100PY (TNFi-experienced) in the Combined Guselkumab group and 196.1/100PY (TNFi-naïve) and 303.0/100PY (TNFi-experienced) in the Placebo group. Among all guselkumab-treated patients (including those who crossed over from placebo), low AE rates were maintained during long-term evaluation in both TNFi-naïve (139.69/100PY) and TNFi-experienced (174.0/100PY) patients. Rates/100PY of AEs leading to treatment discontinuation, serious AEs, and other AEs of interest as well as occurrence of elevated hepatic transaminase levels and decreased neutrophil counts were consistent between placebo and guselkumab-treated patients through Week 24 treatment regardless of prior TNFi use and remained low through the end of the studies.

Conclusion: The safety profile of guselkumab in TNFi-experienced patients was consistent with that in TNFi-naïve patients, which remained favorable for up to 2 years.

ClinicalTrials.gov: Phase 2 (NCT02319759), DISCOVER-1 (NCT03162796), DISCOVER-2 (NCT03158285), and COSMOS (NCT03796858).

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, inflammatory disorder primarily affecting the joints and skin. It is a heterogeneous disorder, affecting multiple domains (peripheral and axial joints, skin and nails, enthesitis, dactylitis, and related conditions of inflammatory bowel disease [IBD] and uveitis), which must be taken into account when assessing long term treatment efficacy.[1,2] Biologics are indicated for patients whose disease is not adequately controlled with nonsteroidal anti-inflammatory drugs (NSAIDs) or conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and those with poor prognostic indicators.[1,2] While tumor necrosis factor-α inhibitors (TNFi) have historically been the first line biologic, failure to achieve response with or intolerance to TNFi treatment can occur, and response rates may decrease with multiple TNFi therapies.[3-10] Subsequently, treatment with biologics with alternate mechanisms of action are often required for these patients.[11] Additionally, because recommendations are focused on providing the most appropriate treatment for the disease domains most relevant to individual patients, TNFi therapy may not be the most appropriate first-line treatment for all patients.[1,2]

A benefit/risk assessment is important for any new medical treatment. Safety data, particularly long-term, is critical for treatment of a chronic disease such as PsA. Additionally, patients receiving biologics for PsA often require concomitant medications, such as methotrexate (MTX), potentially increasing the risk for adverse reactions (eg, infections) or laboratory abnormalities (eg, hepatobiliary events).[12] Other potential safety considerations associated with some biologic treatments include serious infections (including opportunistic infections and tuberculosis [TB]), malignancies, major adverse cardiovascular events (MACE), autoimmune reactions, and IBD.[13-19] Thus, it is important to investigate the long-term safety of these therapies in PsA patients.

Additionally, evaluation of safety in the context of prior TNFi therapy that may result in sustained safety concerns or represent a population with a higher inflammatory burden, and in patients receiving concomitant MTX, that has its own safety profile, is essential.

Guselkumab, a monoclonal antibody that selectively inhibits interleukin (IL)-23 p19, was the first agent in its class approved for patients with active PsA. [19] The safety and efficacy of guselkumab were evaluated through end of study (≤ 2 years) in adults with active PsA enrolled in a Phase 2 study and three Phase 3 studies (DISCOVER-1, DISCOVER-2, COSMOS).[20-26] The majority of these patients were TNFi-naïve, while approximately one-quarter were TNFi-experienced. We present pooled safety data from over 1500 patients (2125 patient-years [PY] of follow-up), allowing assessment of the incidence of adverse events (AEs) by prior TNFi and by concomitant MTX use.

METHODS

Patients and study designs. Details regarding overall study design and patient eligibility criteria for each trial have been reported previously.[20-26] Briefly, patients in DISCOVER-1 and DISCOVER-2 were randomized to receive subcutaneous injections of guselkumab 100 mg every-4-weeks (Q4W) or every-8-weeks (Q8W) or placebo with crossover to Q4W; patients in the Phase 2 study and COSMOS received either guselkumab Q8W or placebo→Q8W (Supplemental Table 1). Inclusion/exclusion criteria, including disease characteristics, prior and concomitant medications, randomized treatments, and study duration were similar across studies with some variation concerning prior use of TNFi. The Phase 2 (ClinicalTrials.gov NCT02319759) and DISCOVER-1 (NCT03162796) studies enrolled both TNFi-experienced and

TNFi-naïve patients. TNFi-experienced patients could have discontinued prior treatment for various reasons, some unrelated to efficacy or intolerance. COSMOS (NCT03796858) enrolled only inadequate responders (i.e., defined as lack of efficacy or intolerance) to prior TNFi treatment while DISCOVER-2 (NCT03158285) enrolled only TNFi-naïve patients.[20,21,23,26] All TNFi-naïve patients were biologic-naïve, as prior biologic agents or targeted synthetic DMARDs were prohibited. Concomitant MTX and corticosteroids were permitted at stable doses in all four studies. Patients were followed through 2 years in DISCOVER-2 and 1 year in the other studies.

All trials were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practices. All patients provided written informed consent, and the protocols were approved by each site's Institutional Review Board/Ethics Committee. Sterling Institutional Review Board approval numbers [US sites] were 5959C and 5910C for DISCOVER-1 and DISCOVER-2, respectively.

Safety assessments and statistical methods.

Patients were monitored throughout the studies for AEs, including AEs leading to discontinuation (AE→D/C) and serious AEs (SAEs). AEs of interest included infections, serious infections, opportunistic infections, SAEs of the Gastrointestinal (GI) System/Organ Class, malignancies, and MACE (ie, cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Opportunistic infections and MACE were identified through medical review.

Injection-site reactions (ISRs; any unfavorable or unintended sign at injection site such as pain, erythema, and/or induration) were identified by study investigators. Blood samples were

collected at regular intervals to assess clinical laboratory abnormalities (elevations in alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin; decreases in neutrophil counts), which were classified using National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE).

Data were integrated through end of the studies (≤2 years: Phase 2 and COSMOS [Week56], DISCOVER-1 [Week60], DISCOVER-2 [Week112]) and presented over two time periods: Week0-24 (placebo-controlled period; Guselkumab Q4W, Guselkumab Q8W, Combined Guselkumab [Q4W+Q8W], and Placebo groups) and through end of study (Q4W, Q8W, and All Guselkumab groups, including patients who crossed over from placebo at Week 24 [W24]).

Incidence rates of AEs were summarized by actual treatment received among patients who received ≥1 study drug administration. To account for the variations in active treatment duration across the Guselkumab and Placebo groups, time-adjusted incidences of events/100 PY of follow-up were reported along with the corresponding 95% confidence intervals (95% CIs). AEs were also summarized based on the number of patients with events/100PY (95% CIs). Laboratory abnormalities were summarized as proportion of patients with maximum NCI-CTCAE toxicity grade (Grade 1-4) by treatment group for all treated patients with ≥1 post-baseline assessment.

To determine the impact of prior TNFi use on the safety of guselkumab, the incidence of AEs and clinical laboratory abnormalities are presented for TNFi-naïve (Phase 2, DISCOVER-1, DISCOVER-2) and TNFi-experienced (Phase 2, DISCOVER-1, COSMOS) patients. As TNFi-

experienced patients could have discontinued due to any reason, safety outcomes are also reported for those who had discontinued due to inadequate efficacy or intolerance. Additionally, because MTX has been associated with specific AEs (including infection and hepatotoxicity),[11,27] results are also summarized by baseline concomitant MTX use (yes/no).

RESULTS

Patient Disposition. A total of 1554 patients were included (n=373, 664, and 517 randomized to guselkumab Q4W, guselkumab Q8W, and placebo, respectively); 1508 patients received ≥1 administration of guselkumab Q4W/Q8W and were followed for a median of 1.2 years (2125 PY). Detailed patient disposition data have been reported through the end of the studies (Phase 2, DISCOVER-1, COSMOS: 1 year; DISCOVER-2: 2 years).[20,22,25,26] Overall, treatment was completed by 89.06% of patients (1384/1554), including 89.54% (1019/1138) of TNFi-naïve patients and 87.7% (365/416) of TNFi- experienced patients (Figure 1).

Baseline demographic and disease characteristics. Baseline disease characteristics were consistent with active PsA and plaque psoriasis (Table 1). Among all patients, 416 (26.77%) were TNFi-experienced and 1138 (73.23%) were TNFi-naïve. The majority of TNFi-experienced patients (n=275 [66.1%]) discontinued their prior TNFi due to inadequate efficacy, and 51 (12.3%) discontinued due to intolerance; 90 (21.6%) patients did not provide a reason. At baseline, 56.31% and 17.57% were receiving concomitant MTX and oral corticosteroids, respectively; rates were similar for TNF-experienced and -naïve patients.

Baseline demographic and disease characteristics were generally similar regardless of TNFi status. TNFi-naïve patients were slightly younger with shorter PsA duration but also reported more NSAID use compared with TNFi-experienced patients. The slightly higher C-reactive protein levels among TNFi-naïve patients may be an artifact of enrollment criteria in DISCOVER-2 (≥0.6 mg/dL vs. ≥0.3 mg/dL for other studies). The proportion of TNFi-experienced patients was comparable across treatment groups within the Phase 2 and DISCOVER-1 studies. However, the Q8W dose was the only guselkumab regimen evaluated in COSMOS, which accounts for the overall imbalance in the number of patients who had received prior TNFi between the Q4W and Q8W groups in the pooled population (10.2% [38/373] vs. 36.0% [239/664]).

Adverse events. Through W24, the incidence of AEs was similar between the Combined Guselkumab (229.05/100PY) and Placebo (222.5/100PY) groups; rates were comparable in the guselkumab groups (including placebo crossovers) through end of study (All Guselkumab [145.73/100PY]; Table 2). Rates/100PY of SAEs and AEs→D/C were low and comparable between the placebo and guselkumab groups through W24 and between the Q4W and Q8W groups during long-term evaluation (Table 2). Among TNFi-experienced patients, rates of AEs, including AEs→D/C, through end of study were comparable between patients who discontinued TNFi due to inadequate efficacy and those who had discontinued TNFi due to intolerance (Supplemental Table 2). Patterns across treatment groups were generally comparable to that observed when evaluating numbers of patients/100PY and number of events/100PY (Supplemental Table 3).

Infections (eg, nasopharyngitis, upper respiratory tract infection) were the most common type of AE, occurring at similar rates across treatment groups through W24 (Combined Guselkumab: 60.30/100PY; Placebo: 64.0/100PY) and end of study (All Guselkumab: 41.97/100PY). Serious infections occurred at rates of 1.05 and 3.1/100PY in the Combined Guselkumab and Placebo groups, respectively, through W24 and at a rate of 1.60/100PY in the All Guselkumab group for up to 2 years. No opportunistic infections occurred through W24, and the rate/100PY in the All Guselkumab group remained low (0.14/100PY; 3 events, all TNFi-naive patients) during long-term evaluation (Table 2). Nonserious oral candidiasis occurred in one guselkumab-treated patient (TNFi-naïve). No cases of active TB were reported.

Rates of malignancies were 0.63/100PY and 0.4/100PY in the Combined Guselkumab and Placebo groups, respectively, through W24 and 0.28/100PY in the All Guselkumab group through end of study (Table 2). Six malignancies were observed in five guselkumab-treated patients (four TNFi-naïve; one TNFi-experienced) across the studies;[20-23,26] most patients had either risk factors or a medical history that was associated with the diagnosis of malignancy.

MACE occurred at a rate of 0.42/100PY and 0.4/100PY in the Combined Guselkumab and Placebo groups, respectively, through W24 and 0.24/100PY in the All Guselkumab group through end of study. Of the six reported MACE, five (3 myocardial infarctions, 2 ischemic strokes) occurred in guselkumab-treated patients; one death secondary to cardiac failure was reported in a placebo-treated patient (Table 2).[21-23,25,26] Four patients were TNFi-naïve, and one was TNFi-experienced; all had multiple cardiovascular risk factors.

Other AEs of interest were uncommon (Table 2). Rates of GI-related SAEs were 0.21/100PY in the Combined Guselkumab group and 1.3/100PY in the Placebo group through W24 and 0.28/100PY in the All Guselkumab group through end of study. No cases of Crohn's disease (CD) or ulcerative colitis (UC) occurred. Two AEs were reported as IBD (unspecified): one suspected case of IBD occurred in a guselkumab-treated patient (lost to follow-up); another possible case was noted in a placebo-treated patient.[23,26] Uveitis occurred at a rate of 0.05/100PY (95% CI, 0.00, 0.26) through end of study (iridocyclitis in one guselkumab-treated and one placebo-treated patient; both TNFi-naïve). Three deaths occurred: one guselkumab-treated patient (road traffic accident) and two placebo-treated patients (cardiac failure and pneumonia).[21,22,25]

When evaluated by prior TNFi use, AEs occurred at rates of 220.8/100PY (TNFi-naïve) and 251.6/100PY (TNFi-experienced) in the Combined Guselkumab group through W24 (Supplemental Figure 1). Similarly, other AEs of interest did not vary by TNFi status (Figure 2). Compared with TNFi-naïve patients, TNFi-experienced patients in the Placebo group (but not the guselkumab groups) had numerically higher numbers of events/100PY for AEs (303.0 vs. 196.1), SAEs (15.9 vs. 6.4), and AE→D/C (10.6 vs. 2.3). AE rates through end of study were 139.69/100PY for TNFi-naïve and 174.0/100PY for TNFi-experienced guselkumab-treated patients. The guselkumab AE profiles of patients who discontinued their prior TNFi due to inadequate efficacy or intolerance were generally comparable to that reported for all patients (Supplemental Table 2).

Concomitant MTX use did not appear to have a clinically meaningful impact on the overall incidence of AEs (Table 2). Of note, numbers of infections/100 PY were similar with MTX (60.6) and without MTX (59.9) in the Combined Guselkumab group through W24 and in the All Guselkumab group through end of study (MTX 42.4; no MTX 41.5); corresponding figures for serious infections were 1.1/100PY (MTX) and 1.0/100PY (no MTX) at W24 and 1.4/100PY (MTX) and 1.9/100PY (no MTX) through end of study.

Laboratory abnormalities. Through W24, NCI-CTCAE toxicity Grade-1 ALT elevations occurred in similar proportions of patients in the Combined Guselkumab (30.20%) and Placebo (26.8%) groups; rates were slightly higher in the Q4W (35.0%) vs Q8W group (27.5%) (Table 3). Similar results were observed for Grade-1 AST elevations, with approximately 19% in both the Combined Guselkumab and Placebo groups; however, the difference between guselkumab dose regimens was less apparent (21.6% [Q4W] vs. 17.5% [Q8W]). Through W24, <3% of patients had Grade-2 or -3 ALT/AST elevations; rates remained low through the end of study. In most cases, confounding factors (eg, underlying medical conditions, obesity, alcohol use, concomitant treatments associated with liver injury) were present.[20,26,28] No Grade-4 elevations occurred in guselkumab-treated patients through end of study. SAEs of increased ALT occurred in two guselkumab-treated patients, both TNFi-experienced (one had underlying autoimmune hepatitis and the other had steatohepatitis), and four TNFi-naïve patients discontinued guselkumab due to hepatobiliary SAEs (acute hepatitis B, isoniazid-induced liver injury, and hepatic steatosis) or persistently increased hepatic transaminases; all had underlying risk factors[25,26] Increased bilirubin levels were infrequent, with all elevations classified as Grade-1 or -2, except one Grade-3 elevation (TNFi-experienced) guselkumab-treated patient) (Table 3).

The rates of neutrophil decreases were low across treatment groups and during long-term follow-up (Table 3). There was no consistent pattern based on prior TNFi status. Most were considered Grade-1 or -2; Grade-3 events occurred in one patient each in the Q8W and Placebo groups, and one patient in the Q4W group had a transient Grade-4 event (all TNFi-naive) through W24. Through end of study, four patients each in the Q4W and Q8W groups had Grade-3 decreases in neutrophil counts and one in the Q4W group had a Grade-4 decrease. No AEs of decreased neutrophil counts were associated with infection, except an AE of mild nasopharyngitis (resolved in 5 days) in one TNFi-naïve guselkumab-treated patient (Q4W) who had Grade-2 neutrophil decrease.[28] Most cases resolved spontaneously and did not necessitate treatment discontinuation, except one guselkumab-treated patient (TNFi-naïve) who discontinued due to an AE of neutropenia and a Grade-3 decreased neutrophil count that then resolved.[20]

The proportions of patients with laboratory abnormalities were low regardless of prior TNFi use (Table 3), with some exceptions, through end of study. Grade-1 ALT elevations in the All Guselkumab Group were somewhat higher in TNF-naïve (39.66%) than TNFi-experienced (31.5%) patients; corresponding proportions with Grade-1 AST elevations were 28.13% and 23.5%. The proportion of patients with Grade-2 or higher elevations in hepatic transaminase and bilirubin levels were generally similar regardless of prior TNFi use.

Through end of study, Grade-1 elevations in hepatic transaminases (ALT/AST) were slightly more common in patients receiving MTX compared with those not receiving MTX (Figure 3). Trends for ALT/AST results by MTX use within the TNFi-experienced and TNFi-naïve

subpopulations were similar to those in the overall population (Figures 3B-3F, Supplemental Table 4). Likewise, rates of all grades of elevated bilirubin and decreased neutrophil levels did not vary based on MTX use within TNFi-experienced and TNFi-naïve subpopulations (Supplemental Table 4).

Injection-site reactions. Among patients who received ≥1 guselkumab administration, ISRs occurred in 1.99% (30/1508) through end of study (TNFi-naïve: 23/1107 [2.08%]; TNFi-experienced: 7/401 [1.7%]). Most reactions were considered mild; two patients discontinued due to an ISR.[25] No cases of anaphylaxis or serum sickness were reported.

DISCUSSION

These findings represent the most comprehensive safety assessment of an IL-23p19 inhibitor in PsA to date, with 1508 patients evaluated for up to 2 years (2125 PY). Integrated analyses across four Phase 2/3 studies of PsA patients demonstrated that the safety profile of guselkumab remained consistent, regardless of prior TNFi or concomitant MTX use. Time-adjusted rates of safety events (events/100PY) and proportions of patients with laboratory abnormalities relevant to PsA patients were generally similar across treatment groups during the placebo-controlled period. No new safety concerns were identified, and no unexpected increases in rates of AEs of interest (including SAEs) or elevated hepatic transaminase levels/decreased neutrophil counts were observed with longer duration of treatment. Nearly 90% of enrolled patients completed assigned treatment through end of study. Furthermore, over one-quarter of patients included in these analyses were TNFi-experienced and more than half were receiving concomitant MTX,

making the results useful in the real-world PsA population in which both switching biologic therapies and the use of concurrent csDMARDs treatment are common.

The rates/100PY of AEs observed for guselkumab were similar between guselkumab- and placebo-treated patients and between the Q4W and Q8W groups through W24. The incidences of AEs were generally consistent between TNFi-naïve and TNFi-experienced patients within the guselkumab treatment groups. However, in the Placebo group, TNFi-experienced patients had numerically higher rates of AEs, SAEs, and AEs→D/C compared with TNF-naïve patients. This may be due to sustained toxicity from prior TNFi treatment or the higher inflammatory burden or dysregulated immune system following treatment nonresponse, as TNFi- experienced patients who do not respond to treatment tend to have more severe disease and higher levels of systemic inflammation.[29] Overall, the rates of laboratory abnormalities assessed were generally similar between the TNFi-naïve and TNFi-experienced patients during both the placebo-controlled period and through the end of the studies. Our results also demonstrated that the incidences of AEs and SAEs (including serious infections) in guselkumab-treated patients did not differ between TNFi-naïve patients and TNFi-experienced patients. Additionally, among patients who previously received TNFi, AE rates were comparable between those who discontinued their TNFi due to inadequate efficacy and those who discontinued due to intolerance. Of note, across the guselkumab groups, increased hepatic transaminase levels were slightly more common in the concomitant MTX subpopulation vs. no concomitant MTX in both TNFi-naïve and -experienced patients.

Regardless of prior TNFi experience or concomitant MTX use, there were no cases of active TB reported in any of the studies. Rates of serious and opportunistic infections and other AEs of interest (eg, malignancies, MACE) were low through the end of study (≤2 years of follow-up). Current guidelines from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recognize uveitis and IBD as distinct comorbidities of PsA.[2] The incidence of uveitis reported as an AE was low in these trials and similar to those reported for secukinumab and ixekizumab, which also target the IL-17/23 axis.[30,31] Cases of IBD have been reported in clinical trials of IL-17A antagonists in PsA.[13,18] Although there was one case of possible IBD in a guselkumab-treated patient from the COSMOS study, the diagnosis had not been confirmed before the patient was lost to follow-up. Furthermore, for up to 2 years, there were no reports of CD or UC among these 1508 guselkumab-treated patients. Of note, results of induction studies in over 300 patients each with moderately-to-severely active CD (GALAXI-1) or UC (QUASAR) demonstrated superior clinical efficacy with a favorable safety profile for guselkumab compared with placebo through week 12; maintenance studies in these indications are ongoing.[32,33] When a history of IBD is present, these long-term safety data for guselkumab may assist physicians and patients in making an appropriate treatment choice.

The recalcitrant nature and high disease burden of PsA, especially in those previously treated with TNFi therapy, could affect treatment persistence. Patients who have received >1 TNFi may be at continued risk of treatment failure owing to a cumulative recalcitrance, and switching to biologic therapy with an alternative mechanism of action may be required for those who develop loss of response or experience intolerance to their current treatment.[4-9] The high treatment retention rate of nearly 90% observed here indicates a positive experience for guselkumab-

treated patients despite prior TNFi use. Notably, treatment persistence among guselkumab-randomized patients was nearly 90% across all four studies, ranging from 87% in COSMOS to 91% in Phase 2.[20,22,25,26] Furthermore, the proportion of patients who discontinued due to AEs was low (4%) and the rate was similar regardless of TNFi status. Therefore, the consistent and durable treatment response to guselkumab among both TNFi-naïve and TNFi-experienced subpopulations reported here indicates the potential utility of guselkumab as an alternative biologic treatment for some patients with refractory disease, as well as a first-line biologic, depending on the disease profile.[1]

The safety profile of guselkumab in this population of PsA patients is generally consistent with the established safety profile in clinical studies in plaque psoriasis with up to 5 years of follow-up.[34] Additionally, guselkumab has demonstrated durable and robust efficacy for both dosing regimens in PsA patients.[20-26] However, in general, elevations in hepatic transaminases occurred more frequently in PsA patients receiving the Q4W dose compared with PsA and psoriasis patients receiving the Q8W dose.[35]

Some limitations of these analyses should be noted. No comparator was evaluated after the first 24 weeks, and DISCOVER-2 was the only study to f follow patients for 2 years, while the Phase 2, DISCOVER-1, and COSMOS studies were limited to 1 year. Exposure-adjusted incidence rates were utilized to account for the difference in study designs. The trials were not powered for rare events; however, the more extended follow-up period in DISCOVER-2 allowed for more sensitive detection of events that require longer latency periods (eg, malignancies). Additional data from the 3-year APEX trial (ClinicalTrials.gov: NCT04882098) will provide longer-term

safety data. All analyses were performed post hoc, as the studies were not designed to compare safety by prior TNFi or concomitant MTX use. Immunogenicity analyses were limited by the small numbers of patients who tested positive for antibodies to guselkumab during the studies, which precluded meaningful evaluation of immunogenicity by prior TNFi status. However, as previously reported, the proportions of patients who tested positive for antibodies to guselkumab were low in the Phase 2, DISCOVER-1, and DISCOVER-2 studies (immunogenicity was not assessed in COSMOS).[20,22,25] Additional analyses in DISCOVER-1 and DISCOVER-2 found no association between antibodies to guselkumab and ISRs,[28] and the presence of antibodies to guselkumab did not preclude clinical response.[22, 25]

These results demonstrate that guselkumab was well tolerated in studies continuing for 1 to 2 years among patients with moderate-to-severe PsA regardless of TNFi experience and concomitant MTX use, making the findings relevant to the PsA population in a clinical setting. Together with the robust efficacy data, these results further support the long-term use of guselkumab as an initial biologic therapy or in those who have failed or were intolerant to TNFi treatment.

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REFERENCES

1. Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, Dougados M, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020;79:700-12.

2. Coates LC, Soriano ER, Corp N, Bertheussen H, Callis Duffin K, Campanholo CB, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): Updated treatment recommendations for psoriatic arthritis 2021. Nature Rev Rheum 2022;18:465-79.

3. Fagerli KM, Kearsley-Fleet, L, Watson KD, Packham J, BSRBR-RA Contributors Group, Symmons DPM, et al. Long-term persistence of TNF-inhibitor treatment in patients with psoriatic arthritis: Data from the British Society for Rheumatology. Biologics Register. RMD Open 2018;4:e000596.

4. Glintborg B, Ostergaard M, Krogh NS, Andersen MD, Tarp U, Loft AG, et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy. Arthritis Rheum 2013;65:1213-23.

5. Harrold LR, Stolshek BS, Rebello S, Collier DH, Mutebi A, Wade SW, et al. Impact of prior biologic use on persistence of treatment in patients with psoriatic arthritis enrolled in the US Corrona registry. Clin Rheumatol 2017;36:895-901.

6. Saad AA, Ashcroft DM, Watson KD, Hyrich KL, Noyce PR, Symmons DPM. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumaology Biologics Register. Arthritis Res Ther 2009;11:R52.

7. Merola JF, Lockshin B, Mody EA. Switching biologics in the treatment of psoriatic arthritis. Semin Arthritis Rheum 2017;47:29-37.

8. Costa L, Perricone C, Chimenti MS, Del Puente A, Caso P, Peluso R, et al. Switching between biological treatments in psoriatic arthritis: a review of the evidence. Drugs R D 2017;17:509-22.

9. Mease PJ, Karki C, Liu M, Li Y, Gershenson B, Feng H, et al. Discontinuation and switching patterns of tumour necrosis factor inhibitors (TNFis) in TNFi-naïve and TNFi-expereinced patients with psoriatic arthritis: an observational study from the the US-based Corrona registry. RMD Open 2019;5:e000880.

10. Girolomoni G, Altomare G, Ayala F, Berardesca E, Calzavara-Pinton P, Chimenti S, et al. Safety of anti-TNFα agents in the treatment of psoriasis and psoriatic arthritis. Immunopharm Immunoto 2012;34:548-60.

11. Van den Bosch F, Coates L. Clinical management of psoriatic arthritis. Lancet 2018;391:2285-94.

12. Costello R, David T, Jani M. Impact of adverse events associated with medications in the treatment and prevention of rheumatoid arthritis. Clin Ther 2019;41:1376-96.

13. COSENTYX® [package insert]. East Hanover, NJ, USA: Novaris Pharmaceuticals Corporation; 2021.

14. HUMIRA® [package insert]. Chicago, IL, USA: AbbVie Inc.; 2021.

15. SILIQ™ [package insert]. Bridgewater, NJ Bausch Health US, LLC; 2020.

16. SKYRIZI® [package insert]. Chicago, IL, USA: AbbVie Inc.; 2022.

17. STELARA® [package insert]. Horsham, PA, USA: Janssen Biotech, LLC; 2020.

18. TALTZ [package insert]. Indianapolis, IN, USA: Eli Lilly and Company; 2022.

19. TREMFYA® [package insert]. Horsham, PA, USA: Janssen Biotech, LLC; 2020.

20. Deodhar A, Gottlieb AB, Boehncke W-H, Dong B, Wang Y, Zhuang Y, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet 2018;391:2213-24.

21. Deodhar A, Helliwell PS, Boehncke W-H, Kollmeier AP, Hsia EC, Subramanian RA, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFa inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet 2020;395:1115-25.

22. Ritchlin CT, Helliwell PS, Boehncke W-H, Soriano ER, Hsia EC, Kollmeier AP, et al. Guselkumab, an inhibitor of the IL-23p19 subunit, provides sustained improvement in signs and symptoms of active psoriatic arthritis: 1-year results of a phase III randomised study of patients who were biologic-naïve or TNF-α inhibitor-experienced. RMD Open 2021:7:e001457.

23. Mease PJ, Rahman P, Gottlieb AB, Kollmeier AP, Hsia EC, Xu XL, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet 2020;395:1126-36.

24. McInnes IB, Rahman P, Gottlieb AB, Hsia EC, Kollmeier AP, Chakravarty SD, et al. Efficacy and safety of guselkumeb, an interleukin-23p19-specific monoclonal antibody, through one year in biologic-naïve patients with psoriatic arthritis. Arthritis Rheum 2021;73:604-16.

25. McInnes IB, Rahman P, Gottlieb AB, Hsia EC, Kollmeier AP, Xu XL, et al. Long-term efficacy and safety of guselkumab, a monoclonal antibody specific to the p19 subunit of interleukin-23, through 2 years: results from a phase III, randomized, double-blind, placebo-controlled study conducted in biologic-naïve patients with actve psoriatic arthritis. Arthritis Rheum 2022;74:475-85.

26. Coates LC, Gossec L, Theander E, Bergmans P, Neuhold M, Karyekar CS, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis who are inadequate responders to tumour necrosis factor inhibitors: results through one year of a phase IIIb, randomised, controlled study (COSMOS). Ann Rheum Dis 2022;81:359-69.

27. Wang W, Zhou H, Liu L. Side effects of methorextae therapy for rheumatoid arthritis: A systematic review. Eur J Med Chem 2018;158:502-16.

28. Rahman P, Ritchlin CT, Helliwell PS, Boehncke W-H, Mease PJ, Gottlieb AB, et al. Pooled safety results through 1 year of 2 phase III trials of guselkumab in patients with psoriatic arthritis. J Rheum 2021;48:1815-23.

29. Woo YR, Park CJ, Kang H, Kim JE. The risk of systemic diseases in those with psoriasis and psoriatic arthritis: from mechanisms to clinic. Int J Mol Sci 2020;21:7041.

30. Gottlieb AB, Deodhar A, McInnes IB, Baraliakos X, Reich K, Schreiber S, et al. Long-term safety of secukinumab over five years in patients with moderate-to-severe plaque

psoriasis, psoriatic arthritis, and ankylosing spondylitis: update on integrated pooled clinical trial and post-marketing surveillance data. Acta Derm Venereol 2022;102:adv00698.

31. Deodhar AA, Combe B, Accioly AP, Bolce R, Zhu D, Gellett AM, et al. Safety of ixekizumab in patients with psoriatic arthritis: data from four clinical trials with over 2000 patient-years of exposure. Ann Rheum Dis 2022;81:944-50.

32. Sandborn WJ, D'Haens GR, Reinisch W, Panés J, Chan D, Gonzalez S, et al. Guselkumab for the treatment of Crohn's disease: induction results from the phase 2 GALAXI-1 study. Gastroenterology 2022;162:1650-64.

33. Esteban JP, Dinani A. The efficacy and safety of guselkumab induction therapy in patients with moderately to severely active ulcerative colitis: Phase 2b QUASAR Study results through week 12. Gastroenterol Hepatol 2022;18:12.

34. Blauvelt A, Tsai TF, Langley RG, Miller M, Shen Y-K, You Y, et al. Consistent safety profile with up to 5 years of continuous treatment with guselkumab: Pooled anlayses from the phase 3 VOYAGE 1 and VOYAGE 2 trials of patients with moderate-to-severe psoriasis. J Am Acad Dermatol 2022;86:827-34.

35. Rahman P, Gottlieb AB, Merola JF, Armstrong A, Langley R, Lebwohl M, et al (2022; June 2-5). Comparable safety profile of guselkumab in psoriatic arthritis and psoriasis patients: Results from the phase 3 guselkumab clinical program through 1 year. [Poster

presentation]. European Alliance of Associations for Rheumatology (EULAR); virtual congress.

FIGURE LEGENDS

Figure 1. Patient disposition across Phase 2/3 trials of guselkumab in PsA through end of study: (A) TNFi-naive patients and (B) TNFi-experienced patients; GUS, guselkumab; PsA, psoriatic arthritis; Q4W, every-4-weeks; Q8W, every-8-weeks, TNFi, tumor necrosis factor-α inhibitor.

Figure 2. Adverse events per 100PY in TNFi-experienced and TNFi-naïve patients across Phase 2/3 trials of guselkumab in PsA through end of study: (A) SAEs, (B) Study agent d/c due to AEs, (C) Serious infections, (D) GI SAEs, (E) MACE, and (F) Malignancies. AEs, adverse events; CI, confidence interval; D/C, discontinuation; GI, gastrointestinal; GUS, guselkumab; MACE, major adverse cardiovascular event; PBO, placebo; PsA, psoriatic arthritis; PY, patient-years; Q4W, every-4-weeks; Q8W, every-8-weeks; SAEs, serious adverse events, TNFi, tumor necrosis factor-α inhibitor; W, weeks; Y, years.

Figure 3. Proportion of patients with maximum increase of NCI-CTCAE Toxicity Grade 1 by MTX use and TNFi status at baseline across Phase 2/3 trials of guselkumab in PsA through end of study: (A) ALT increases in All patients, (B) ALT increases in TNFi-naïve patients, (C) ALT increases in TNFi-experienced patients, (D) AST increases in All patients, (E) AST increases in TNFi-naïve patients, and (F) AST increases in TNFi-experienced patients. ALT, alanine transaminase; AST, aspartate transaminase; GUS, guselkumab; MTX, methotrexate; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PBO, placebo; PsA, psoriatic arthritis; Q4W, every-4-weeks; Q8W, every-8-weeks; TNFi, tumor necrosis factor-α inhibitor.

Table 1. Demographics, disease characteristics, and medication history at baseline by TNFi status in patients with active PsA across Phase 2/3 trials of guselkumab

	TNFi-naïve (N=1138)	TNFi-experienced (N=416)[a]	Overall (N=1554)
Demographics			
Age, years	46.2 ± 11.9	49.4 ± 11.7	47.1 ± 11.9
Sex, male	589 (51.76)	208 (50.0)	797 (51.29)
BMI, kg/m^2	29.1 ± 6.2	29.8 ± 6.2	29.3 ± 6.2
Disease characteristics			
PsA duration, years	5.6 ± 6.0	8.8 ± 7.4	6.5 ± 6.5
Swollen joint counts (0-66)	11.5 ± 7.3	10.1 ± 7.1	11.2 ± 7.3
Tender joint counts (0-68)	20.4 ± 13.0	20.7 ± 13.3	20.5 ± 13.0
CRP, mg/dL, median (IQR)	0.93 (0.48-2.15)	0.62 (0.20-1.57)	0.85 (0.40-2.01)
Psoriasis BSA, %	16.1 ± 18.9	16.2 ± 20.2	16.1 ± 19.3
PASI score (0-72)	9.6 ± 10.5	10.6 ± 11.1	9.9 ± 10.7
Prior/concomitant medications			
Concomitant			
csDMARDs	733 (64.41)	272 (65.4)	1005 (64.67)
MTX	637 (55.98)	238 (57.2)	875 (56.31)
Mean dose (mg/week)	15.5 ± 4.8	15.5 ± 4.6	15.5 ± 4.7
Oral corticosteroids	192 (16.87)	81 (19.5)	273 (17.57)
Mean dose (mg/day)[b]	7.0 ± 2.5	6.5 ± 2.3	6.9 ± 2.4
NSAIDs	749 (65.82)	235 (56.5)	984 (63.32)

Data are presented as mean ± standard deviation or n (%) unless otherwise noted. BMI, body mass index; BSA, body surface area; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; IQR, interquartile range; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; TNFi, tumor necrosis factor-α inhibitor

[a]The TNFi-experienced subpopulation comprised 8.7% of patients (13/149) from the Phase 2 study, 31.0% from DISCOVER-1 (118/381), and 100% (n=285) from COSMOS.[20,21,26]

[b]Prednisone or equivalent dose

Table 2. Number of adverse events per 100PY (95% confidence intervals[a]) for all patients and by concomitant MTX use at baseline in patients with active PsA treated through end of study across Phase 2/3 trials of guselkumab

	Placebo--controlled period (Weeks 0-24)				Through end of study[b]		
	Guselkumab 100 mg				Guselkumab 100 mg[c]		
	Q4W	Q8W	Combined	Placebo	Q4W	Q8W	All
All patients, n	373	664	1037	517	725	783	1508
Total PY	172	305	478	230	1106	1019	2125
AEs	222.7 (201.01-246.17)	232.6 (215.82-250.37)	229.05 (215.68-243.03)	222.5 (203.64-242.67)	132.6 (125.91-139.57)	160.0 (152.30-167.93)	145.73 (140.64-150.95)
SAEs	5.2 (2.39-9.91)	4.9 (2.75-8.11)	5.02 (3.22-7.48)	8.7 (5.32-13.45)	5.2 (3.90-6.68)	6.3 (4.84-8.02)	5.69 (4.72-6.80)
AEs→D/C	7.0 (3.60-12.16)	3.6 (1.80-6.45)	4.82 (3.05-7.23)	4.4 (2.09-8.01)	3.1 (2.13-4.29)	2.4 (1.51-3.50)	2.73 (2.07-3.53)
Infections	62.6 (51.39-75.63)	59.0 (50.67-68.25)	60.30 (53.53-67.68)	64.0 (54.08-75.24)	40.6 (36.92-44.52)	43.5 (39.52-47.72)	41.97 (39.26-44.82)
Serious infections	1.7 (0.36-5.09)	0.7 (0.08-2.37)	1.05 (0.34-2.44)	3.1 (1.23-6.28)	1.5 (0.90-2.46)	1.7 (0.97-2.67)	1.60 (1.11-2.24)
Opportunistic infections[d]	0.0 (0.00-1.74)	0.0 (0.00-0.98)	0.00 (0.00-0.63)	0.0 (0.00-1.30)	0.1 (0.00-0.50)	0.2 (0.02-0.71)	0.14 (0.03-0.41)
GI-related SAEs	0.0	0.3	0.21	1.3	0.3	0.3	0.28

	(0.00-1.74)	(0.01-1.83)	(0.01-1.17)	(0.27-3.82)	(0.06-0.79)	(0.06-0.86)	(0.10-0.61)
Malignancies[e]	0.0 (0.00-1.74)	1.0 (0.20-2.87)	0.63 (0.13-1.84)	0.4 (0.01-2.43)	0.2 (0.02-0.65)	0.4 (0.11-1.01)	0.28 (0.10-0.61)
MACE[f]	0.6 (0.01-3.23)	0.3 (0.01-1.83)	0.42 (0.05-1.51)	0.4 (0.01-2.43)	0.3 (0.06-0.79)	0.2 (0.02-0.71)	0.24 (0.08-0.55)
Concomitant MTX use, n	218	361	579	296	432	421	853
Total PY	101	166	267	133	666	557	1223
AEs	236.8 (207.77-268.86)	240.4 (217.37-265.10)	239.0 (220.85-258.30)	219.6 (195.18-246.34)	125.6 (117.18-134.36)	160.1 (149.74-170.93)	141.3 (134.70-148.10)
SAEs	6.0 (2.18-12.94)	5.4 (2.47-10.27)	5.6 (3.14-9.25)	9.0 (4.66-15.77)	5.1 (3.54-7.14)	5.9 (4.08-8.32)	5.5 (4.25-6.96)
AEs→D/C	9.9 (4.75-18.22)	3.0 (0.98-7.01)	5.6 (3.14-9.25)	5.3 (2.12-10.85)	3.8 (2.43-5.54)	2.0 (0.99-3.53)	2.9 (2.06-4.07)
Infections	58.5 (44.51-75.42)	62.0 (50.52-75.06)	60.6 (51.63-70.68)	67.0 (53.76-82.39)	38.9 (34.30-43.93)	46.4 (40.99-52.50)	42.4 (38.78-46.16)
Serious infections	2.0 (0.24-7.16)	0.6 (0.02-3.35)	1.1 (0.23-3.28)	3.8 (1.22-8.78)	1.5 (0.72-2.76)	1.3 (0.51-2.59)	1.4 (0.81-2.23)
Opportunistic infections	0.0 (0.00-2.97)	0.0 (0.00-1.80)	0.0 (0.00-1.12)	0.0 (0.00-2.25)	0.2 (0.00-0.84)	0.2 (0.00-1.00)	0.16 (0.02-0.59)
GI-related SAEs	0.0 (0.00-2.97)	0.0 (0.00-1.80)	0.0 (0.00-1.12)	0.8 (0.02-4.19)	0.2 (0.00-0.84)	0.2 (0.00-1.00)	0.16 (0.02-0.59)

Malignancies	0.0 (0.00-2.97)	1.2 (0.15-4.34)	0.8 (0.09-2.70)	0.8 (0.02-4.19)	0.0 (0.00-0.45)	0.4 (0.04-1.30)	0.2 (0.02-0.59)
MACE	1.0 (0.03-5.52)	0.6 (0.02-3.35)	0.8 (0.09-2.70)	0.8 (0.02-4.19)	0.3 (0.04-1.09)	0.4 (0.04-1.30)	0.3 (0.09-0.84)
No Concomitant MTX use, n	155	303	458	221	293	362	655
Total PY	71	139	210	97	440	462	902
AEs	202.8 (171.15-238.64)	223.4 (199.17-249.64)	216.4 (196.94-237.19)	226.4 (197.45-258.51)	143.3 (132.31-154.90)	159.8 (148.52-171.80)	151.8 (143.82-160.01)
SAEs	4.2 (0.87-12.26)	4.3 (1.59-9.41)	4.3 (1.96-8.12)	8.3 (3.57-16.30)	5.2 (3.31-7.84)	6.7 (4.56-9.53)	6.0 (4.50-7.81)
AEs→D/C	2.8 (0.34-10.11)	4.3 (1.59-9.41)	3.8 (1.64-7.50)	3.1 (0.64-9.07)	2.0 (0.93-3.88)	2.8 (1.50-4.81)	2.44 (1.53-3.69)
Infections	68.5 (50.70-90.61)	55.5 (43.78-69.34)	59.9 (49.91-71.34)	60.0 (45.54-77.53)	43.1 (37.22-49.73)	39.8 (34.30-46.04)	41.5 (37.36-45.88)
Serious infections	1.4 (0.04-7.79)	0.72 (0.02-4.01)	1.0 (0.12-3.44)	2.1 (0.25-7.47)	1.6 (0.64-3.27)	2.2 (1.04-3.98)	1.9 (1.10-3.02)
Opportunistic infections	0.0 (0.00-4.19)	0.0 (0.00-2.16)	0.0 (0.00-1.42)	0.0 (0.00-3.10)	0.0 (0.00-0.68)	0.2 (0.01-1.21)	0.1 (0.00-0.62)
GI-related SAEs	0.0 (0.00-4.19)	0.7 (0.02-4.01)	0.5 (0.01-2.65)	2.1 (0.25-7.47)	0.4 (0.05-1.64)	0.4 (0.05-1.56)	0.4 (0.12-1.14)
Malignancies	0.0 (0.00-4.19)	0.7 (0.02-4.01)	0.5 (0.01-2.65)	0.0 (0.00-3.10)	0.4 (0.05-1.64)	0.4 (0.05-1.56)	0.4 (0.12-1.14)

MACE	0.0 (0.00-4.19)	0.0 (0.00-2.16)	0.00 (0.00-1.42)	0.0 (0.00-3.10)	0.2 (0.01-1.27)	0.0 (0.00-0.65)	0.1 (0.00-0.62)

Data are reported as number of events/100PY (95% confidence interval). AE-adverse event; AE→DC-adverse events leading to discontinuation; GI-gastrointestinal; MACE-major adverse cardiovascular events; MTX-methotrexate; PsA-psoriatic arthritis; PY-patient-years; Q4W-every-4-weeks; Q8W-every8 weeks; SAE-serious adverse event.

[a] Confidence internals based on exact method assuming the observed number of events followed a Poisson distribution.

[b] Includes data through week 56 in Phase 2 and COSMOS-week 60 in DISCOVER-1-and week 112 in DISCOVER-2.

[c] Includes patients randomized to the placebo groups who crossed over to receive guselkumab; however-only data collected on or after the first administration of guselkumab were captured.

[d] Includes meningitis listeria-herpes zoster disseminated-and fungal esophagitis in 3 guselkumab-treated patients.[25]

[e] Includes basal cell carcinoma-malignant melanoma/squamous cell carcinoma (same patient)-multiple myeloma-melanoma in situ-and prostatic adenocarcinoma in guselkumab-treated patients and renal clear cell carcinoma in one placebo-treated patients.[20-23,26]

[f] Includes three myocardial infarctions and two ischemic strokes in guselkumab-treated patients.[20,23,25,26] Additionally-one patient in the placebo group died of cardiac failure.[21]

Table 3. Proportion of patients with post-baseline laboratory abnormalities by maximum NCI-CTCAE toxicity grade and TNFi status at baseline in patients with active PsA treated through end of study across Phase 2/3 trials of guselkumab

	Placebo-controlled period (Weeks 0-24)				Through end of study[a]		
	Guselkumab 100 mg				Guselkumab 100 mg[b]		
	Q4W	Q8W	Combined	Placebo[c]	Q4W	Q8W	All
All patients, n	371	662	1033	514	722	780	1502
ALT increased[d]							
Grade 1	130 (35.0)	182 (27.5)	312 (30.20)	138 (26.8)	286 (39.6)	277 (35.5)	563 (37.48)
Grade 2	10 (2.7)	7 (1.1)	17 (1.65)	5 (1.0)	31 (4.3)	16 (2.1)	47 (3.13)
Grade 3	4 (1.1)	3 (0.5)	7 (0.68)	4 (0.8)	6 (0.8)	6 (0.8)	12 (0.80)
Grade 4	0	0	0	2 (0.4)	0	0	0
AST increased[d]							
Grade 1	80 (21.6)	116 (17.5)	196 (18.97)	97 (18.9)	204 (28.3)	200 (25.6)	404 (26.90)
Grade 2	6 (1.6)	10 (1.5)	16 (1.55)	3 (0.6)	21 (2.9)	20 (2.6)	41 (2.73)
Grade 3	6 (1.6)	2 (0.3)	8 (0.77)	4 (0.8)	12 (1.7)	6 (0.8)	18 (1.20)
Grade 4	0	0	0	1 (0.2)	0	0	0
Bilirubin increased[e]							
Grade 1	21 (5.7)	27 (4.1)	48 (4.65	11 (2.1)	49 (6.8)	38 (4.9)	87 (5.79)
Grade 2	2 (0.5)	7 (1.1)	9 (0.87)	6 (1.2)	8 (1.1)	18 (2.3)	26 (1.73)
Grade 3	0	0	0	0	0	1 (0.1)	1 (0.07)
Grade 4	0	0	0	0	0	0	0
Neutrophil decreased[f]							
Grade 1	22 (5.9)	41 (6.2)	63 (6.10)	18 (3.5)	50 (6.9)	78 (10.0)	128 (8.52)
Grade 2	6 (1.6)	15 (2.3)	21 (2.03)	3 (0.6)	21 (2.9)	25 (3.2)	46 (3.06)
Grade 3	0	1 (0.2)	1 (0.10)	1 (0.2)	4 (0.6)	4 (0.5)	8 (0.53)
Grade 4	1 (0.3)	0	1 (0.10)	0	1 (0.1)	0	1 (0.07)

TNFi-naïve, n	333	423	756	377	652	450	1102
ALT increased[d]							
Grade 1	118 (35.4)	121 (28.6)	239 (31.6)	113 (30.0)	260 (39.9)	177 (39.3)	437 (39.66)
Grade 2	10 (3.0)	6 (1.4)	16 (2.1)	4 (1.1)	30 (4.6)	14 (3.1)	44 (3.99)
Grade 3	4 (1.2)	3 (0.7)	7 (0.9)	3 (0.8)	6 (0.9)	4 (0.9)	10 (0.91)
Grade 4	0	0	0	1 (0.3)	0	0	0
AST increased[d]							
Grade 1	72 (21.6)	72 (17.0)	144 (19.0)	74 (19.6)	188 (28.8)	122 (27.1)	310 (28.13)
Grade 2	6 (1.8)	8 (1.9)	14 (1.9)	1 (0.3)	20 (3.1)	16 (3.6)	36 (3.27)
Grade 3	6 (1.8)	2 (0.5)	8 (1.1)	4 (1.1)	12 (1.8)	4 (0.9)	16 (1.45)
Grade 4	0	0	0	0	0	0	0
Bilirubin increased[e]							
Grade 1	19 (5.7)	19 (4.5)	38 (5.0)	5 (1.3)	44 (6.7)	22 (4.9)	66 (5.99)
Grade 2	2 (0.6)	5 (1.2)	7 (0.9)	5 (1.3)	7 (1.1)	14 (3.1)	21 (1.91)
Grade 3	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0
Neutrophil decreased[f]							
Grade 1	19 (5.7)	30 (7.1)	49 (6.5)	13 (3.4)	45 (6.9)	58 (12.9)	103 (9.35)
Grade 2	6 (1.8)	7 (1.7)	13 (1.7)	3 (0.8)	21 (3.2)	13 (2.9)	34 (3.09)
Grade 3	0	1 (0.2)	1 (0.1)	1 (0.3)	4 (0.6)	3 (0.7)	7 (0.64)
Grade 4	1 (0.3)	0	1 (0.1)	0	1 (0.2)	0	1 (0.09)
TNFi-experienced, n	38	239	277	137	70	330	400
ALT increased[d]							
Grade 1	12 (32)	61 (25.5)	73 (26.4)	25 (18.2)	26 (37)	100 (30.3)	126 (31.5)
Grade 2	0	1 (0.4)	1 (0.4)	1 (0.7)	1 (1)	2 (0.6)	3 (0.8
Grade 3	0	0	0	1 (0.7)	0	2 (0.6)	2 (0.5)
Grade 4	0	0	0	1 (0.7)	0	0	0
AST increased[d]							
Grade 1	8 (21)	44 (18.4)	52 (18.8)	23 (16.8)	16 (22.9)	78 (23.6)	94 (23.5)
Grade 2	0	2 (0.8)	2 (0.7)	2 (1.5)	1 (1.4)	4 (1.2)	5 (1.3)

Grade 3	0	0	0	0	0	2 (0.6)	2 (0.50)
Grade 4	0	0	0	1 (0.7)	0	0	0
Bilirubin increased[e]							
Grade 1	2 (5)	8 (3.3)	10 (3.6)	6 (4.4)	5 (7)	16 (4.8)	21 (5.3
Grade 2	0	2 (0.8)	2 (0.7)	1 (0.7)	1 (1)	4 (1.2)	5 (1.3)
Grade 3	0	0	0	0	0	1 (0.3)	1 (0.3)
Grade 4	0	0	0	0	0	0	0
Neutrophil decreased[f]							
Grade 1	3 (8)	11 (4.6)	14 (5.1)	5 (3.6)	5 (7)	20 (6.1)	25 (6.3)
Grade 2	0	8 (3.3)	8 (2.9)	0	0	12 (3.6)	12 (3.0)
Grade 3	0	0	0	0	0	1 (0.3)	1 (0.3)
Grade 4	0	0	0	0	0	0	0

Data presented as number (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; LLN, lower limit of normal; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PsA, psoriatic arthritis; Q4W, every-4-weeks, Q8W, every-8-weeks; TNFi, tumor necrosis factor-α inhibitor; ULN, upper limit of normal.

[a]Includes data through week 56 in Phase 2 and COSMOS, week 60 in DISCOVER-1, week 112 in DISCOVER-2.

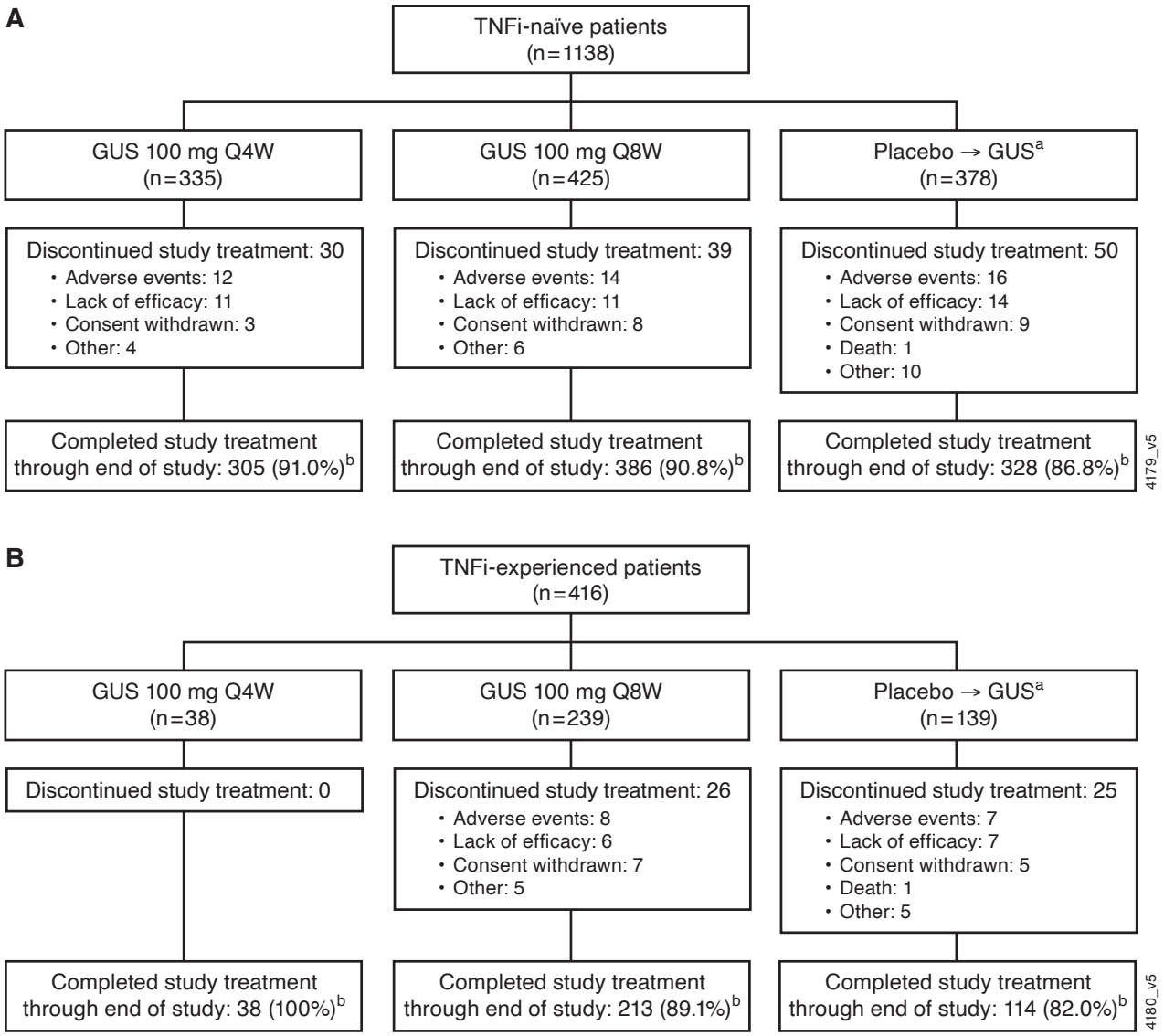
[b]Includes data collected after the first administration of guselkumab in patients randomized to placebo who crossed over to guselkumab.

[c]Includes data collected from patients randomized to placebo before crossover to guselkumab.

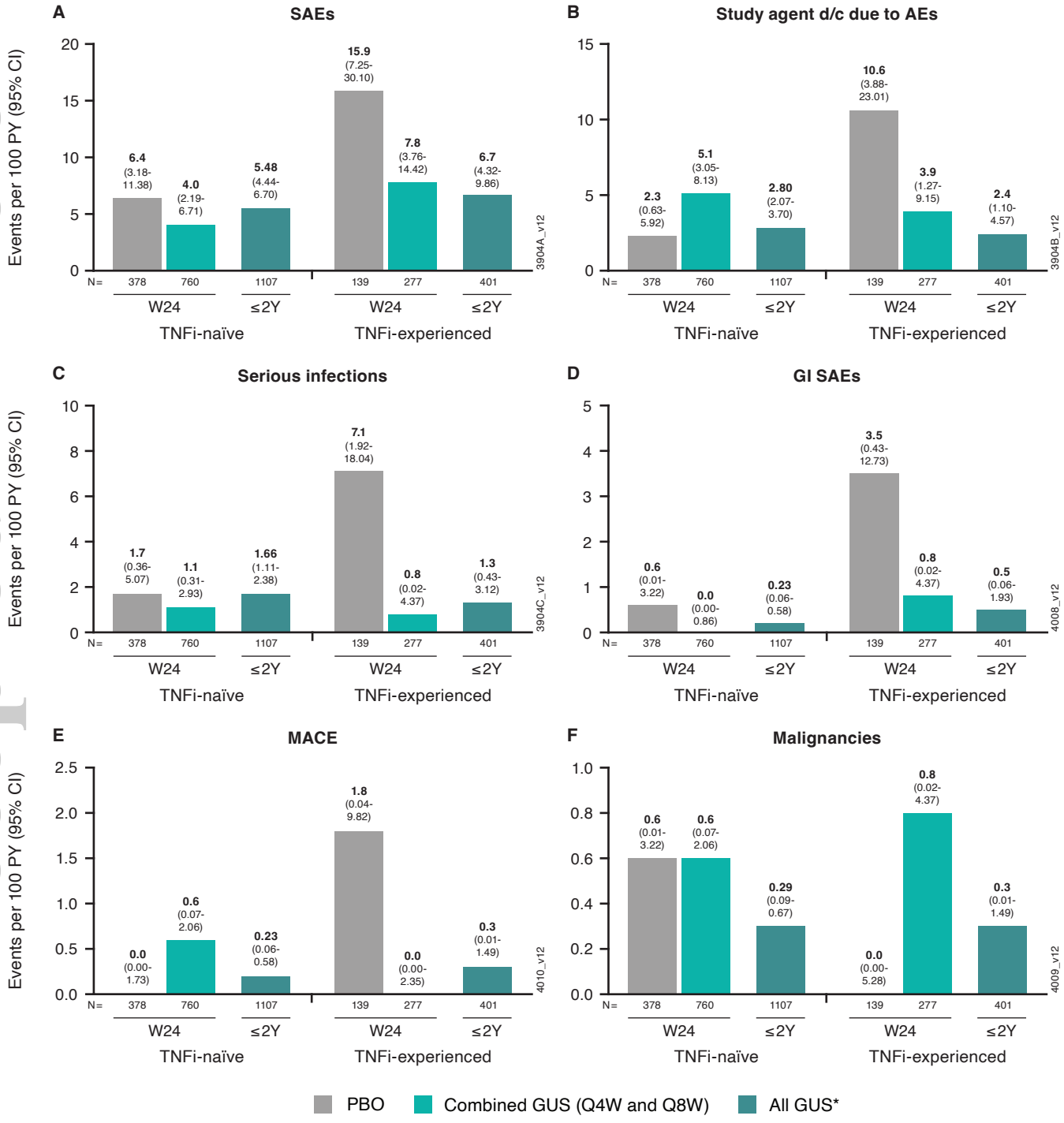
[d]NCI-CTCAE toxicity grades for increased ALT/AST values were defined as follows: Grade 1 (>1.0 to 3.0 x ULN), Grade 2 (>3.0 to 5.0 x ULN), Grade 3 (>5.0 to 20.0 x ULN), and Grade 4 (>20.0 x ULN).

[e]NCI-CTCAE toxicity grades for increased bilirubin values were defined as follows: Grade 1 (>ULN to 1.5 x ULN), Grade 2 (>1.5 to 3.0 x ULN), Grade 3 (>3.0 to 10.0 x ULN) and Grade 4 (>10.0 x ULN).

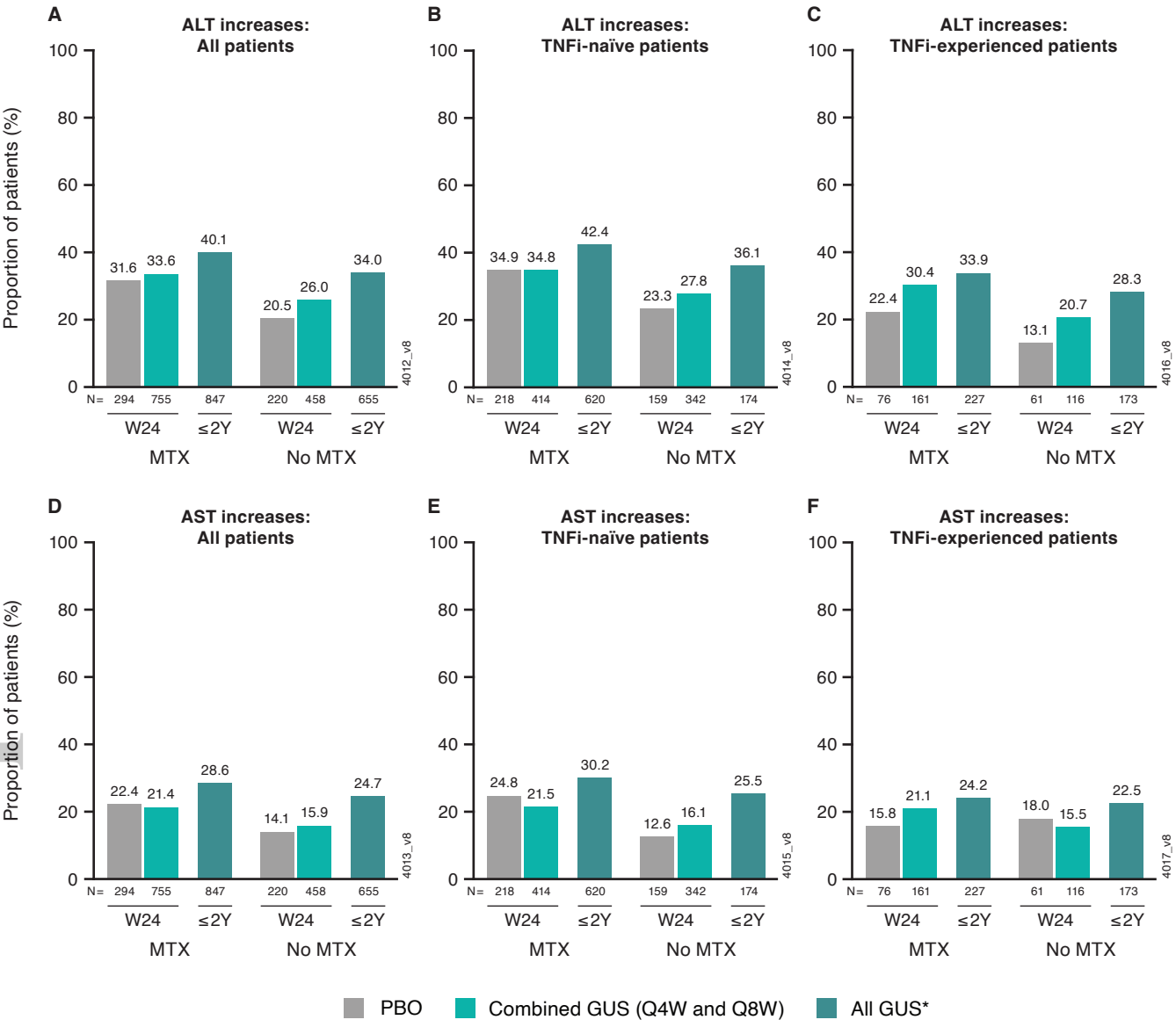
[f]NCI-CTCAE toxicity grades for decreased neutrophil values were defined as follows: Grade 1 (<LLN to 1.5 x 10^9/L), Grade 2 (<1.5 to 1.0 x 10^9/L), Grade 3 (<1.0 to 0.5 x 10^9/L), and Grade 4 (>0.5 x 10^9/L).



[a] Includes patients who crossed over to receive guselkumab (Q4W in Phase 2, DISCOVER-1, and DISCOVER-2 and Q8W in COSMOS).
[b] Includes data through week 56 in Phase 2 and COSMOS, week 60 in DISCOVER 1, and week 112 in DISCOVER 2.



* All GUS includes patients randomized to the placebo groups at baseline who crossed over to receive guselkumab; however, only data collected on or after first administration of guselkumab were captured.



* All GUS includes patients randomized to the placebo groups at baseline who crossed over to receive guselkumab; however, only data collected on or after first administration of guselkumab were captured.