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Safety of Guselkumab With and Without Prior Tumor Necrosis Factor Inhibitor Treatment: Pooled Results Across 4 Studies in Patients With Psoriatic Arthritis

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ABSTRACT. ***Objective.*** Assess pooled safety results through the end of the phase II/III studies of guselkumab (GUS; ≤ 2 years) in tumor necrosis factor inhibitor (TNFi)-naïve and -experienced patients with psoriatic arthritis (PsA).

Methods. Data were pooled from the Phase 2 and DISCOVER-1 (both TNFi-naïve and -experienced), DISCOVER-2 (TNFi-naïve), and COSMOS (TNFi-experienced) studies. Patients with active PsA were randomized to GUS 100 mg every 4 or 8 weeks (Q4W + Q8W = Combined GUS) or placebo (PBO) with crossover to GUS 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 PBO-controlled period and through end of study (≤ 2 years).

Results. Of 1554 randomized patients (n = 373 [GUS Q4W], 664 [GUS Q8W], and 517 [PBO]), 1138 (73.23%) were TNFi-naïve and 416 (26.77%) were TNFi-experienced. Respective AE rates through week 24 were 220.8/100 PY (TNFi-naïve) and 251.6/100 PY (TNFi-experienced) in the Combined GUS group and 196.1/100 PY (TNFi-naïve) and 303.0/100 PY (TNFi-experienced) in the PBO group. Among all GUS-treated patients (including those who crossed over from PBO), low AE rates were maintained during long-term evaluation in both TNFi-naïve (139.7/100 PY) and TNFi-experienced (174.0/100 PY) patients. Rates/100 PY 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 PBO and GUS-treated patients through week 24 regardless of prior TNFi use and remained low through the end of the studies.

Conclusion. The safety profile of GUS 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)]

Key Indexing Terms: adverse effects, biologic therapy, guselkumab, hepatic transaminase, psoriatic arthritis, safety

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Psoriatic arthritis (PsA) is a chronic, inflammatory disease 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 antiinflammatory drugs (NSAIDs) or conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and those with poor prognostic indicators.[1,2] Although tumor necrosis factor 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, biologic treatments 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, are 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 patients with PsA. Additionally, evaluation of safety is essential in the context of prior TNFi therapy, which may result in sustained safety concerns or represent a population with a higher inflammatory burden, as well as in patients receiving concomitant MTX, which has its own safety profile.

Guselkumab (GUS), a fully human monoclonal antibody that selectively inhibits interleukin (IL)-23p19, was the first agent in its class approved for patients with active PsA.[19] The safety and efficacy of GUS were evaluated through end of study (≤ 2 years) in adults with active PsA in 1 phase II study and 3 phase III studies (Phase 2, DISCOVER-1, DISCOVER-2, and COSMOS).[20-26] The majority of these patients were TNFi-naïve, whereas 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 GUS 100 mg every 4 weeks (Q4W) or every 8 weeks (Q8W), or placebo (PBO) with crossover to GUS Q4W; patients in the Phase 2 study and COSMOS received either GUS Q8W or PBO with crossover to GUS Q8W (Supplementary Table S1, available with online version of this article). Inclusion/exclusion criteria, including disease characteristics, prior and concomitant medications, randomized treatments, and study duration were similar across the 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 (defined as lack of efficacy or intolerance) to prior TNFi treatment, whereas 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 4 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 (IRB)/ethics committee. Sterling IRB 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 (AEs leading to D/C) and serious AEs (SAEs). AEs of interest included infections, serious infections, opportunistic infections, SAEs of the gastrointestinal (GI) Medical Dictionary for Regulatory Activities (MedDRA) 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).

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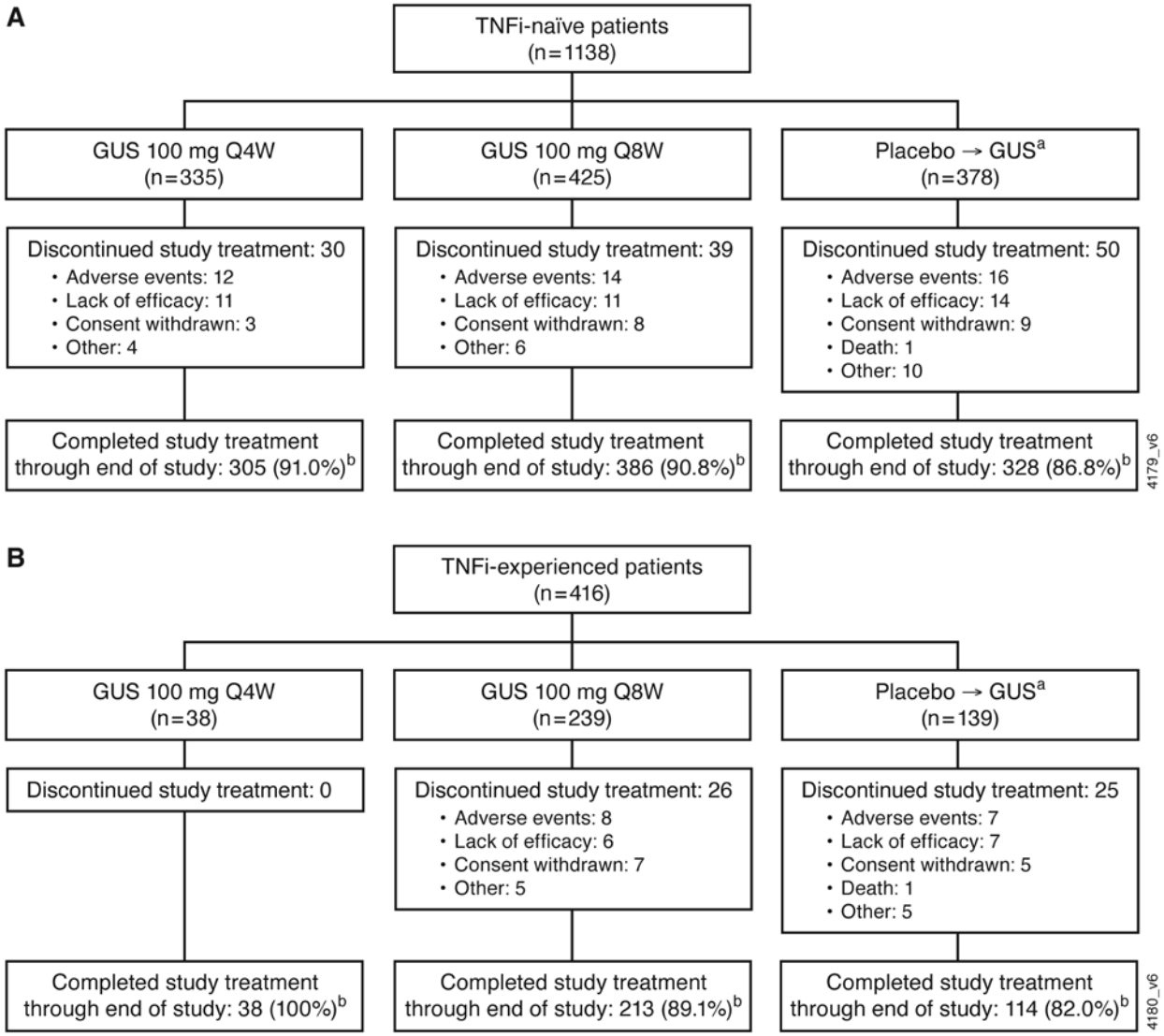
Data were integrated through the end of the studies (≤ 2 years: Phase 2 and COSMOS [week 56], DISCOVER-1 [week 60], DISCOVER-2 [week 112]) and presented over 2 time periods: week 0 to 24 (PBO-controlled period; GUS Q4W, GUS Q8W, Combined GUS [Q4W + Q8W], and PBO groups) and through end of study (GUS Q4W, GUS Q8W, and All GUS groups, including patients who crossed over from PBO 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 GUS and PBO groups, time-adjusted incidences of events/100 PY of follow-up were reported along with the corresponding 95% CIs. AEs were also summarized by the number of patients with events/100 PY (95% CIs). Laboratory abnormalities were summarized as the 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 effect of prior TNFi use on the safety of GUS, 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 GUS Q4W, GUS Q8W, and PBO, respectively); 1508 patients received ≥ 1 administration of GUS 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, and COSMOS: 1 year; DISCOVER-2: 2 years).[20,22,25,26] Overall,



[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.

Figure 1. Patient disposition across phase II/III trials of GUS in PsA through end of study: (A) TNFi-naïve patients and (B) TNFi-experienced patients. GUS: guselkumab; PsA: psoriatic arthritis; Q4W: every 4 weeks; Q8W: every 8 weeks; TNFi: tumor necrosis factor inhibitor.

treatment was completed by 89.06% of patients (1384/1554), including 89.54% (1019/1138) of TNFi-naïve patients and 87.74% (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% of all patients were receiving concomitant MTX and oral corticosteroids, respectively; rates were similar for TNFi-experienced and -naïve patients.

Baseline demographic and disease characteristics were generally similar regardless of prior 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 GUS 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% [239/664]).

Adverse events. Through W24, the incidence of AEs was similar between the Combined GUS (229.1/100 PY) and PBO (222.5/100 PY) groups; rates were comparable in the GUS groups (including PBO crossovers) through end of study (All GUS [145.7/100 PY]; Table 2). Rates/100 PY of SAEs and AEs leading to D/C were low and comparable between the PBO and GUS 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 leading to 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 (Supplementary Table S2, available with the online version of this article). Patterns across treatment groups were generally comparable to those observed when evaluating numbers of patients/100 PY and number of events/100 PY (Supplementary Table S3).

Infections (eg, nasopharyngitis, upper respiratory tract infection) were the most common type of AE, occurring at similar rates across treatment groups through W24 (Combined GUS: 60.3/100 PY; PBO: 64.0/100 PY) and end of study (All GUS: 42.0/100 PY). Serious infections occurred at rates of 1.1/100 PY and 3.1/100 PY in the Combined GUS and PBO

Table 1. Demographics, disease characteristics, and medication history at baseline by TNFi status in patients with active PsA across phase II/III trials of GUS.

	TNFi-Naïve n = 1138	TNFi-Experienced n = 416[a]	Total N = 1554
Demographics			
Age, yrs	46.2 ± 11.9	49.4 ± 11.7	47.1 ± 11.9
Sex, male	589 (51.76)	208 (50)	797 (51.29)
BMI[b]	29.1 ± 6.2	29.8 ± 6.2	29.3 ± 6.2
Disease characteristics			
PsA duration, yrs	5.6 ± 6.0	8.8 ± 7.4	6.5 ± 6.5
SJC-66	11.5 ± 7.3	10.1 ± 7.1	11.2 ± 7.3
TJC-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 (65.38)	1005 (64.67)
MTX	637 (55.98)	238 (57.21)	875 (56.31)
Mean dose, mg/wk	15.5 ± 4.8	15.5 ± 4.6	15.5 ± 4.7
Oral corticosteroids	192 (16.87)	81 (19.47)	273 (17.57)
Mean dose, mg/d[c]	7.0 ± 2.5	6.5 ± 2.3	6.9 ± 2.4
NSAIDs	749 (65.82)	235 (56.49)	984 (63.32)

Data are presented as mean ± SD or n (%) unless otherwise noted. [a] The TNFi-experienced subpopulation comprised 8.7% (n = 13/149) of patients from the Phase 2 study, 31% (n = 118/381) from DISCOVER-1, and 100% (n = 285) from COSMOS.[20,21,26] [b] BMI is calculated as weight in kilograms divided by height in meters squared. [c] Prednisone or equivalent dose. BSA: body surface area; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; GUS: guselkumab; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drug; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; SJC-66: 66-joint swollen join count; TJC-68: 68-joint tender joint count; TNFi: tumor necrosis factor inhibitor.

Table 2. Number of AEs per 100 PY (95% CI)[a] for all patients and by concomitant MTX use at baseline in patients with active PsA treated through end of study across phase II/III trials of GUS.

	PBO-Controlled Period (Weeks 0-24)				Through End of Study[b]		
	GUS 100 mg				GUS 100 mg[c]		
	Q4W	Q8W	Combined	PBO	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)	229.1 (215.68-243.03)	222.5 (203.64-242.67)	132.6 (125.91-139.57)	160.0 (152.30-167.93)	145.7 (140.64-150.95)
SAEs	5.2 (2.39-9.91)	4.9 (2.75-8.11)	5.0 (3.22-7.48)	8.7 (5.32-13.45)	5.2 (3.90-6.68)	6.3 (4.84-8.02)	5.7 (4.72-6.80)
AEs leading to D/C	7.0 (3.60-12.16)	3.6 (1.80-6.45)	4.8 (3.05-7.23)	4.4 (2.09-8.01)	3.1 (2.13-4.29)	2.4 (1.51-3.50)	2.7 (2.07-3.53)
Infections	62.6 (51.39-75.63)	59.0 (50.67-68.25)	60.3 (53.53-67.68)	64.0 (54.08-75.24)	40.6 (36.92-44.52)	43.5 (39.52-47.72)	42.0 (39.26-44.82)
Serious infections	1.7 (0.36-5.09)	0.7 (0.08-2.37)	1.1 (0.34-2.44)	3.1 (1.23-6.28)	1.5 (0.90-2.46)	1.7 (0.97-2.67)	1.6 (1.11-2.24)
Opp infections[d]	0.0 (0.00-1.74)	0.0 (0.00-0.98)	0.0 (0.00-0.63)	0.0 (0.00-1.30)	0.1 (0.00-0.50)	0.2 (0.02-0.71)	0.1 (0.03-0.41)
GI-related SAEs	0.0 (0.00-1.74)	0.3 (0.01-1.83)	0.2 (0.01-1.17)	1.3 (0.27-3.82)	0.3 (0.06-0.79)	0.3 (0.06-0.86)	0.3 (0.10-0.61)
Malignancies[e]	0.0 (0.00-1.74)	1.0 (0.20-2.87)	0.6 (0.13-1.84)	0.4 (0.01-2.43)	0.2 (0.02-0.65)	0.4 (0.11-1.01)	0.3 (0.10-0.61)
MACE[f]	0.6 (0.01-3.23)	0.3 (0.01-1.83)	0.4 (0.05-1.51)	0.4 (0.01-2.43)	0.3 (0.06-0.79)	0.2 (0.02-0.71)	0.2 (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 leading to 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)
Opp 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)	0.2 (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)	0.2 (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 leading to 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)	2.4 (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)	0.7 (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)

Table 2. Continued.

	PBO-Controlled Period (Weeks 0-24)				Through End of Study[b]		
	GUS 100 mg				GUS 100 mg[c]		
	Q4W	Q8W	Combined	PBO	Q4W	Q8W	All
Opp 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)	0.0 (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/100 PY (95% CI) unless otherwise indicated. [a] CIs 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 PBO groups who crossed over to receive GUS; however, only data collected on or after the first administration of GUS were included. [d] Includes meningitis listeria-herpes zoster disseminated and fungal esophagitis in 3 GUS-treated patients.[25] [e] Malignant melanoma and squamous cell carcinoma (same patient), basal cell carcinoma, multiple myeloma, melanoma in situ, and prostatic adenocarcinoma in GUS-treated patients and renal clear cell carcinoma in 1 PBO-treated patient.[20-23,26] [f] 3 myocardial infarctions and 2 ischemic strokes in GUS-treated patients.[20,23,25,26] Additionally, 1 patient in the PBO group died of cardiac failure.[21] AE: adverse event; D/C: discontinuation; GI: gastrointestinal; GUS: guselkumab; MACE: major adverse cardiovascular events; MTX: methotrexate; Opp: opportunistic; PBO: placebo; PsA: psoriatic arthritis; PY: patient-years; Q4W: every 4 weeks; Q8W: every 8 weeks; SAE: serious adverse event.

groups, respectively, through W24 and at a rate of 1.6/100 PY in the All GUS group for up to 2 years. No opportunistic infections occurred through W24, and the rate/100 PY in the All GUS group remained low (0.1/100 PY; 3 events, all TNFi-naïve patients) during long-term evaluation (Table 2). Nonserious oral candidiasis occurred in 1 GUS-treated patient (TNFi-naïve). No cases of active TB were reported.

Rates of malignancies were 0.6/100 PY and 0.4/100 PY in the Combined GUS and PBO groups, respectively, through W24 and 0.3/100 PY in the All GUS group through end of study (Table 2). Six malignancies were observed in 5 GUS-treated patients (4 TNFi-naïve; 1 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.

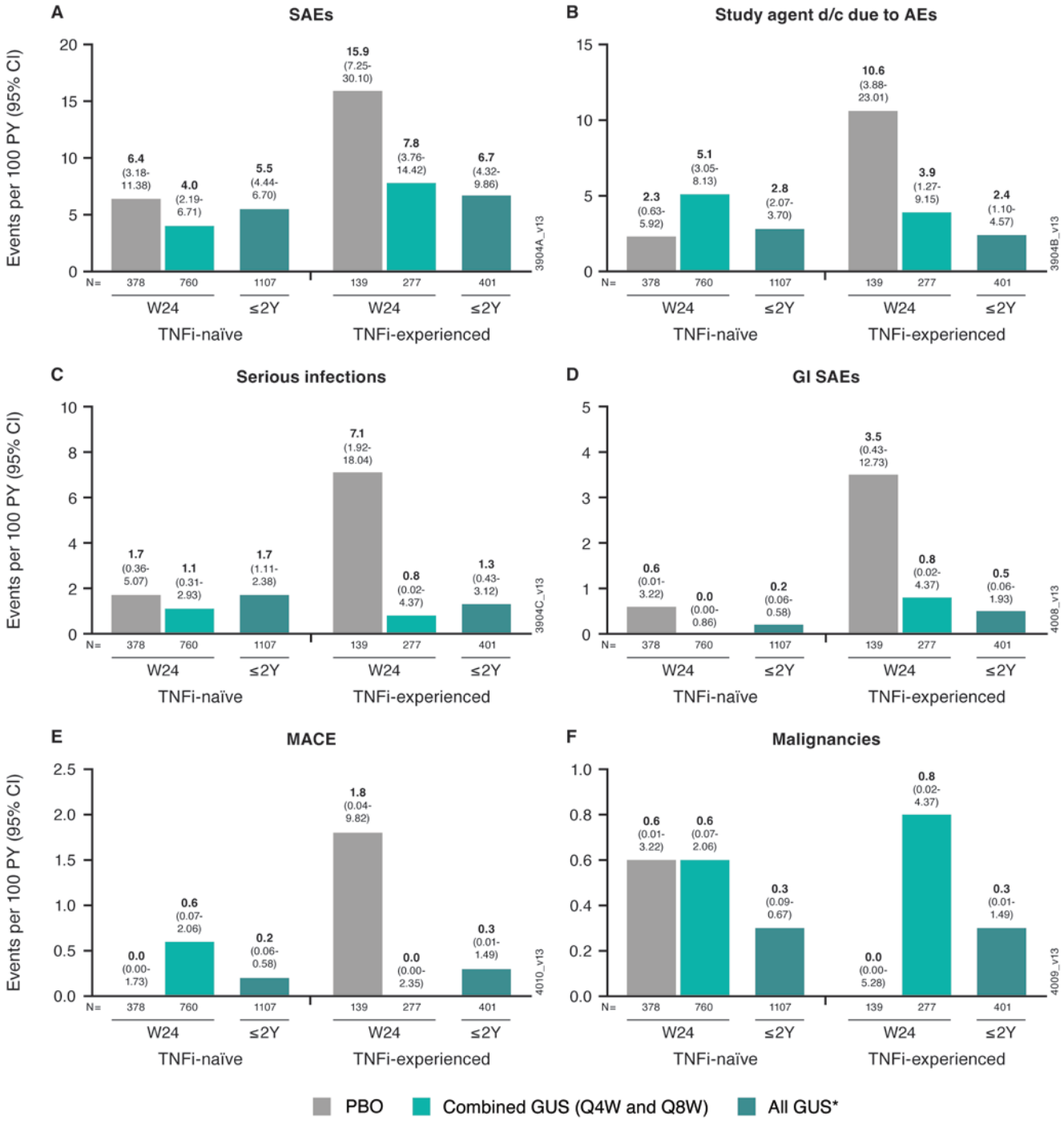
MACE occurred at a rate of 0.4/100 PY and 0.4/100 PY in the Combined GUS and PBO groups, respectively, through W24 and 0.2/100 PY in the All GUS group through end of study. Of the 6 reported MACE, 5 (3 myocardial infarctions, 2 ischemic strokes) occurred in GUS-treated patients; 1 death secondary to cardiac failure was reported in a PBO-treated patient (Table 2).[21-23,25,26] Of the 5 GUS-treated patients, 4 patients were TNFi-naïve and 1 was TNFi-experienced; all had multiple cardiovascular risk factors.

Other AEs of interest were uncommon (Table 2). Rates of GI-related SAEs were 0.2/100 PY in the Combined GUS group and 1.3/100 PY in the PBO group through W24 and 0.3/100 PY in the All GUS group through end of study. No cases of Crohn disease (CD) or ulcerative colitis (UC) occurred. Two AEs were reported as IBD (unspecified); 1 suspected case of IBD occurred in a GUS-treated patient (lost to follow-up) and another possible case was noted in a PBO-treated patient.[23,26] Uveitis occurred in 1 PBO-treated patient (TNFi-naive; 0.44/100PY [95%CI 0.01-2.43]) and no GUS-treated patient (0.00/100PY [0.00-0.63]) through the PBO-controlled period and 1 GUS-treated patient through end of study (TNFi-naïve; 0.05/100PY [0.00-0.26]). Three deaths occurred: 1 GUS-treated patient (road traffic accident) and 2 PBO-treated patients (cardiac failure and pneumonia).[21,22,25]

When evaluated by prior TNFi use, AEs occurred at rates of 220.8/100 PY (TNFi-naïve) and 251.6/100 PY (TNFi-experienced) in the Combined GUS group through W24 (Supplementary Figure S1, available with the online version of this article). Similarly, other AEs of interest did not vary by TNFi status (Figure 2). Compared with TNFi-naïve patients, TNFi-experienced patients in the PBO group (but not the GUS groups) had numerically higher numbers of events/100 PY for AEs (303.0 vs 196.1), SAEs (15.9 vs 6.4), and AE leading to D/C (10.6 vs 2.3). AE rates through end of study were 139.7/100 PY for TNFi-naïve and 174.0/100 PY for TNFi-experienced GUS-treated patients. The GUS AE profiles of patients who discontinued their prior TNFi due to inadequate efficacy or intolerance were generally comparable to that reported for all patients (Supplementary Table S2).

Concomitant MTX use did not appear to have a clinically meaningful effect 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 GUS group through W24 and in the All GUS group through end of study (MTX: 42.4; no MTX: 41.5); corresponding figures for serious infections were 1.1/100 PY (MTX) and 1.0/100 PY (no MTX) at W24 and 1.4/100 PY (MTX) and 1.9/100 PY (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 GUS (30.2%) and PBO (26.8%) groups; rates were somewhat higher in the Q4W (35%) vs Q8W group (27.5%; Table 3). Similar results were observed for Grade 1 AST elevations, with approximately 19% in both the Combined GUS and PBO groups; however, the numerical



* 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.

Figure 2. AEs/100 PY in TNFi-experienced and TNFi-naïve patients across phase II/III trials of GUS 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; 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; SAE: serious adverse event; TNFi: tumor necrosis factor inhibitor; W: weeks; Y: years.

difference between GUS 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 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 GUS-treated patients through end of study. SAEs of increased ALT occurred in 2 GUS-treated patients, both TNFi-experienced (one had underlying autoimmune hepatitis and the other had steatohepatitis), and 4 TNFi-naïve

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 II/III trials of GUS.

	PBO-Controlled Period (Weeks 0-24)				Through End of Study[a]		
	GUS 100 mg				GUS 100 mg[b]		
	Q4W	Q8W	Combined	PBO[c]	Q4W	Q8W	All
All patients, n	371	662	1033	514	722	780	1502
ALT increased[d]							
Grade 1	130 (35)	182 (27.5)	312 (30.2)	138 (26.8)	286 (39.6)	277 (35.5)	563 (37.5)
Grade 2	10 (2.7)	7 (1.1)	17 (1.6)	5 (1)	31 (4.3)	16 (2.1)	47 (3.1)
Grade 3	4 (1.1)	3 (0.5)	7 (0.7)	4 (0.8)	6 (0.8)	6 (0.8)	12 (0.8)
Grade 4	0 (0)	0 (0)	0 (0)	2 (0.4)	0 (0)	0 (0)	0 (0)
AST increased[d]							
Grade 1	80 (21.6)	116 (17.5)	196 (19)	97 (18.9)	204 (28.3)	200 (25.6)	404 (26.9)
Grade 2	6 (1.6)	10 (1.5)	16 (1.5)	3 (0.6)	21 (2.9)	20 (2.6)	41 (2.7)
Grade 3	6 (1.6)	2 (0.3)	8 (0.8)	4 (0.8)	12 (1.7)	6 (0.8)	18 (1.2)
Grade 4	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)
Bilirubin increased[e]							
Grade 1	21 (5.7)	27 (4.1)	48 (4.6)	11 (2.1)	49 (6.8)	38 (4.9)	87 (5.8)
Grade 2	2 (0.5)	7 (1.1)	9 (0.9)	6 (1.2)	8 (1.1)	18 (2.3)	26 (1.7)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	1 (0.1)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Neutrophil decreased[f]							
Grade 1	22 (5.9)	41 (6.2)	63 (6.1)	18 (3.5)	50 (6.9)	78 (10)	128 (8.5)
Grade 2	6 (1.6)	15 (2.3)	21 (2)	3 (0.6)	21 (2.9)	25 (3.2)	46 (3.1)
Grade 3	0 (0)	1 (0.2)	1 (0.1)	1 (0.2)	4 (0.6)	4 (0.5)	8 (0.5)
Grade 4	1 (0.3)	0 (0)	1 (0.1)	0 (0)	1 (0.1)	0 (0)	1 (0.1)
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)	260 (39.9)	177 (39.3)	437 (39.7)
Grade 2	10 (3)	6 (1.4)	16 (2.1)	4 (1.1)	30 (4.6)	14 (3.1)	44 (4)
Grade 3	4 (1.2)	3 (0.7)	7 (0.9)	3 (0.8)	6 (0.9)	4 (0.9)	10 (0.9)
Grade 4	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)
AST increased[d]							
Grade 1	72 (21.6)	72 (17)	144 (19)	74 (19.6)	188 (28.8)	122 (27.1)	310 (28.1)
Grade 2	6 (1.8)	8 (1.9)	14 (1.9)	1 (0.3)	20 (3.1)	16 (3.6)	36 (3.3)
Grade 3	6 (1.8)	2 (0.5)	8 (1.1)	4 (1.1)	12 (1.8)	4 (0.9)	16 (1.5)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bilirubin increased[e]							
Grade 1	19 (5.7)	19 (4.5)	38 (5)	5 (1.3)	44 (6.7)	22 (4.9)	66 (6)
Grade 2	2 (0.6)	5 (1.2)	7 (0.9)	5 (1.3)	7 (1.1)	14 (3.1)	21 (1.9)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)	0 (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 (9.3)
Grade 2	6 (1.8)	7 (1.7)	13 (1.7)	3 (0.8)	21 (3.2)	13 (2.9)	34 (3.1)
Grade 3	0 (0)	1 (0.2)	1 (0.1)	1 (0.3)	4 (0.6)	3 (0.7)	7 (0.6)
Grade 4	1 (0.3)	0 (0)	1 (0.1)	0 (0)	1 (0.2)	0 (0)	1 (0.1)
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 (0)	1 (0.4)	1 (0.4)	1 (0.7)	1 (1)	2 (0.6)	3 (0.8)
Grade 3	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	2 (0.6)	2 (0.5)
Grade 4	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	0 (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 (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 (0)	0 (0)	0 (0)	2 (0.6)	2 (0.5)
Grade 4	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)

Table 3. Continued.

	PBO-Controlled Period (Weeks 0-24)				Through End of Study[a]		
	GUS 100 mg				GUS 100 mg[b]		
	Q4W	Q8W	Combined	PBO[c]	Q4W	Q8W	All
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 (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 (0)	0 (0)	0 (0)	1 (0.3)	1 (0.3)
Grade 4	0 (0)	0 (0)	0 (0)	0 (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 (0)	8 (3.3)	8 (2.9)	0 (0)	0 (0)	12 (3.6)	12 (3)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)	1 (0.3)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Data presented as n (%). [a] Includes data through week 56 in Phase 2 and COSMOS, week 60 in DISCOVER-1, and week 112 in DISCOVER-2. [b] Includes data collected after the first administration of GUS in patients randomized to PBO who crossed over to GUS. [c] Includes data collected from patients randomized to PBO before crossover to GUS. [d] NCI-CTCAE toxicity grades for increased ALT/AST values were defined as follows: Grade 1 (> 1.0 to 3.0 × ULN), Grade 2 (> 3.0 to 5.0 × ULN), Grade 3 (> 5.0 to 20.0 × ULN), and Grade 4 (> 20.0 × ULN). [e] NCI-CTCAE toxicity grades for increased bilirubin values were defined as follows: Grade 1 (> ULN to 1.5 × ULN), Grade 2 (> 1.5 to 3.0 × ULN), Grade 3 (> 3.0 to 10.0 × ULN), and Grade 4 (> 10.0 × ULN). [f] NCI-CTCAE toxicity grades for decreased neutrophil values were defined as follows: Grade 1 (< LLN to 1.5 × 10^9/L), Grade 2 (< 1.5 to 1.0 × 10^9/L), Grade 3 (< 1.0 to 0.5 × 10^9/L), and Grade 4 (> 0.5 × 10^9/L). ALT: alanine aminotransferase; AST: aspartate aminotransferase; GUS: guselkumab; LLN: lower limit of normal; 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 inhibitor; ULN: upper limit of normal.

patients discontinued GUS 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 1 Grade 3 elevation (TNFi-experienced GUS-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 1 patient each in the Q8W and PBO groups, and 1 patient in the Q4W group had a transient Grade 4 event (all TNFi-naïve) through W24. Through end of study, 4 patients each in the Q4W and Q8W groups had Grade 3 decreases in neutrophil counts, and 1 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 1 TNFi-naïve GUS-treated patient (Q4W) who had a Grade 2 neutrophil decrease.[28] Most cases resolved spontaneously and did not necessitate treatment discontinuation, except 1 GUS-treated patient (TNFi-naïve) who discontinued due to an AE of neutropenia and a Grade 3 decreased neutrophil count that then resolved.[20]

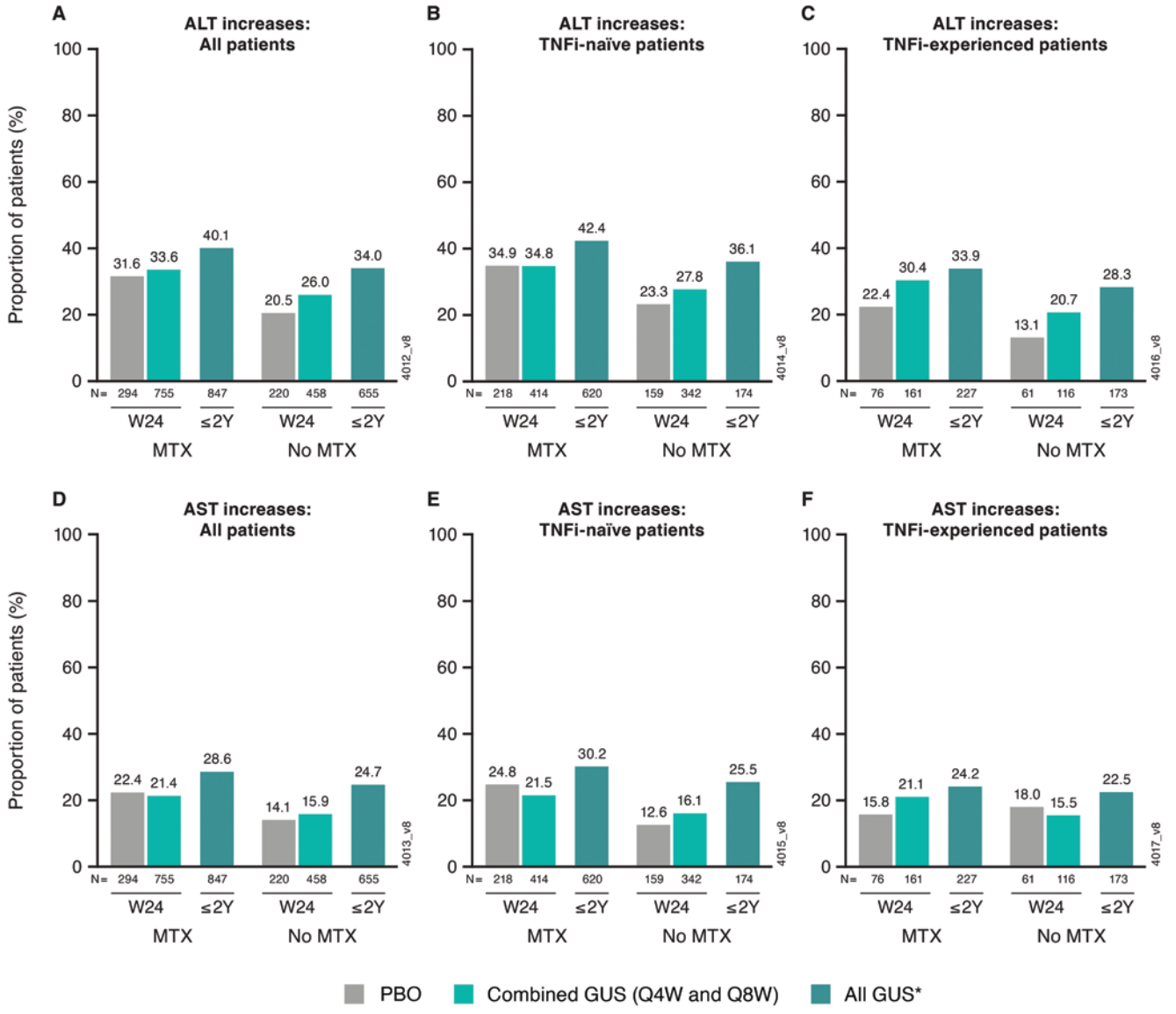
The proportions of patients with laboratory abnormalities were low through end of study regardless of prior TNFi use (Table 3), with some exceptions. Grade 1 ALT elevations in the All GUS group were somewhat higher in TNFi-naïve (39.7%) than in TNFi-experienced (31.5%) patients; corresponding proportions with Grade 1 AST elevations were 28.1% and 23.5%. The proportions 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 (Supplementary Table S4, available with the online version of this article). 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 (Supplementary Table S4).

Injection-site reactions. Among patients who received ≥ 1 GUS administration, ISRs occurred in 1.99% (30/1508) through end of study (TNFi-naïve: 23/1107 [2.08%]; TNFi-experienced: 7/401 [1.75%]). Most reactions were considered mild; 2 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 that we know of to date, with 1508 patients evaluated for up to 2 years (2125 PY). Integrated analyses across 4 phase II/III studies of patients with active PsA demonstrated that the safety profile of GUS remained consistent, regardless of prior TNFi or concomitant MTX use. Time-adjusted rates of safety events (events/100 PY) and proportions of patients with laboratory abnormalities relevant to patients with PsA were generally similar across treatment groups during the PBO-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



* 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.

Figure 3. Proportion of patients with maximum increase of NCI-CTCAE toxicity Grade 1 by MTX use and TNFi status at baseline across phase II/III trials of GUS 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 inhibitor; W: weeks; Y: years.

longer duration of treatment. Nearly 90% of enrolled patients completed assigned treatment through end of study. Further, 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 are common.

The rates/100 PY of AEs observed for GUS were similar between GUS- and PBO-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 GUS treatment groups. However, in the PBO group, TNFi-experienced patients had numerically higher rates of AEs, SAEs, and AEs leading to D/C compared with TNFi-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 PBO-controlled period and through end of study. Our results also demonstrated that the incidences of AEs and SAEs (including serious infections) in GUS-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 GUS 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 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 1 case of possible IBD in a GUS-treated patient from the COSMOS study, the diagnosis had not been confirmed before the patient was lost to follow-up. Further, for up to 2 years, there were no reports of CD or UC among these 1508 GUS-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 GUS compared with PBO 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 GUS 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 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 GUS-treated patients despite prior TNFi use. Notably, treatment persistence among GUS-randomized patients was nearly 90% across all 4 studies, ranging from 87% in COSMOS to 91% in Phase 2.[20,22,25,26] Further, 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 GUS among both TNFi-naïve and TNFi-experienced subpopulations reported here indicates the potential utility of GUS 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 GUS in this population of patients with PsA is generally consistent with the established safety profile in clinical studies in plaque psoriasis with up to 5 years of follow-up.[34] Additionally, GUS has demonstrated durable and robust efficacy for both dosing regimens in patients with PsA.[20-26] However, in general, elevations in hepatic transaminases occurred more frequently in patients with PsA receiving Q4W compared with patients with PsA and psoriasis receiving Q8W.[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 follow patients for 2 years, whereas the Phase 2, DISCOVER-1, and COSMOS studies were limited to 1 year. Exposure-adjusted incidence rates were used to account for the differences 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 ongoing 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 GUS 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 GUS 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 GUS and ISRs,[28] and the presence of antibodies to GUS did not preclude clinical response.[22,25]

These results demonstrate that GUS was well tolerated in studies continuing for 1 to 2 years among patients with active 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 GUS as an initial biologic therapy or in those who have failed or were intolerant to TNFi treatment.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Gossec L, Baraliakos X, Kerschbaumer A, 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, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. Nature Rev Rheumatol 2022;18:465-79.
3. Fagerli KM, Kearsley-Fleet L, Watson KD, 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, et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy: results from the Danish nationwide DANBIO registry. Arthritis Rheum 2013;65:1213-23.
5. Harrold LR, Stolshek BS, Rebello S, 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; British Society for Rheumatology Biologics Register. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology 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, 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, et al. Discontinuation and switching patterns of tumour necrosis factor inhibitors (TNFis) in TNFi-naive and TNFi-experienced patients with psoriatic arthritis: an observational study from the US-based Corrona registry. RMD Open 2019;5:e000880.
10. Girolomoni G, Altomare G, Ayala F, 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: Novartis Pharmaceuticals Corp.; 2021.
14. HUMIRA [package insert]. Chicago, IL: AbbVie Inc.; 2021.
15. SILIQ [package insert]. Bridgewater, NJ: Bausch Health US, LLC; 2020.
16. SKYRIZI [package insert]. Chicago, IL: AbbVie Inc.; 2022.
17. STELARA [package insert]. Horsham, PA: Janssen Biotech, LLC; 2020.
18. TALTZ [package insert]. Indianapolis, IN: Eli Lilly and Company; 2022.
19. TREMFYA [package insert]. Horsham, PA: Janssen Biotech, LLC; 2020.
20. Deodhar A, Gottlieb AB, Boehncke WH, 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 WH, 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 WH, 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, et al; DISCOVER-2 Study Group. 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, et al. Efficacy and safety of guselkumab, 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, 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 active psoriatic arthritis. Arthritis Rheumatol 2022;74:475-85.
26. Coates LC, Gossec L, Theander E, 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 methotrexate therapy for rheumatoid arthritis: a systematic review. Eur J Med Chem 2018;158:502-16.
28. Rahman P, Ritchlin CT, Helliwell PS, et al. Pooled safety results through 1 year of 2 phase III trials of guselkumab in patients with psoriatic arthritis. J Rheumatol 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, 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, 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, et al; GALAXI-1 Investigators. Guselkumab for the treatment of Crohn's disease: induction results from the phase 2 GALAXI-1 study. Gastroenterology 2022;162:1650-64.
33. Dignass A, Rubin D, Bressler B, et al. 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 (ECCO Abstract OP23). J Crohns Colitis 2022;16 Suppl 1:i025-6.
34. Blauvelt A, Tsai TF, Langley RG, et al. Consistent safety profile with up to 5 years of continuous treatment with guselkumab: pooled analyses 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. Gottlieb AB, Merola JF, Armstrong A, et al. Comparable safety profile of guselkumab in psoriatic arthritis and psoriasis: Results from phase 3 trials through 1 year (EULAR abstract AB0528). Ann Rheum Dis 2021;80:1293-4.
36. DeTora LM, Toroser D, Sykes A, et al. Good Publication Practice (GPP) guidelines for company-sponsored biomedical research: 2022 update. Ann Intern Med 2022;175:1298-304.