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CLINICAL SCIENCE

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)

Laura C Coates ,[1] Laure Gossec ,[2,3] Elke Theander ,[4] Paul Bergmans,[5] Marlies Neuhold,[6] Chetan S Karyekar ,[7] May Shawi,[8] Wim Noël ,[6] Georg Schett ,[9] Iain B McInnes [10]

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For numbered affiliations see end of article.

Correspondence to
Dr Laura C Coates, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK; laura.coates@ndorms.ox.ac.uk

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ABSTRACT

Objective To evaluate efficacy and safety of guselkumab, an anti-interleukin-23p19-subunit antibody, in patients with psoriatic arthritis (PsA) with prior inadequate response (IR) to tumour necrosis factor inhibitors (TNFi).

Methods Adults with active PsA (≥3 swollen and ≥3 tender joints) who discontinued ≤2 TNFi due to IR (lack of efficacy or intolerance) were randomised (2:1) to subcutaneous guselkumab 100 mg or placebo at week 0, week 4, then every 8 weeks (Q8W) through week 44. Patients receiving placebo crossed over to guselkumab at week 24. The primary (ACR20) and key secondary (change in HAQ-DI, ACR50, change in SF-36 PCS and PASI100) endpoints, at week 24, underwent fixed-sequence testing (two-sided α=0.05). Adverse events (AEs) were assessed through week 56.

Results Among 285 participants (female (52%), one (88%) or two (12%) prior TNFi), 88% of 189 guselkumab and 86% of 96 placebo→guselkumab patients completed study agent through week 44. A statistically significantly higher proportion of patients receiving guselkumab (44.4%) than placebo (19.8%) achieved ACR20 (%difference (95% CI): 24.6 (14.1 to 35.2); multiplicity-adjusted p<0.001) at week 24. Guselkumab was superior to placebo for each key secondary endpoint (multiplicity-adjusted p<0.01). ACR20 response (non-responder imputation) in the guselkumab group was 58% at week 48; >80% of week 24 responders maintained response at week 48. Through week 24, serious AEs/serious infections occurred in 3.7%/0.5% of 189 guselkumab-randomised and 3.1%/0% of 96 placebo-randomised patients; the guselkumab safety profile was similar through week 56, with no deaths or opportunistic infections.

Conclusion Guselkumab significantly improved joint and skin manifestations and physical function in patients with TNFi-IR PsA. A favourable benefit–risk profile was demonstrated through 1 year.

Trial registration number NCT03796858.

Key messages

What is already known about this subject?

- Patients with psoriatic arthritis (PsA) with an inadequate response or intolerance to tumour necrosis factor inhibitors (TNFi) often have lower response rates to additional TNFi, and current treatment guidelines generally support only one switch within the TNFi class before selecting an alternate mechanism of action.
- Guselkumab, a fully human interleukin (IL)–23 p19-subunit inhibitor, is efficacious in improving the signs and symptoms of active PsA both in TNFi-naïve and TNFi-experienced patients.

What does this study add?

- In the phase III, randomised, placebo-controlled COSMOS study in adults with active PsA, guselkumab-treated patients had significantly higher response rates and greater mean improvements in assessments of the signs and symptoms of PsA at week 24 when compared with placebo; response rates and mean improvements were maintained or improved through 1 year in the guselkumab group.
- The COSMOS safety results were consistent with the known safety profile of guselkumab in biologic-naïve patients with PsA.

How might this impact on clinical practice or future developments?

- The efficacy and safety results of COSMOS suggest that guselkumab may be an appropriate therapy for patients with PsA with lack or efficacy from or intolerance to TNFi.

INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous, chronic, inflammatory disease, with distinct classes of therapy now increasingly recommended based on the disease domains predominantly involved, such as enthesitis and dactylitis, in the individual patient.[1 2] Current treatment guidelines[3] recommend the use of a biologic disease-modifying antirheumatic drug (bDMARD) when conventional synthetic DMARDs (csDMARDs) have proven ineffective. The introduction of tumour necrosis factor inhibitors (TNFi) into the rheumatologist's armamentarium has substantially improved the ability

to achieve lower states of PsA activity[3]; however, up to 40% of patients receiving their first TNFi do not achieve response (assessed by ≥20% improvement in American College of Rheumatology criteria (ACR20)) with 6 months of treatment.[3] An analysis of patients with PsA in the DANBIO registry who switched biologics after initiating TNFi therapy found decreased ACR20 response rates with the second and third TNFi (47%, 22% and 18%, respectively).[4] In addition, real-world registry data have demonstrated diminished drug persistence with each successive TNFi.[4–6]

Alternate mechanisms of action may prove more beneficial in patients who experience a lack of response to TNFi,[7] highlighting the need for treatments targeting alternate disease pathways. Accordingly, several bDMARDs with alternative mechanisms of action are now approved for PsA,[8–10] including those targeting interleukin (IL)−17A, p40 (IL-12/23), and p19 (IL-23).

Guselkumab, a high-affinity, human monoclonal antibody targeting the IL-23p19-subunit, demonstrated efficacy and safety across two phase III PsA studies (DISCOVER-1 (TNFi-experienced and biologic-naïve), DISCOVER-2 (biologic-naïve only)).[8 9] Approximately 31% of the 381 patients in DISCOVER-1 were previously exposed to 1–2 TNFi, and of those, 37% had discontinued TNFi therapy due to inadequate efficacy. The objective of the phase IIIb COSMOS study was to further assess the efficacy and safety of guselkumab through 1 year in patients with PsA with an inadequate response (IR; inadequate efficacy or intolerance) to TNFi.

PATIENTS AND METHODS

Patients

Eligible adults had a diagnosis of PsA according to the ClASsification criteria for Psoriatic ARthritis (CASPAR) at screening and had active disease (≥3 swollen; ≥3 tender joints) and active (≥1 psoriatic plaque of ≥2 cm) or documented history of plaque psoriasis or current nail psoriasis, and who had also demonstrated lack of benefit or intolerance to 1–2 TNFi. Patients could continue stable baseline use of methotrexate (MTX), sulfasalazine, hydroxychloroquine or leflunomide; oral corticosteroids; and non-steroidal anti-inflammatory drugs (NSAIDs)/other analgesics. Targeted synthetic DMARDs were prohibited before and during study participation. Patients with active tuberculosis (TB) were excluded; those with latent TB received appropriate prophylaxis.

Study design

This phase IIIb, randomised, double-blind study (COSMOS) was conducted at 84 European sites from March 2019 to November 2020 (see online supplemental methods). The study comprised a 6-week screening period and placebo-controlled (weeks 0–24) and active-treatment (weeks 24–48; final study intervention at week 44) periods. The primary endpoint assessment was at week 24, with final efficacy and safety assessments at week 48 and week 56, respectively.

At week 0, participants were randomised (2:1) to receive subcutaneous injections of either guselkumab 100 mg (week 0, week 4, then every 8 weeks (Q8W) through week 44) or placebo (weeks 0, 4, 12, 20, followed by guselkumab 100 mg at weeks 24, 28, 36, 44). Randomisation was stratified by baseline csDMARD use (yes/no) and number of prior TNFi (1 or 2). Study personnel, including independent joint assessors and the study team, were blinded throughout the study. Participants with <5% improvement from baseline in both tender and swollen joint counts at week 16 qualified for early escape (EE); patients receiving guselkumab continued randomised treatment (receiving placebo at week 16 to maintain blinding), while those in the placebo group received guselkumab at week 16, week 20 and Q8W thereafter (figure 1). After EE, participants could initiate or increase the dose of one permitted concomitant medication up to the maximum allowed dose at the physician's discretion. Sample size estimation is detailed in online supplemental methods.

This study was conducted per the Declaration of Helsinki and Good Clinical Practice guidelines. Each site's ethical body approved the protocol. Patients provided written informed consent.

Patient and public involvement statement

Patients and the public were not involved in the design or analysis of this study.

Procedures

Independent assessors evaluated joints for tenderness, swelling and presence/severity of enthesitis (Leeds Enthesitis Index (LEI))[11] and dactylitis (Dactylitis Severity Score (DSS)).[12 13] Patients reported pain and global arthritis activity (0–10 cm visual analogue scale (VAS)), and physical function (Health Assessment Questionnaire-Disability Index (HAQ-DI)).[14] Investigators determined global disease activity (0–10 cm VAS), serum C reactive protein (CRP) and extent (% body surface area (BSA) with psoriasis) and severity of skin symptoms using the Investigator's Global Assessment of psoriasis (IGA)[15] and the Psoriasis Area and Severity Index (PASI).[16] During the study, the protocol was amended to allow self-administration of study agent injections post-week 24 when site visits were not possible due to local COVID-19 restrictions.

The 36-item Short-Form Health Survey (SF-36) physical and mental component summary (PCS and MCS) scores assessed health-related quality of life (HRQoL).[17] The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue measured fatigue.[18] Adverse events (AEs) and routine clinical laboratory parameters were monitored.

Outcomes

The primary endpoint was the proportion of patients with an ACR20 response at week 24. Major secondary endpoints, also at week 24, were (1) mean changes in HAQ-DI, (2) ACR50 response, (3) mean changes in SF-36 PCS and (4) PASI100 response (in patients with ≥3% BSA with psoriasis involvement and IGA ≥2 at baseline). Maintenance of ACR20/50/70 response at week 48 was also assessed in patients who achieved response at week 24. Additional secondary and safety outcomes assessed are shown in online supplemental methods.

Data analyses

Efficacy results were analysed by randomised treatment group, regardless of actual treatment received. The 'Primary' efficacy analysis included randomised participants who received ≥1 dose of study agent. Patients with missing data and those who met treatment failure (TF) criteria through week 24 (discontinued study agent and/or study participation for any reason, initiated or increased the dose of allowed csDMARDs or oral corticosteroids for PsA, initiated protocol prohibited medications/therapies for PsA or met EE criteria; online supplemental figure 1) were considered non-responders for binary endpoints or having no change for continuous endpoints (non-responder imputation (NRI)). Through week 24, least squares (LS) mean changes from baseline were determined for continuous endpoints using a Mixed-Effect Model Repeated Measures (MMRM) model

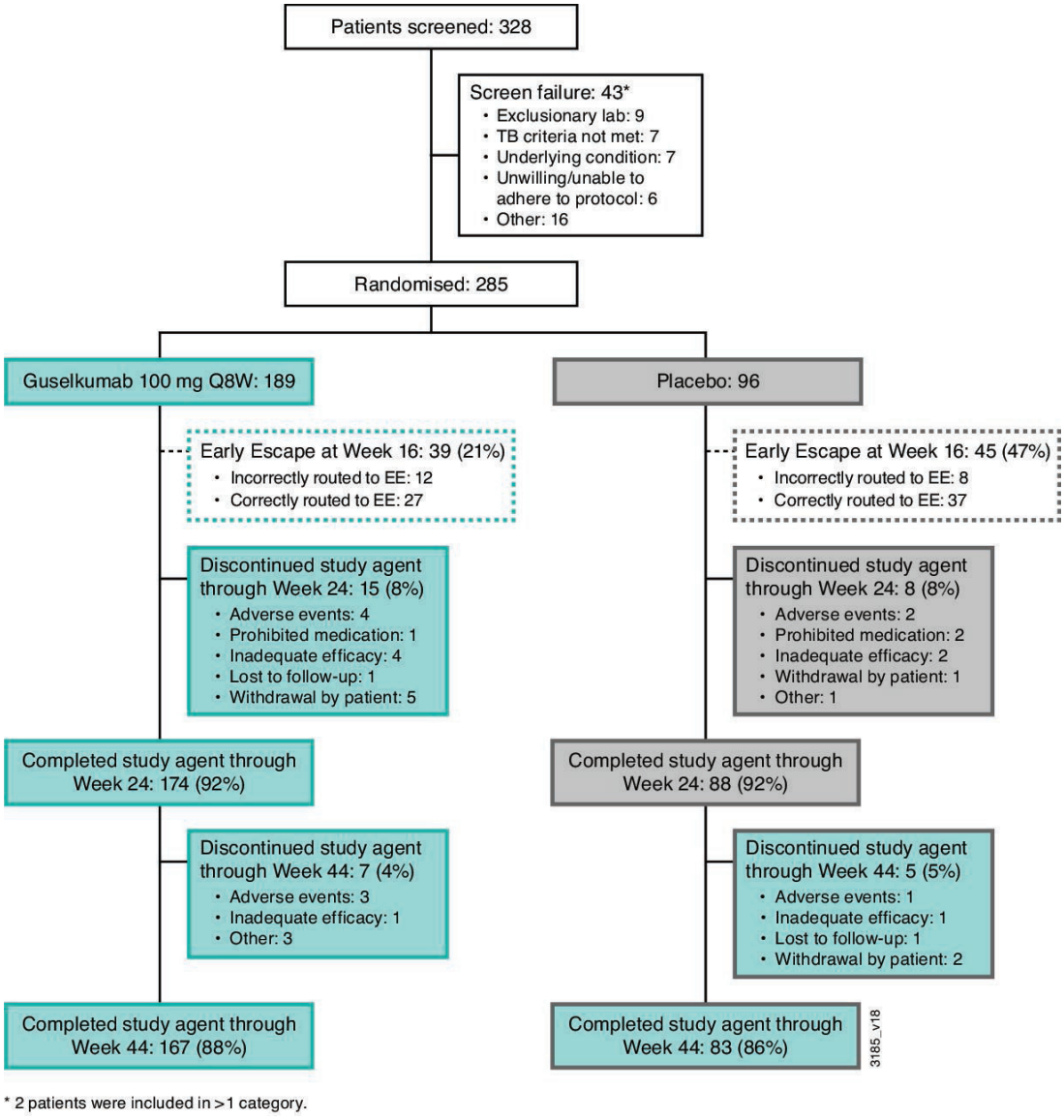


Figure 1 Disposition of patients through 1 year of COSMOS. EE, early escape; Q8W, every 8 weeks; TB, tuberculosis.

including all available data through week 24 (additional details in online supplemental methods). Subgroup analyses evaluated consistency of the primary endpoint based on demographics, baseline disease characteristics and prior medications.

The overall type I error was controlled across the primary and major secondary endpoints at 5% by testing treatment differences (two-sided $\alpha=0.05$) in a fixed sequence (ie, ACR20 response, change from baseline in HAQ-DI, ACR50 response, change from baseline in SF-36 PCS, PASI100 response; online supplemental figure 2), whereby subsequent endpoints were only tested if the previous endpoint achieved statistical significance ($p<0.05$). For endpoints not included in the multiplicity control procedure, the unadjusted (nominal) p values are descriptive in nature.

Supplemental sensitivity analyses, prespecified prior to the week 24 database lock, included a 'Per-Protocol' (PP) analysis (excluded patients with major protocol deviations (MPDs) with potential to impact efficacy assessments; online supplemental figure 3), and an 'EE-Correction' analysis (online supplemental figure 4). The latter analysis was conducted to address 20 patients (12 guselkumab, 8 placebo) incorrectly routed to EE and considered non-responders in the Primary analysis. In the EE-correction analysis, 12 affected patients in the guselkumab group did not meet any other TF criteria (eg, the introduction/change in dose of concomitant therapy) through week 24 and their response was included with those of other guselkumab-treated patients. The eight placebo patients received guselkumab as EE therapy at week 16 and week 20, thus met TF criteria, and were considered non-responders in the EE-correction analysis.

Through week 24, treatment group comparisons for binary endpoints used a Cochran–Mantel–Haenszel test stratified at the study level by baseline csDMARD use (yes/no) and number of prior TNFi (1/2) for binary endpoints or an MMRM model for continuous data (see online supplemental methods). Statistical analyses used SAS (V.9.4), with SAS/STAT (V.14.2; SAS Institute, Inc, Cary, NC, USA).

In post hoc analyses after week 24, results for the placebo→guselkumab group are reported for patients who crossed over to receive guselkumab at week 24. In addition, NRI was applied: patients who discontinued treatment and/or met EE criteria before week 24 (guselkumab group; excluding those who were incorrectly assigned to EE) were imputed as no response for binary endpoints or no change for continuous endpoints; missing data were imputed as no response or using multiple imputation (MI; assumed to be missing-at-random),

respectively. After week 24, changes from baseline are reported as mean (SD). No treatment group comparisons were performed post-week 24.

Safety summaries included participants receiving ≥1 partial or complete administration of study agent, according to actual treatment received; numbers of events/100 patient-years (PY) of follow-up were determined for select AEs of interest.

RESULTS

Patient disposition and characteristics

At week 0, 285 patients were randomised to guselkumab (n=189) or placebo (n=96); at week 16, 39 (21%) participants in the guselkumab group and 45 (47%) in the placebo group were assigned to EE. Through week 24, 15 (8%) and 8 (8%) participants, respectively, in the guselkumab and placebo groups discontinued study agent (figure 1). In total, 167 (88%) patients in the guselkumab group and 83 (86%) in the placebo-crossover group completed study treatment.

Although baseline characteristics were generally similar across treatment groups, several numerical imbalances existed, for example, a higher proportion of females and a lower mean body weight in the guselkumab (54%, 84 kg) than placebo (46%, 92 kg) group. The guselkumab group was characterised by more prominent joint symptoms (tender joint count: 21 vs 18) and skin involvement (mean PASI: 11.7 vs 9.2). Prior and concomitant medications were similar across groups (table 1).

Although self-administration was permitted during the COVID-19 pandemic, when site visits were restricted, MPDs related to COVID-19 did occur. These were classified mostly as drug administration or study visit missed or outside of the prespecified window, and most were considered to have no effect on efficacy assessments.

Table 1 Baseline characteristics of COSMOS participants

Randomised, treated participants, N	Guselkumab 100 mg Q8W 189	Placebo 96	Total 285
Age, years	49 [12]	49 [12]	49 [12]
<65	169 (89%)	89 (93%)	258 (91%)
≥65	20 (11%)	7 (7%)	27 (9%)
Sex			
Male	86 (46%)	52 (54%)	138 (48%)
Female	103 (54%)	44 (46%)	147 (52%)
Weight, kg	84 [17]	92 [23]	86 [20]
Body mass index, kg/m^2	29 [6]	31 [7]*	30 [6]†
Swollen joint count, 0–66	10 [7]	9 [6]	10 [6]
Tender joint count, 0–68	21 [13]	18 [11]	20 [12]
PsA disease duration, years	8.3 (7.8)	8.7 (7.2)	8.4 (7.6)
Patient assessment of pain, 0–10 cm VAS	6.5 (1.9)	6.0 (1.8)	6.3 (1.9)
Patient global assessment of arthritis, 0–10 cm VAS	6.5 (1.7)	6.2 (1.7)	6.4 (1.7)
Physician global assessment of disease, 0–10 cm VAS	6.9 (1.5)	6.4 (1.7)	6.7 (1.6)
HAQ-DI, 0–3	1.3 (0.6)‡	1.2 (0.6)	1.3 (0.6)†
CRP, mg/dL	1.2 (2.0)‡	1.2 (2.5)	1.2 (2.2)†
Enthesitis (LEI score ≥1)	126 (67%)	64 (67%)	190 (67%)
LEI score, 1–6	2.9 (1.5)	2.7 (1.5)	2.8 (1.5)
Dactylitis (DSS ≥1)	67 (36%)	36 (38%)	103 (36%)
DSS, 1–60	6.7 (6.5)	7.4 (8.3)	6.7 (7.1)
DAPSA score	45.5 (19.9)	40.6 (15.8)	43.8 (18.7)
Psoriatic BSA, %	17.9 (21.5)	13.4 (17.7)	16.4 (20.4)
PASI score, 0–72, N	188	96	284
Mean (SD)	11.7 (11.9)	9.2 (9.4)	10.9 (11.2)
<12	119 (63%)	65 (68%)	184 (65%)
≥12 and <20	33 (18%)	19 (20%)	52 (18%)
≥20	36 (19%)	12 (13%)	48 (17%)
IGA score, 0–4, N	189	96	285
<2	40 (21%)	29 (30%)	69 (24%)
≥2	149 (79%)	67 (70%)	216 (76%)
SF-36, standard norm=50			
PCS score	33.0 (7.0)‡	33.9 (7.7)	33.3 (7.3)†
MCS score	47.1 (12.1)‡	46.1 (11.5)	46.8 (11.9)†
FACIT-F score, 0–52	29.2 (11.3)‡	29.2 (10.6)	29.2 (11.0)†
No of prior TNFi			
1	167 (88%)	85 (89%)	252 (88%)
2	22 (12%)	11 (11%)	33 (12%)
Reason for prior TNFi discontinuation			
Inadequate efficacy	159 (84%)	79 (82%)	238 (84%)
Intolerance	30 (16%)	17 (18%)	47 (16%)
MTX use at baseline	105 (56%)	51 (53%)	156 (55%)

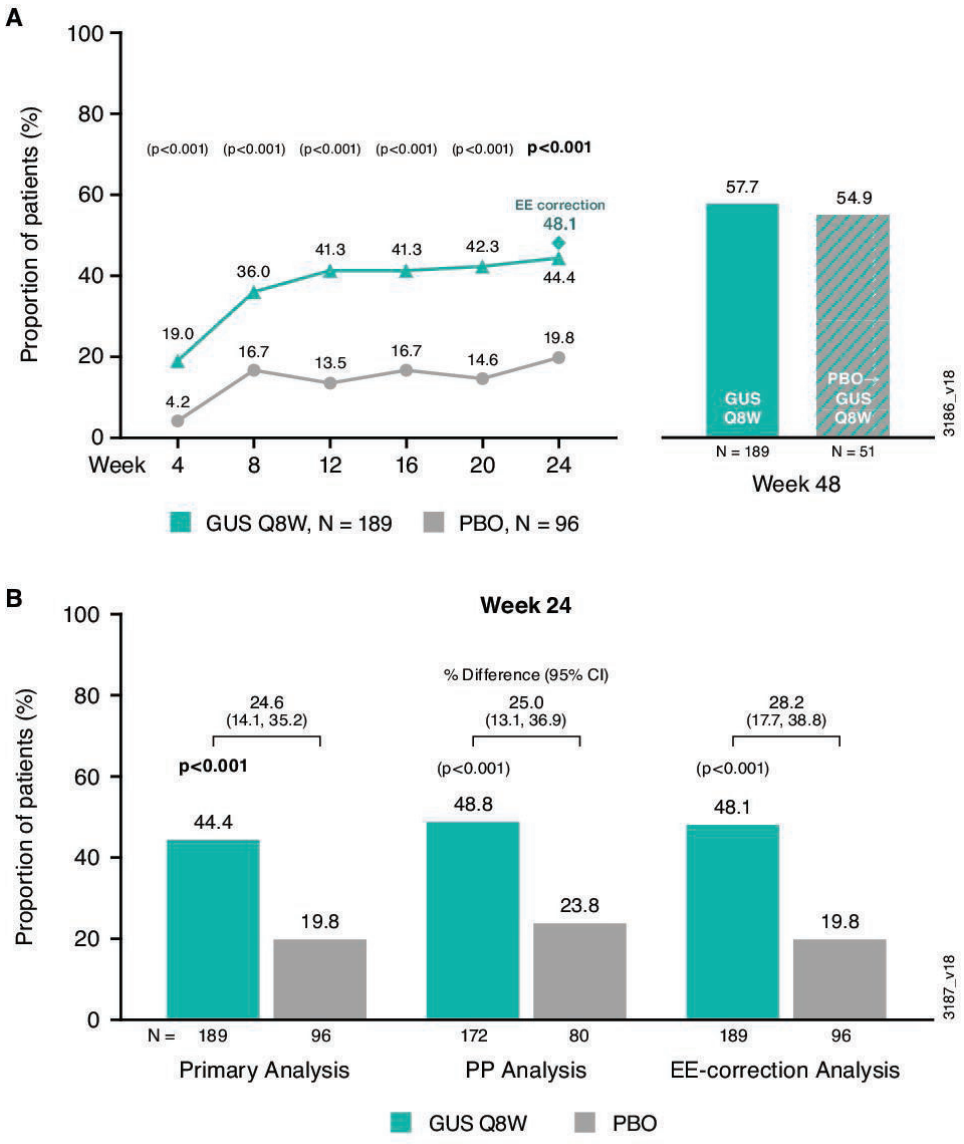
Data are mean (SD) or n (%) unless stated otherwise.
*N=95
†N=284
‡N=188
BSA, body surface area; CRP, C reactive protein; DAPSA, Disease Activity in Psoriatic Arthritis; DSS, Dactylitis Severity Score; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; IGA, Investigator's Global Assessment of psoriasis; LEI, Leeds Enthesitis Index; MCS, mental component summary; MTX, methotrexate; PASI, Psoriasis Area and Severity Index; PCS, physical component summary; PsA, psoriatic arthritis; Q8W, every 8 weeks; SF-36, 36-item Short-Form Health Survey; TNFi, tumour necrosis factor inhibitor; VAS, visual analogue scale.

Efficacy

The primary endpoint was met. At week 24, based on the Primary analysis population (online supplemental figure 1), 44.4% (84/189) of guselkumab versus 19.8% (19/96) of placebo patients achieved ACR20 (%difference (95% CI): 24.6 (14.1 to 35.2); multiplicity-adjusted p<0.001), with treatment effect seen by week 4 (figure 2A). Results of the PP and EE-correction sensitivity analyses supported the Primary analysis. Specific to the EE-correction analysis, 48.1% (91/189) of guselkumab versus 19.8% (19/96) of placebo patients achieved ACR20 (%difference (95% CI): 28.2 (17.7 to 38.8)) (figure 2B). The benefit of guselkumab over placebo was consistent across subgroups defined by baseline patient, disease and prior/concomitant medication characteristics, including participants who discontinued prior TNFi use due to inadequate efficacy or intolerance (figure 3). Employing NRI, the proportion of guselkumab-randomised patients achieving ACR20 at week 48 was 57.7%. Among 51 placebo patients who crossed over to guselkumab at week 24, 54.9% (n=28) achieved ACR20 at week 48 (figure 2A).

The testing hierarchy did not fail in analyses of the major secondary endpoints; guselkumab was superior to placebo in all four endpoints. At week 24, guselkumab patients demonstrated statistically significantly greater improvements or response rates versus placebo in HAQ-DI score (LSmean (95% CI) change: −0.18 (−0.27 to −0.09) vs −0.01 (−0.12 to 0.10); multiplicity-adjusted p=0.003; figure 4A), ACR50 (19.6% (37/189) vs 5.2% (5/96); multiplicity-adjusted p=0.001; figure 4B), SF-36 PCS score (LSmean (95% CI) change: 3.51 (2.31 to 4.72) vs −0.39 (−1.84 to 1.07); multiplicity-adjusted p<0.001; figure 4C) and PASI100 (in patients with ≥3% BSA with psoriasis and IGA ≥2 at baseline; 30.8% vs 3.8%; multiplicity-adjusted p<0.001; figure 4D). Results of PP and EE-correction sensitivity analyses were consistent with the Primary analysis (Supplemental Figure 5A−D).

Additional secondary endpoints at week 24 also showed benefit of guselkumab over placebo for achieving ACR70 (7.9% vs 1.0%; nominal p=0.018), minimal disease activity (MDA;



Bolded p values are adjusted for multiplicity of testing; p values shown in parentheses are not adjusted for multiplicity of testing

Figure 2 ACR20 response through week 48 of COSMOS. Proportions of randomised and treated patients achieving ACR20 response through week 24 in the Primary analysis (treatment failure rules applied) (A) and ACR20 response at week 24 across the Primary, PP and EE-correction analyses (B). After week 24, analyses were performed using non-responder imputation methods, including imputation of EE patients as non-responders (see Patients and methods). Results for the placebo→guselkumab group at week 48 are reported for patients who did not enter EE and crossed over to guselkumab at week 24. ACR20, ≥20% improvement in American College of Rheumatology response criteria; EE, early escape; GUS, guselkumab; PBO, placebo; PP, per protocol; Q8W, every 8 weeks.

14.8% vs 3.1%; nominal p=0.003), and PASI75 (59.4% vs 9.4%; nominal p<0.001) and PASI90 (51.1% vs 7.5%; nominal p<0.001) in patients with ≥3% BSA with psoriasis and IGA ≥2 at baseline; 3.7% guselkumab-treated and no placebo-treated patients achieved very low disease activity. At week 24, guselkumab-treated patients also had a greater LSmean change in Disease Activity in Psoriatic Arthritis (DAPSA) score (−14.5 vs −5.7; nominal p<0.001) and a higher DAPSA low disease activity (LDA) response rate (29.6% vs 13.5%, nominal p=0.003) versus placebo; the proportion of patients achieving DAPSA remission was numerically higher in the guselkumab group versus placebo (5.3% vs 2.1%). Among participants affected at baseline, numerically higher proportions of guselkumab than placebo patients had resolved enthesitis (39.7% vs 18.8%; nominal p=0.003) or dactylitis (44.8% vs 25.0%; nominal p=0.040) at week 24. Guselkumab-treated patients also had greater LSmean improvements across all ACR components compared with placebo (Supplemental Figure 6A–G). The LSmean changes in SF-36 MCS were 2.10 and 0.36, respectively, in the guselkumab and placebo groups (table 2). In addition, higher proportions of guselkumab than placebo patients achieved clinically meaningful improvements in HAQ-DI (37.5% vs 16.1%; nominal p<0.001; table 2), FACIT-F (42.9% vs 20.8%; nominal p<0.001; table 2), and SF-36 PCS (42.3% vs 15.6%; nominal p<0.001) and MCS (28.6% vs 15.6%; nominal p=0.016) scores.

After week 24, response rates and mean improvements for secondary endpoints were sustained or numerically improved through week 48 in guselkumab-randomised patients (figure 4A–D and table 2). Among placebo→guselkumab patients, response rates and mean changes in the secondary endpoints increased at week 48 (figure 4A–D and table 2).

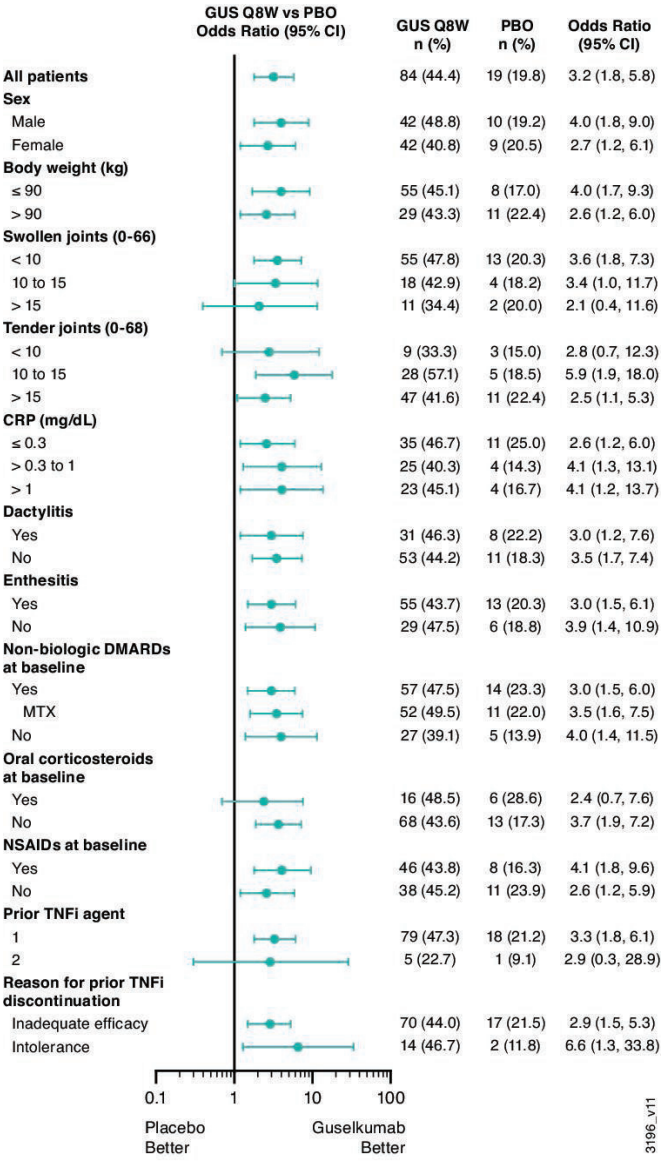


Figure 3 ACR20 response at week 24 by baseline characteristics of COSMOS participants. ACR20, ≥20% improvement in American College of Rheumatology response criteria; CRP, C reactive protein; DMARD, disease-modifying antirheumatic drug; GUS, guselkumab; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PBO, placebo; Q8W, every 8 weeks; TNFi, tumour necrosis factor inhibitor.

Maintenance of response was evaluated for guselkumab-randomised patients achieving an ACR20, ACR50 or ACR70 response at week 24; of these patients, 83.3% (70/84), 81.1% (30/37) and 86.7% (13/15), respectively, maintained response at week 48.

Safety

Through week 24, similar proportions of patients in the guselkumab (42% (80/189)) and placebo (48% (46/96)) groups reported ≥1 AE. Through week 56, 144.9 AEs/100PY were reported among the 279 guselkumab-treated patients (vs 369.8/100PY for placebo). The most common AEs in guselkumab-randomised patients through week 24, ie, nasopharyngitis (5%) and upper respiratory tract infection (4%), occurred with similar incidence in the placebo group (5% and 3%, respectively) (table 3). Infections remained the most common AEs in guselkumab-treated patients through week 56 (37.2/100PY vs 99.6/100PY for placebo).

The incidences of serious AEs (SAEs) and AEs leading to treatment discontinuation were 6.3/100PY and 2.7/100PY, respectively, among guselkumab-treated patients through week 56. One patient experienced a major adverse cardiovascular event at week 44 (non-fatal myocardial infarction (preferred term: acute coronary syndrome)); risk factors included concomitant cyclooxygenase-2-inhibitor therapy and a body mass index of 31. One malignancy occurred: prostatic adenocarcinoma in a guselkumab-randomised patient (4-year history of prostatitis). One patient discontinued study agent (influenza-like illness) after the third guselkumab administration and was diagnosed with suspected inflammatory bowel disease and coeliac disease ~3 weeks and 2 months, respectively, later. Neither diagnosis was confirmed; the patient was lost to follow-up.

One patient (guselkumab group) experienced two events of conversion disorder, requiring hospitalisation; study drug was discontinued after the second instance, which was reported as resolved. Another patient in the guselkumab group (history of previous suicide attempt) reported depression (SAE) 1 week after receiving the second guselkumab administration; study agent was discontinued, with no further follow-up. Other non-serious psychiatric-related AEs were singular events of anxiety and depressed mood in the placebo group (through week 24) and insomnia in the guselkumab group.

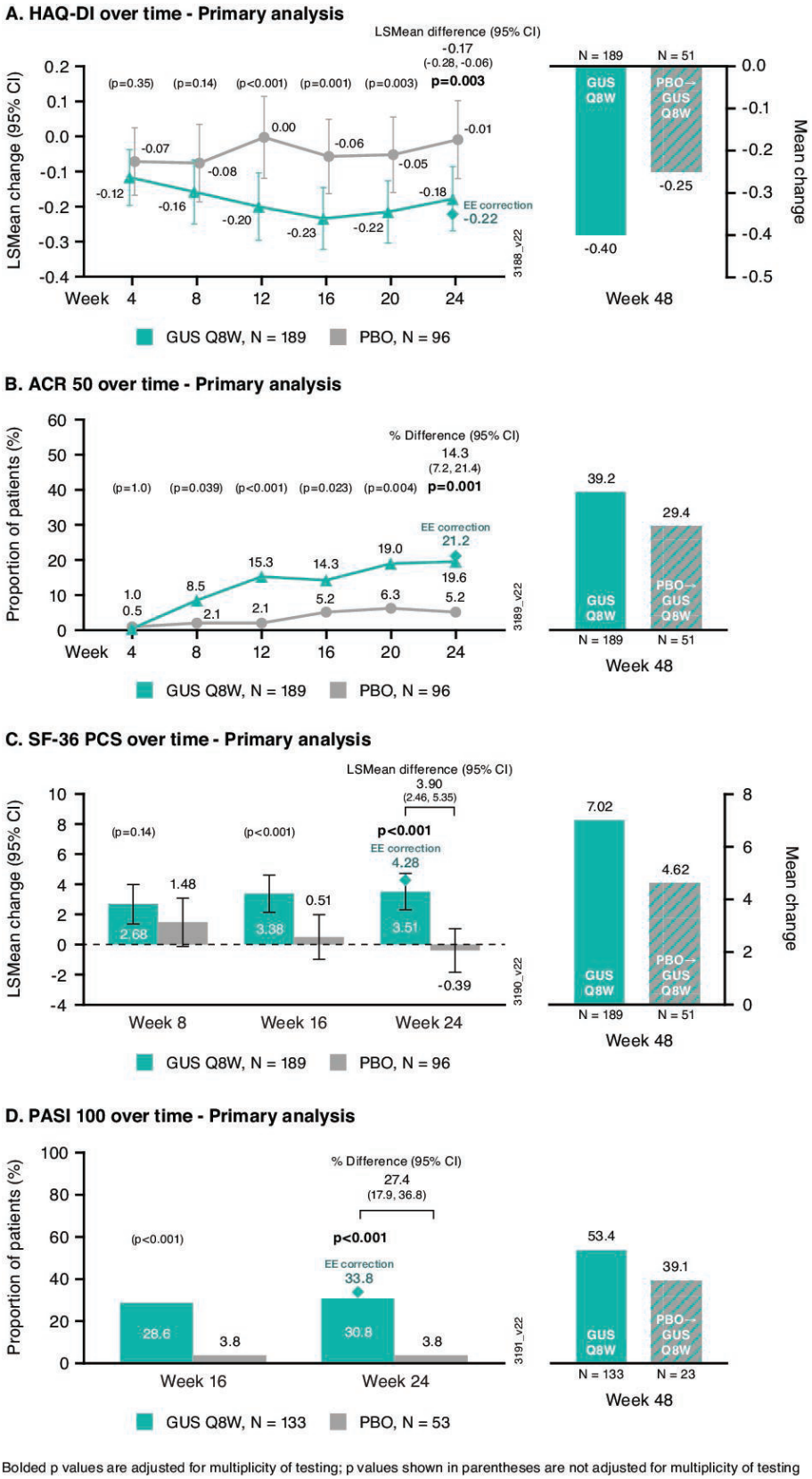
Two serious infections occurred. One guselkumab-randomised patient was hospitalised with community-acquired pneumonia diagnosed at week 12 (history of chronic obstructive pulmonary disease and heart disease); the patient recovered with antibiotic treatment and resumed study agent. A placebo→guselkumab patient was hospitalised with acute pneumonia (week 48); the patient recovered following antibiotic therapy and continued study participation. No opportunistic infections, cases of active TB, or deaths occurred (table 3).

Injection-site reactions, all considered of mild intensity, occurred in 1.8% of guselkumab-treated patients (table 3). No anaphylactic or serum sickness-like reactions occurred through week 56.

Through week 56, AEs of decreased neutrophil and white blood cell counts were uncommon. Neither type of haematological abnormality was reported as an SAE or led to study agent discontinuation, and all were National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade ≤2 (online supplemental table 1). The majority of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations were maximum NCI-CTCAE Grade 1 (online supplemental table 1). Two guselkumab-treated patients had elevated ALT reported as an SAE. The first patient, whose liver enzymes were elevated at baseline, was confirmed to have autoimmune hepatitis via biopsy and imaging studies and discontinued study agent. While ALT levels normalised by week 24, other symptoms (jaundice, nausea) persisted. A second patient had elevated AST and ALT at week 48 and was diagnosed with steatohepatitis; the patient was treated with ademetionine and recovered. ALT and AST elevations occurred in 37% and 28%, respectively, in patients receiving concomitant MTX and in 28% and 24% of those not receiving concomitant MTX.

DISCUSSION

Guselkumab-treated patients had statistically significant improvements in the signs and symptoms of PsA in TNFi-IR patients compared with placebo. The primary endpoint was



Bolded p values are adjusted for multiplicity of testing; p values shown in parentheses are not adjusted for multiplicity of testing

Figure 4 Key secondary outcomes through week 48 of COSMOS. Primary analysis through week 24 and post hoc NRI analysis at week 48 of LSmean change and mean change in HAQ-DI score (A), ACR50 response (B), LSmean change and mean change in SF-36 PCS score (C), and PASI100 response (D). After week 24, analyses were performed using NRI (including imputation of EE patients as non-responders in the guselkumab group; see Patients and methods). Results for the placebo→guselkumab group at week 48 are reported for patients who did not enter EE and crossed over to guselkumab at week 24. ACR50, ≥50% improvement in American College of Rheumatology response criteria; GUS, guselkumab; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; NRI, non-responder imputation; PASI100, 100% improvement in Psoriasis Area and Severity Index; PBO, placebo; Q8W, every 8 weeks; SF-36 PCS, 36-item Short-Form Health Survey Physical Component Summary.

Table 2 Additional secondary efficacy assessments at week 24 and week 48 analysed using non-responder imputation*

	Week 24		Week 48	
	Guselkumab 100 mg Q8W	Placebo	Guselkumab 100 mg Q8W	Placebo→guselkumab 100 mg Q8W
Treated participants according to randomised group, N	189	96	189	51
ACR70 response	15 (7.9%)	1 (1.0%)	45 (23.8%)	9 (17.6%)
% difference (95% CI)†	6.8 (2.6 to 11.1)			
Unadjusted p value vs placebo‡	0.018			
Enthesitis resolution (LEI score=0)§	50/126 (39.7%)	12/64 (18.8%)	70/126 (55.6%)	14/35 (40.0%)
% difference (95% CI)†	21.6 (8.8 to 34.4)			
Unadjusted p value vs placebo‡	0.003			
Dactylitis resolution (DSS=0)¶	30/67 (44.8%)	9/36 (25.0%)	45/67 (67.2%)	11/13 (84.6%)
% difference (95% CI)†	19.9 (2.7 to 37.1)			
Unadjusted p value vs placebo‡	0.040			
IGA response (IGA 0/1 and ≥2-grade improvement from baseline)**	64/133 (48.1%)	5/53 (9.4%)	87/133 (65.4%)	14/23 (60.9%)
% difference (95% CI)†	38.8 (27.3 to 50.4)			
Unadjusted p value vs placebo‡	<0.001			
PASI75 response**	79/133 (59.4%)	5/53 (9.4%)	99/133 (74.4%)	19/23 (82.6%)
% difference (95% CI)†	49.6 (38.3 to 60.9)			
Unadjusted p value vs placebo‡	<0.001			
PASI90 response**	68/133 (51.1%)	4/53 (7.5%)	89/133 (66.9%)	14/23 (60.9%)
% difference (95% CI)†	43.7 (32.7 to 54.7)			
Unadjusted p value vs placebo‡	<0.001			
HAQ-DI response (≥0.35 improvement from baseline)††	66/176 (37.5%)	14/87 (16.1%)	94 (53.4%)	17 (37.0%)
% difference (95% CI)†	21.5 (11.1 to 31.9)			
Unadjusted p value vs placebo‡	<0.001			
SF-36 MCS score				
LSmean change from baseline‡‡	2.10 (0.54 to 3.65)	0.36 (−1.52 to 2.25)	–	–
LSmean difference (95% CI)†	1.73 (−0.14 to 3.61)		–	–
Unadjusted p value vs placebo‡‡	0.070			
Mean change from baseline (SD)§§	–	–	3.05 (9.95)	3.82 (8.91)
FACIT-F response (≥4-point improvement from baseline)	81 (42.9%)	20 (20.8%)	105 (55.6%)	26 (51.0%)
% difference (95% CI)†	21.9 (11.2 to 32.7)			
Unadjusted p value vs placebo‡	<0.001			
DAPSA score				
LSmean change from baseline‡‡	−14.5	−5.7	–	–
LSmean difference (95% CI)†	−8.8 (12.5 to −5.0)		–	–
Unadjusted p value vs placebo‡‡	<0.001			
Mean change from baseline (SD)§§	–	–	−23.4 (19.8)	−20.3 (15.9)
DAPSA LDA (≤14)	56 (29.6%)	13 (13.5%)	84 (44.4%)	21 (41.2%)
% difference (95% CI)†	16.0 (6.7 to 25.4)			
Unadjusted p value vs placebo‡	0.003			
DAPSA remission (≤4)	10 (5.3%)	2 (2.1%)	30 (15.9%)	6 (11.8%)
% difference (95% CI)†	3.2 (−1.1 to 7.5)			
Unadjusted p value vs placebo‡	0.202			
MDA	28 (14.8%)	3 (3.1%)	51 (27.0%)	14 (27.5%)
% difference (95% CI)†	11.7 (5.6 to 17.7)			
Unadjusted p value vs placebo‡	0.003			
VLDA	7 (3.7%)	0	21 (11.1%)	2 (3.9%)
% difference (95% CI)†	3.7 (1.0 to 6.4)			
Unadjusted p value vs placebo‡	0.057			

Data shown are n (%) or n/N (%) unless stated otherwise.
*Through week 24, patients who discontinued study agent/study participation for any reason, initiated or increased the dose of allowed csDMARDs/oral corticosteroids over baseline for PsA, initiated protocol-prohibited medications/therapies for PsA or met EE criteria (including those incorrectly assigned to EE) were considered to be non-responders or to have no improvement from baseline at subsequent timepoints. After week 24, patients who met the EE criteria (excluding those who were incorrectly assigned to EE) and patients who discontinued study agent/study participation for any reason were considered to be non-responders or to have no improvement from baseline at subsequent timepoints; missing data were imputed as non-response or multiple imputation (assumed to be missing-at-random). Among patients randomised to placebo, only those who crossed over to guselkumab at week 24 were included in the week 48 analyses.
†CIs based on Wald statistic.
‡Unadjusted (nominal) p values based on the Cochran–Mantel–Haenszel test, stratified by baseline use of csDMARD (yes/no) and prior exposure to TNFi (1 vs 2).
§In patients with LEI score ≥1 at baseline.
¶In patients with DSS ≥1 at baseline.
**In patients with ≥3% BSA psoriasis involvement and IGA ≥2 at baseline.
††In patients with HAQ-DI score ≥0.35 at baseline.
‡‡LSmeans and unadjusted (nominal) p values based on a mixed model for repeated measures under the missing-at-random assumption for missing data. LSmeans were determined only through week 24.
§§Post-week 24, mean changes from baseline were determined using change of 0 for patients who discontinued or met the EE criteria prior to week 24 (excluding patients incorrectly assigned to EE) and multiple imputation (assumed to be missing-at-random) for missing data.
ACR, American College of Rheumatology; BSA, body surface area; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAPSA, Disease Activity in Psoriatic Arthritis; DSS, Dactylitis Severity Score; EE, early escape; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; IGA, Investigator's Global Assessment of psoriasis; LDA, low disease activity; LEI, Leeds Enthesitis Index; LS, least squares; MDA, Minimal Disease Activity; PASI75/90, ≥75%/90% improvement in Psoriasis Area and Severity Index; PsA, psoriatic arthritis; Q8W, every 8 weeks; SF-36 MCS, 36-item Short-Form Health Survey Mental Component Summary; TNFi, tumour necrosis factor inhibitor; VLDA, very low disease activity.

Table 3 Summary of adverse events through week 56 of COSMOS

	Placebo*	Placebo→guselkumab		Randomised to guselkumab†		All guselkumab‡
	(Weeks 0–24)	(Weeks 16–56)§	(Weeks 24–56)¶	(Weeks 0–24)	(Weeks 24–56)	(Weeks 0–56)
Randomised patients by treatment received	96	45	45	189	174	279
Patient-years of follow-up	28.1	32.9	27.2	87.7	107.6	255.4
AEs						
Events/100PY (95% CI)	369.8 (302.2 to 448.1)	127.5 (91.9 to 172.4)	143.3 (101.9 to 195.9)	229.2 (198.6 to 263.2)	81.8 (65.6 to 100.8)	144.9 (130.5 to 160.4)
Patients with ≥1 AE	46 (47.9%)	21 (46.7%)	20 (44.4%)	80 (42.3%)	53 (30.5%)	139 (49.8%)
Common AEs (>3% in any group)						
Nasopharyngitis	5 (5.2%)	2 (4.4%)	0	10 (5.3%)	5 (2.9%)	16 (5.7%)
Upper respiratory tract infection	3 (3.1%)	1 (2.2%)	1 (2.2%)	7 (3.7%)	2 (1.1%)	10 (3.6%)
Alanine aminotransferase increased	4 (4.2%)	1 (2.2%)	3 (6.7%)	5 (2.6%)	3 (1.7%)	11 (3.9%)
Faecal calprotectin increased	3 (3.1%)	0	1 (2.2%)	2 (1.1%)	1 (0.6%)	4 (1.4%)
Psoriatic arthropathy	4 (4.2%)	2 (4.4%)	0	3 (1.6%)	4 (2.3%)	10 (3.6%)
Hyperglycaemic	5 (5.2%)	1 (2.2%)	0	3 (1.6%)	0	4 (1.4%)
Hypertension	3 (3.1%)	0	0	1 (0.5%)	3 (1.7%)	4 (1.4%)
Infections						
Events/100PY (95% CI)	99.6 (66.2 to 143.9)	30.4 (14.6 to 55.9)	29.4 (12.7 to 57.9)	63.9 (48.2 to 82.9)	19.5 (12.1 to 29.8)	37.2 (30.1 to 45.5)
Patients with ≥1 infection	19 (19.8%)	7 (15.6%)	6 (13.3%)	40 (21.2%)	16 (9.2%)	61 (21.9%)
Serious infections						
Events/100PY (95% CI)	0	0	3.7 (0.1 to 20.5)	1.1 (0.03 to 6.4)	0	0.8 (0.1 to 2.8)
Patients with ≥1 serious infection	0	0	1 (2.2%)	1 (0.5%)	0	2 (0.7%)
SAEs						
Events/100PY (95% CI)	10.7 (2.2 to 31.2)	6.1 (0.7 to 21.9)	7.4 (0.9 to 26.5)	8.0 (3.2 to 16.5)	4.7 (1.5 to 10.8)	6.3 (3.6 to 10.2)
Patients with ≥1 SAE	3 (3.1%)	2 (4.4%)	2 (4.4%)	7 (3.7%)	5 (2.9%)	15 (5.4%)
Abdominal pain	0	0	0	0	1 (0.6%)	1 (0.4%)
Acute coronary syndrome	0	0	0	0	1 (0.6%)	1 (0.4%)
Atrial fibrillation	0	0	0	0	1 (0.6%)	1 (0.4%
Buttock injury	0	1 (2.2%)	0	0	0	1 (0.4%)
Conversion disorder	0	0	0	1 (0.5%)	1 (0.6%)	1 (0.4%)
Depression	0	0	0	1 (0.5%)	0	1 (0.4%)
Increased alanine aminotransferase	0	0	0	1 (0.5%)	0	1 (0.4%)
Increased liver enzymes	0	0	1 (2.2%)	0	0	1 (0.4%)
Intervertebral disc protrusion	1 (1.0%)	0	0	1 (0.5%)	0	1 (0.4%)
Lumbosacral radiculopathy	0	0	0	1 (0.5%)	0	1 (0.4%)
Pneumonia	0	0	1 (2.2%)	1 (0.5%)	0	2 (0.7%)
Prostate cancer	0	0	0	1 (0.5%)	0	1 (0.4%)
Pulmonary embolism	0	0	0	0	1 (0.6%)	1 (0.4%)
Umbilical hernia	1 (1.0%)	0	0	0	0	0
Varicose vein	0	1 (2.2%)	0	0	0	1 (0.4%)
Vomiting	1 (1.0%)	0	0	0	0	0
AEs leading to study agent discontinuation						
Events/100PY (95% CI)	7.1 (0.9 to 25.7)	0	0	4.6 (1.2 to 11.7)	2.8 (0.6 to 8.2)	2.7 (1.1 to 5.7)
Patients with an AE leading to study agent discontinuation	2 (2.1%)	0	0	4 (2.1%)	3 (1.7%)	7 (2.5%)
Arthralgia	1 (1.0%)	0	0	0	0	0
Conversion disorder	0	0	0	0	1 (0.6%)	1 (0.4%)
Fatigue	0	0	0	0	1 (0.6%)	1 (0.4%)
Increased alanine aminotransferase	0	0	0	1 (0.5%)	0	1 (0.4%)
Influenza-like illness	0	0	0	1 (0.5%)	0	1 (0.4%)
Prostate cancer	0	0	0	1 (0.5%)	0	1 (0.4%)
Psoriatic arthropathy	0	0	0	0	1 (0.6%)	1 (0.4%)
Urticaria	0	0	0	1 (0.5%)	0	1 (0.4%)
Vomiting	1 (1.0%)	0	0	0	0	0
Participants with ≥1 malignancy	0	0	0	1 (0.5%)	0	1 (0.4%)
Participants with ≥1 ISR	1 (1.0%)	0	1 (2.2%)	4 (2.1%)	0	5 (1.8%)

Highlighted SAEs also led to study agent discontinuation in the same patient.
*AEs that occurred during placebo treatment in placebo-randomised patients.
†Includes guselkumab-randomised patients who received an EE placebo injection at week 16.
‡AEs that occurred in all patients who received at least one administration of guselkumab, including those randomised to placebo.
§AEs that occurred during guselkumab treatment in placebo-randomised patients who crossed over to guselkumab prior to week 24.
¶AEs that occurred in placebo-randomised patients who crossed over to guselkumab at week 24.
AE, adverse event; EE, early escape; ISR, injection-site reaction; PY, patient-years; SAE, serious adverse event.

achieved (ACR20: guselkumab, 44% vs placebo, 20%). Guselkumab 100 mg Q8W afforded higher ACR20 and ACR50 response rates, as early as week 4 and week 8, respectively. Furthermore, >80% of patients who achieved ACR20/50/70 at week 24 maintained response at week 48. In addition, this study demonstrated the efficacy of guselkumab in resolving enthesitis and dactylitis, achieving clear skin and achieving MDA in patients with TNFi-IR PsA. The guselkumab group also had greater improvements in fatigue, physical function and HRQoL scores than placebo at week 24, with approximately 30%–40% of guselkumab-randomised patients achieving an improvement greater than the minimal clinically important differences at week 24.

Importantly in this TNF-IR population, improvements in signs and symptoms of PsA were maintained or numerically increased through week 48 among guselkumab-randomised patients. Among placebo→guselkumab patients, response rates and mean improvements increased through week 48. Thus, guselkumab 100 mg Q8W demonstrated efficacy through 1 year across the diverse symptoms in patients with TNFi-IR PsA.

Prespecified sensitivity analyses (eg, excluding patients with MPDs relevant to efficacy outcomes and correcting errors in EE patients thus providing a more accurate assessment of treatment effect) confirmed those of the primary endpoint (ACR20 at week 24). Although absolute response rates tended to be numerically lower in COSMOS patients relative to the primarily biologic-naïve populations in previous studies, the treatment effect of guselkumab as measured by the difference between the Q8W group and placebo at week 24 (ACR20 %differences: 25—28% across primary and sensitivity analyses) was generally consistent with that observed for guselkumab 100 mg Q8W in largely biologic-naïve patients with active PsA in the similarly designed pivotal DISCOVER-1 and DISCOVER-2 studies (ACR20 %differences: 30—31%).[8 9]

Guselkumab was well tolerated by participants, demonstrating a safety profile similar to placebo. Two guselkumab-treated patients had a serious infection. Two placebo-treated patients and three guselkumab-treated patients reported psychiatric disorders; two were SAEs, one occurring in a patient with a prior history of suicide attempt. One case of suspected, but unconfirmed, inflammatory bowel disease was reported ~1 month after the patient discontinued guselkumab due to an influenza-like illness. Abnormal clinical laboratory findings were uncommon; no participant died or developed an opportunistic infection or TB. Thus, these safety findings in patients with TNFi-IR PsA through week 56 of COSMOS expand on, and are consistent with, the accumulated guselkumab safety profile established in patients with psoriasis receiving guselkumab through 5 years[19] and that seen in DISCOVER-1 (1 year)[20] and DISCOVER-2 (2 years).[21 22]

Although head-to-head trials comparing guselkumab with other targeted or biologic therapies have not been conducted in patients with PsA, results from a recent network meta-analysis found that guselkumab had comparable efficacy with TNFi and IL-17A inhibitors in achieving ACR response in biologic-naïve patients.[23] In addition, the rates of AEs and SAEs were generally similar across treatment modalities; however, comparisons were limited by the significant uncertainty in the comparisons.[23] It is generally recommended to switch to an alternate mechanism of action following biologic treatment failure,[1 2] with only one switch between TNFi now recommended by the European Alliance of Associations for Rheumatology.[2] The demonstrated efficacy of therapies targeting the IL-12/23p40-subunit, IL-17A, and Janus kinases in TNFi-experienced patients with PsA[24–27] further supports the use of novel therapies to target alternative disease pathways.

However, patients who have experienced IR with a biologic, such as those enrolled in COSMOS, are at continued risk of treatment failure with subsequent therapies, thus highlighting the recalcitrant nature of the disease course in some patients with PsA.[4–6] Of note, 88% of guselkumab-randomised patients in COSMOS remained on treatment, and 94% of placebo patients who received guselkumab after week 24 completed study treatment through week 44. High study retention in COSMOS may thus reflect a positive benefit–risk profile for patients who had inadequate response to previous TNFi therapy. Patients who did not achieve an ACR20 response may have experienced substantial improvement in other symptoms (eg, skin disease). Other factors, such as comorbidities and limited availability or concerns about adverse effects of alternative treatment options in this refractory population, may have also contributed to patient retention.

Numerical imbalances in baseline characteristics (eg, gender, weight, joint counts and severity of skin disease) and errors in EE assignment may have influenced efficacy, although predominately not in favour of guselkumab. The slight imbalance between the treatment groups in the proportion of women is noteworthy considering research demonstrating that among patients with PsA, women tend to report having a higher disease burden and lower levels of response to treatment compared with men.[28] In addition, a separate analysis of 855 patients with PsA treated at a single rheumatology clinic found that being overweight was associated with not achieving treatment goals, specifically for women; however, no information was provided on the specific treatments these patients received.[29]

The COSMOS study was conducted across Europe, limiting ethnic diversity. COVID-related regulations during the latter half of study conduct may have increased MPDs; however, most were related to timing of study visits and did not impact efficacy. While the positive guselkumab benefit–risk profile observed through week 24 was maintained through 1 year, real-world evidence will further inform long-term guselkumab persistence in TNFi-IR patients.

In conclusion, guselkumab 100 mg Q8W was effective in patients with TNFi-IR PsA and demonstrated a favourable benefit–risk profile through 1 year. The statistically significant improvements observed with guselkumab across multiple clinical disease domains suggest a broad impact of targeting the p19 subunit of IL-23 in TNFi treatment-resistant PsA.

Author affiliations
[1]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK
[2]INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Universite, Paris, France
[3]APHP, Rheumatology Department, Hopital Universitaire Pitie Salpetriere, Paris, France
[4]Janssen Scientific Affairs, LLC, Solna, Sweden
[5]Janssen, Breda, The Netherlands
[6]Janssen Scientific Affairs, LLC, Brussels, Belgium
[7]Janssen Research & Development, LLC, Spring House, Pennsylvania, USA
[8]Immunology Global Medical Affairs, Janssen Pharmaceutical Companies of Johnson & Johnson, Horsham, Pennsylvania, USA
[9]Rheumatology, University of Erlangen, Erlangen, Germany
[10]MVLS College Office, University of Glasgow, Glasgow, UK

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ORCID iDs
Laura C Coates http://orcid.org/0000-0002-4756-663X
Laure Gossec http://orcid.org/0000-0002-4528-310X
Elke Theander http://orcid.org/0000-0002-6533-2263
Chetan S Karyekar http://orcid.org/0000-0002-5596-3117
Wim Noël http://orcid.org/0000-0002-5988-4627
Georg Schett http://orcid.org/0000-0001-8740-9615
Iain B McInnes http://orcid.org/0000-0003-4449-8501

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ONLINE SUPPLEMENT

Methods

This phase IIIb, randomized, double-blind study was conducted at 84 European sites (Belgium-1, Bulgaria-5, France-3, Germany-5, Hungary-6, Israel-4, Italy-3, Poland-6, Portugal-1, Russia-19, Spain-11, Ukraine-15, United Kingdom-5).

Additional secondary endpoints included American College of Rheumatology 70% improvement response, proportions of patients achieving 20% improvement in the ACR components, proportions of patients with resolution of enthesitis (Leeds Enthesitis Index score=0) or dactylitis (Dactylitis Severity Score=0) among participants with respective scores ≥1 at baseline, Investigator's Global Assessment of psoriasis (IGA score=0/1 and ≥2-grade improvement from baseline), and PASI75/PASI90 responses in patients with ≥3% body surface area and IGA ≥2 at baseline, 36-item Short-Form Health Survey Mental Component Summary (MCS) change scores, proportion of patients with ≥4-point increase (improvement) in Functional Assessment of Chronic Illness Therapy-Fatigue scores; change in Disease Activity in Psoriatic Arthritis (DAPSA) score; and overall disease status per Minimal Disease Activity (MDA) and Very Low Disease Activity (VLDA) composite indices. Additional post hoc analyses determined the proportions of patients with ≥5-point improvement in SF-36 PCS and MCS scores; patients with HAQ-DI response (improvement ≥0.35 in patients with baseline HAQ-DI ≥0.35); and patients achieving DAPSA low disease activity (LDA; ≤14) and remission (≤4).

Coates LC, *et al. Ann Rheum Dis* 2021;0:1–11. doi: 10.1136/annrheumdis-2021-220991

Safety outcomes included adverse events (AEs), serious AEs, AEs necessitating study drug discontinuation, infections, serious infections, injection-site reactions, malignancies, and laboratory abnormalities per National Cancer Institute Common Terminology Criteria for Adverse Events. Treatment-emergent AEs, i.e., those that occurred or worsened after the first dose of study intervention, were coded using the Medical Dictionary for Regulatory Activities (version 23.0). Major adverse cardiovascular events were defined as nonfatal stroke, nonfatal myocardial infarction, or cardiac death.

Assuming week24 ACR20 response rates of 41% and 20%, respectively, in the guselkumab and placebo arms, respective sample sizes of 163 and 82 were estimated to provide 90% power to detect a treatment difference.

Treatment group comparisons utilized a Cochran-Mantel Haenszel test stratified at the study level by baseline use of csDMARDs (yes/no) and number of prior tumor necrosis factor-inhibitors (TNFi; 1 vs. 2) for binary endpoints or an MMRM model (missing-at-random assumption) for continuous data. Explanatory variables of the MMRM model included treatment group, an interaction term of visit with treatment group, an interaction term of visit with baseline use of csDMARDs (yes/no), an interaction term of visit with number of prior TNFi (1 vs. 2), and an interaction term of visit with baseline score.

Supplemental Table 1. Summary of clinical laboratory abnormalities reported as AEs by maximum NCI-CTCAE grade[a] through week56 of the COSMOS study

	Placebo[b]	Placebo→Guselkumab			Randomized to Guselkumab[e]	
	(Week 0-24)	(Week 16-56)[c]	(Week 24-56)[d]	Total	(Week 0-24)	(Week 0-56)
Randomized participants by treatment received	96	45	45	90	189	189
Participants with ≥1 AE						
Neutrophil count decreased	0	2 (4.4%)	0	2 (2.2%)	1 (0.5%)	2 (1.1%)
Neutropenia	0	0	0	0	3 (1.6%)	3 (1.6%)
White blood cell count decreased	1 (1.0%)	2 (4.4%)	0	2 (2.2%)	1 (0.5%)	2 (1.1%)
Leukopenia	0	0	0	0	1 (0.5%)	2 (1.1%)
Lymphopenia	1 (1.0%)	1 (2.2%)	0	1 (1.1%)	1 (0.5%)	1 (0.5%)
Alanine aminotransferase increased	4 (4.2%)	1 (2.2%)	3 (6.7%)	4 (4.4%)	5 (2.6%)	8 (4.2%)
Aspartate aminotransferase increased	2 (2.1%)	0	2 (4.4%)	2 (2.2%)	1 (0.5%)	4 (2.1%)
Participants with ≥1 postbaseline assessment	**95**	**45**	**45**	**90**	**188**	**189**
Neutrophil Count Decreased						
Grade 1 (<LLN–1.5 x 10^9/L)	4 (4.2%)	4 (8.9%)	2 (4.4%)	6 (6.7%)	9 (4.8%)	13 (6.9%)
Grade 2 (<1.5–1.0 x 10^9/L)	2 (2.1%)	2 (4.4%)	1 (2.2%)	3 (3.3%)	6 (3.2%)	7 (3.7%)
Grade 3 (<1.0–0.5 x 10^9/L)	0	1 (2.2%)	0	1 (1.1%)	0	0
Grade 4 (<0.5 x 10^9/L)	0	0	0	0	0	0
White Blood Cell Count Decreased						
Grade 1 (<LLN–3.0x 10^9/L)	3 (3.2%)	2 (4.4%)	1 (2.2%)	3 (3.3%)	10 (5.3%)	16 (8.5%)
Grade 2 (<3.0–2.0x 10^9/L)	1 (1.1%)	2 (4.4%)	0	2 (2.2%)	1 (0.5%)	3 (1.6%)
Grade 3 or 4 (<2.0x 10^9/L)	0	0	0	0	0	0
Alanine Aminotransferase Increased				0		
Grade 1 (>ULN–3.0x ULN)	16 (16.8%)	7 (15.6%)	14 (31.1%)	21 (23.3%)	46 (24.5%)	65 (34.4%)
Grade 2 (>3.0–5.0x ULN)	0	0	1 (2.2%)	1 (1.1%)	1 (0.5%)	1 (0.5%)
Grade 3 (>5.0–20.0x ULN	1 (1.1%)	0	2 (4.4%)	2 (2.2%)	0	0
Grade 4 (>20.0x ULN)	1 (1.1%)	1 (2.2%)	0	1 (1.1%)	0	0
Aspartate Aminotransferase Increased						
Grade 1 (>ULN–3.0x ULN)	14 (14.7%)	6 (13.3%)	15 (33.3%)	21 (23.3%)	33 (17.6%)	48 (25.4%)
Grade 2 (>3.0–5.0x ULN)	0	1 (2.2%)	0	1 (1.1%)	1 (0.5%)	1 (0.5%)
Grade 3 (>5.0–20.0x ULN	1 (1.1%)	0	2 (4.4%)	2 (2.2%)	0	0
Grade 4 (>20.0x ULN)	1 (1.1%)	1 (2.2%)	0	1 (1.1%)	0	0

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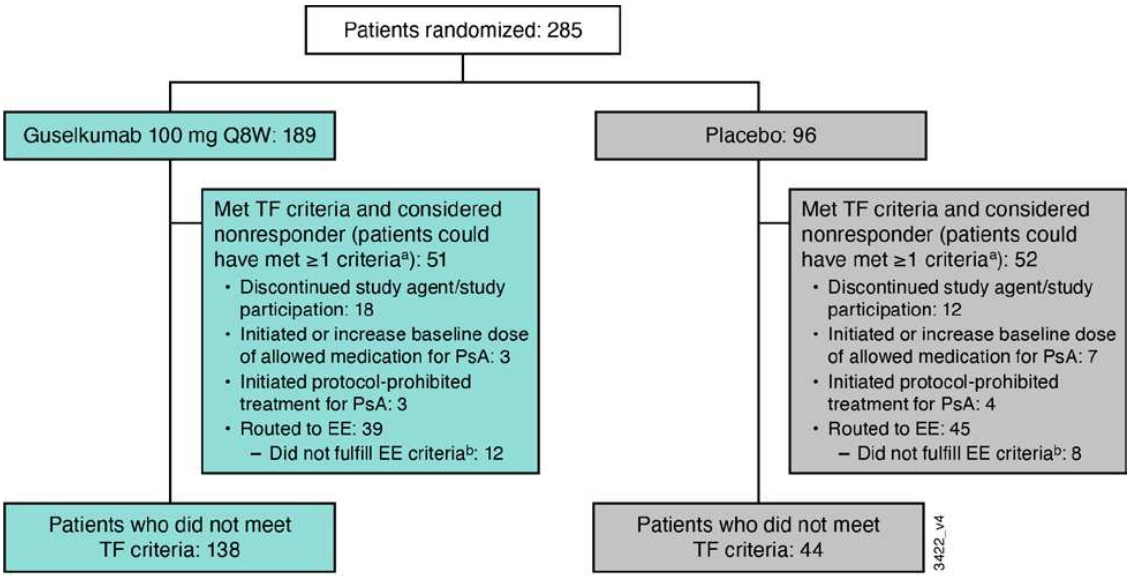
	Placebo[b]	Placebo→Guselkumab			Randomized to Guselkumab[e]	
	(Week 0-24)	(Week 16-56)[c]	(Week 24-56)[d]	Total	(Week 0-24)	(Week 0-56)

[a] Adverse events were coded using the Medical Dictionary for Regulatory Actions (MedDRA), Version 23.0. Laboratory findings were evaluated using National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE), Version 4.03.
[b] AEs that occurred during placebo treatment in placebo-randomized patients.
[c] AEs that occurred in placebo-randomized patients who entered early escape at week 16 and received ≥1 guselkumab administration.
[d] AEs that occurred in placebo-randomized patients who crossed over to guselkumab at week 24 received ≥1 guselkumab administration.
[e] Includes guselkumab-randomized patients who received ≥1 guselkumab administration and those who received an EE placebo injection at week 16.
AE, adverse event; EE, early escape, LLN, lower limit of normal, NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events, ULN, upper limit of normal

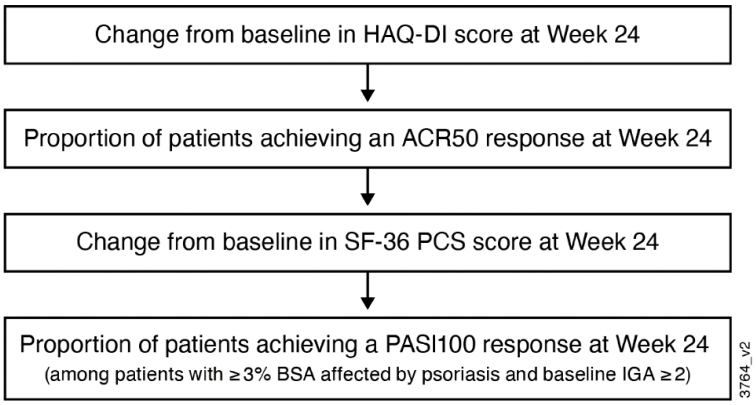
Supplemental Figure 1. Patients included in the Primary analysis population. Treated participants analyzed by randomized group, with those meeting treatment failure (TF) criteria considered nonresponders. csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; EE, early escape; PsA, psoriatic arthritis; Q8W, every 8 weeks



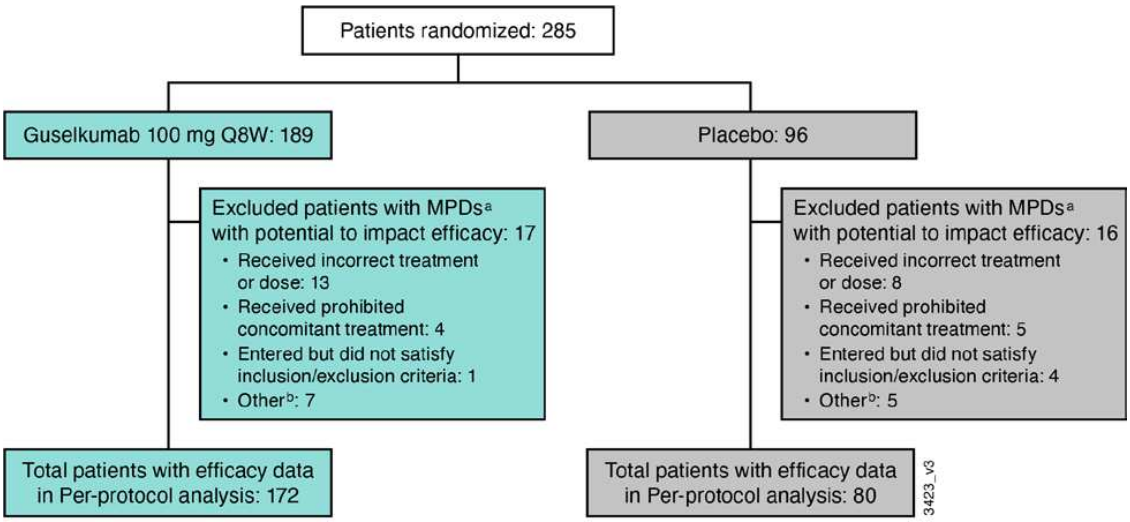
[a] TF criteria were: discontinuation of study agent/study participation for any reason, initiation of or increase in the dose of allowed csDMARDs or oral corticosteroids for PsA, initiation of protocol-prohibited medications/therapies for PsA, or met EE criteria.

[b] Patients who were improperly classified as having met the EE criteria and were considered nonresponders in the primary endpoint analysis.

Supplemental Figure 2. Hierarchical ordering of major secondary endpoints in COSMOS.
ACR50, ≥50% improvement in American College of Rheumatology response criteria; BSA, body surface area; HAQ-DI, Health Assessment Questionnaire-Disability Index; IGA, Investigator's Global Assessment; PASI100, 100% improvement in Psoriasis Area and Severity Index; SF-36 PCS, 36-item Short-Form Health Survey Physical Component Summary



Supplemental Figure 3. Patients included in the Per-protocol population. Treated participants according to randomized group, excluding those with major protocol deviations (MPDs) with potential to impact efficacy. CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; Q8W, every 8 weeks



[a] Patients could have >1 MPD that led to their exclusion from the Per-protocol analysis.

[b] Reasons in this category included lack of serum samples for CRP measurement (guselkumab, n=4; placebo, n=1), not receiving prior csDMARDs as indicated at screening (guselkumab, n=2; placebo, n=1), and efficacy assessments performed by someone other than the study-trained investigator (guselkumab, n=1; placebo, n=1).

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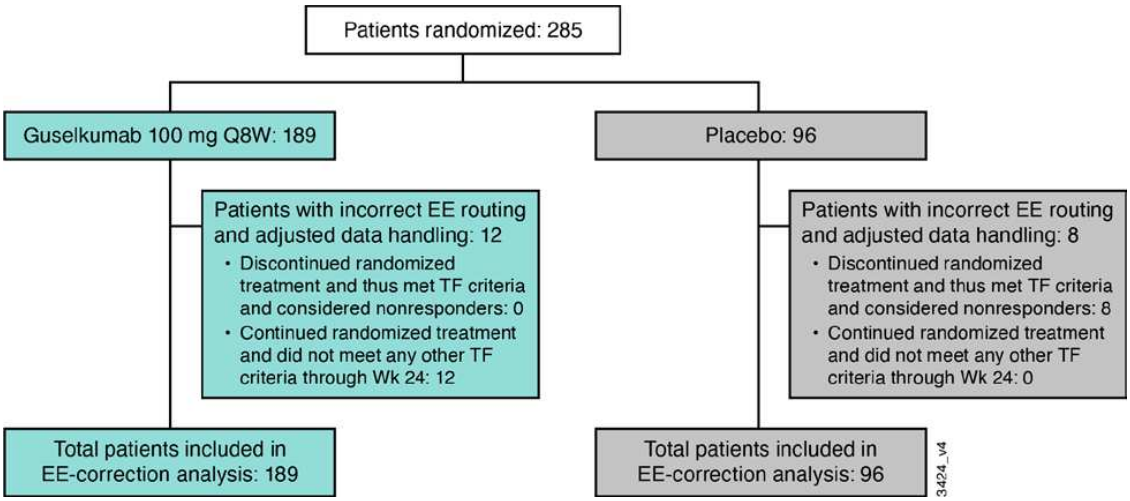
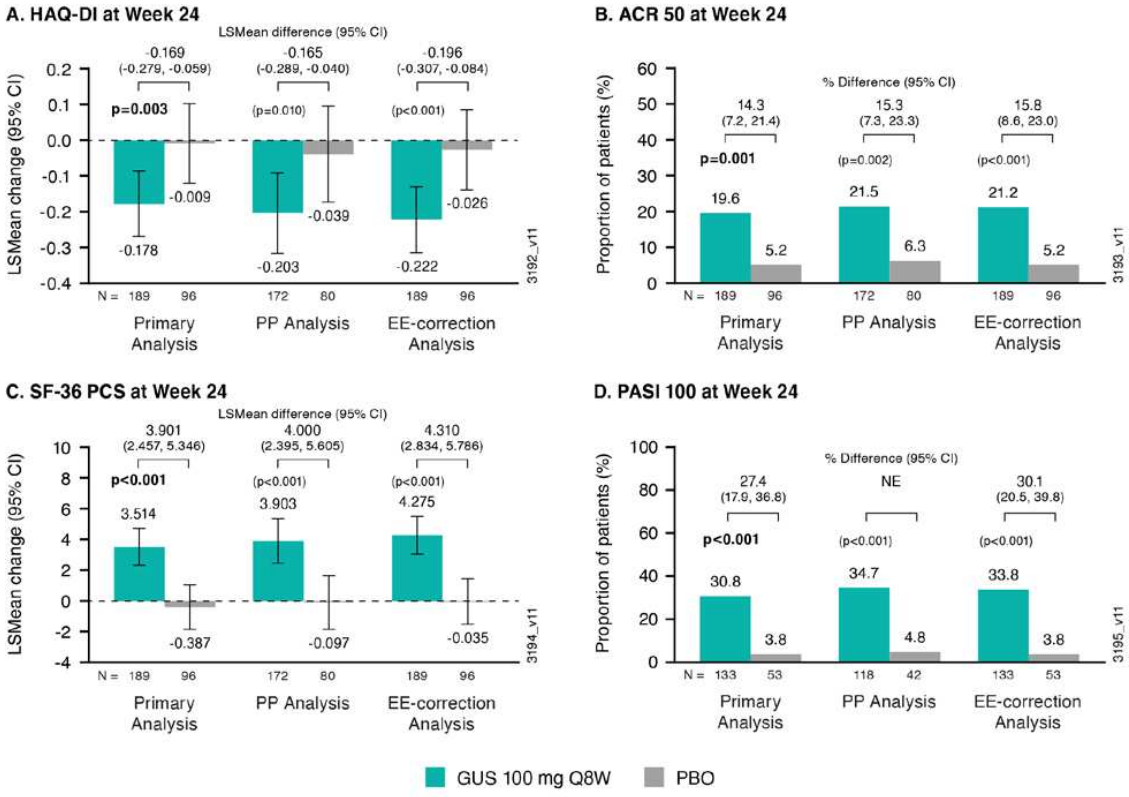
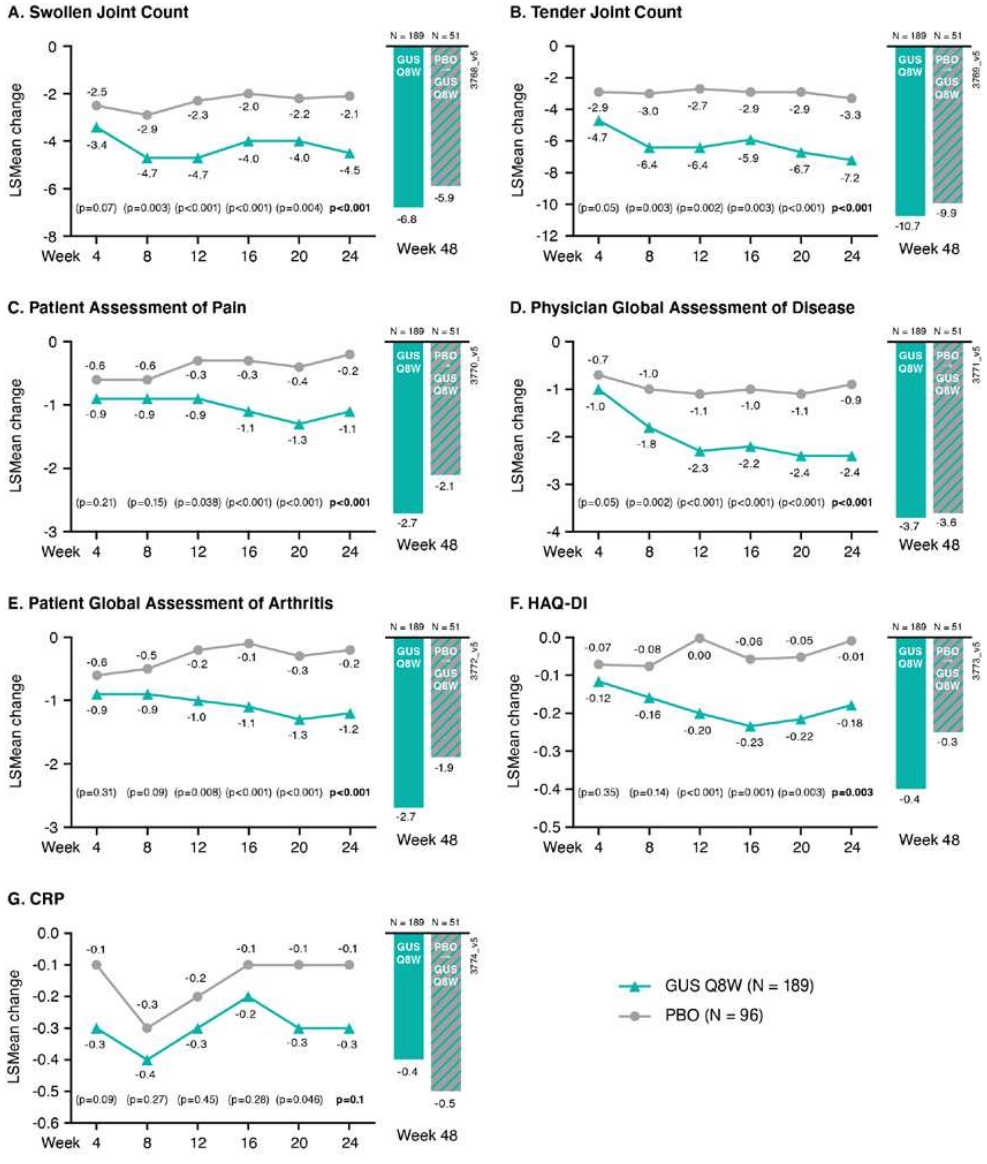


Supplemental Figure 5. Key secondary outcomes through week 24 of COSMOS. Results at week 24 across the Primary, PP, and EE-correction analyses for LSmean HAQ-DI change scores **(A),** ACR50 response (**B**), LSmean SF-36 PCS change scores (**C**), and PASI100 response (**D**). ACR50, ≥50% improvement in American College of Rheumatology criteria; CI, confidence interval; EE, early escape; GUS, guselkumab; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; PASI100, 100% improvement in Psoriasis Area and Severity Index; PBO, placebo; PP, per-protocol; Q8W, every 8 weeks; SF-36 PCS, 36-item Short-Form Health Survey Physical Component Summary



Bolded p values are adjusted for multiplicity of testing; p values shown in parentheses are not adjusted for multiplicity of testing
NE – not estimable

Supplemental Figure 6. Changes in ACR components through week 48 of COSMOS. Primary analysis through week24 and post hoc NRI analysis at week48 of LSmean change and mean change in swollen joint count **(A),** tender joint count **(B),** patient assessment of pain (VAS 0-100) **(C),** physician global assessment of disease (VAS 0-100) **(D),** patient assessment of arthritis (VAS 0-100) **(E),** HAQ-DI score **(F),** and CRP (mg/dL) **(G).** After week 24, analyses were performed using NRI (including imputation of EE patients as nonresponders in the guselkumab group; see Patients and Methods). Results for the placebo → guselkumab group at week 48 are reported for patients who did not enter EE and crossed over to guselkumab at week24. ACR, American College of Rheumatology; CRP, C-reactive protein; EE, early escape; GUS, guselkumab; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; NRI, nonresponder imputation; PBO, placebo; Q8W, every 8 weeks; VAS, visual analog scale



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ONLINE SUPPLEMENT

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Neutropenia	0	0	0	0	3 (1.6%)	3 (1.6%)
White blood cell count decreased	1 (1.0%)	2 (4.4%)	0	2 (2.2%)	1 (0.5%)	2 (1.1%)
Leukopenia	0	0	0	0	1 (0.5%)	2 (1.1%)
Lymphopenia	1 (1.0%)	1 (2.2%)	0	1 (1.1%)	1 (0.5%)	1 (0.5%)
Alanine aminotransferase increased	4 (4.2%)	1 (2.2%)	3 (6.7%)	4 (4.4%)	5 (2.6%)	8 (4.2%)
Aspartate aminotransferase increased	2 (2.1%)	0	2 (4.4%)	2 (2.2%)	1 (0.5%)	4 (2.1%)
Participants with ≥1 postbaseline assessment	**95**	**45**	**45**	**90**	**188**	**189**
Neutrophil Count Decreased						
Grade 1 (<LLN–1.5 x 10^9/L)	4 (4.2%)	4 (8.9%)	2 (4.4%)	6 (6.7%)	9 (4.8%)	13 (6.9%)
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Grade 3 (<1.0–0.5 x 10^9/L)	0	1 (2.2%)	0	1 (1.1%)	0	0
Grade 4 (<0.5 x 10^9/L)	0	0	0	0	0	0
White Blood Cell Count Decreased						
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Grade 2 (>3.0–5.0x ULN)	0	0	1 (2.2%)	1 (1.1%)	1 (0.5%)	1 (0.5%)
Grade 3 (>5.0–20.0x ULN	1 (1.1%)	0	2 (4.4%)	2 (2.2%)	0	0
Grade 4 (>20.0x ULN)	1 (1.1%)	1 (2.2%)	0	1 (1.1%)	0	0
Aspartate Aminotransferase Increased						
Grade 1 (>ULN–3.0x ULN)	14 (14.7%)	6 (13.3%)	15 (33.3%)	21 (23.3%)	33 (17.6%)	48 (25.4%)
Grade 2 (>3.0–5.0x ULN)	0	1 (2.2%)	0	1 (1.1%)	1 (0.5%)	1 (0.5%)
Grade 3 (>5.0–20.0x ULN	1 (1.1%)	0	2 (4.4%)	2 (2.2%)	0	0
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AE, adverse event; EE, early escape, LLN, lower limit of normal, NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events, ULN, upper limit of normal

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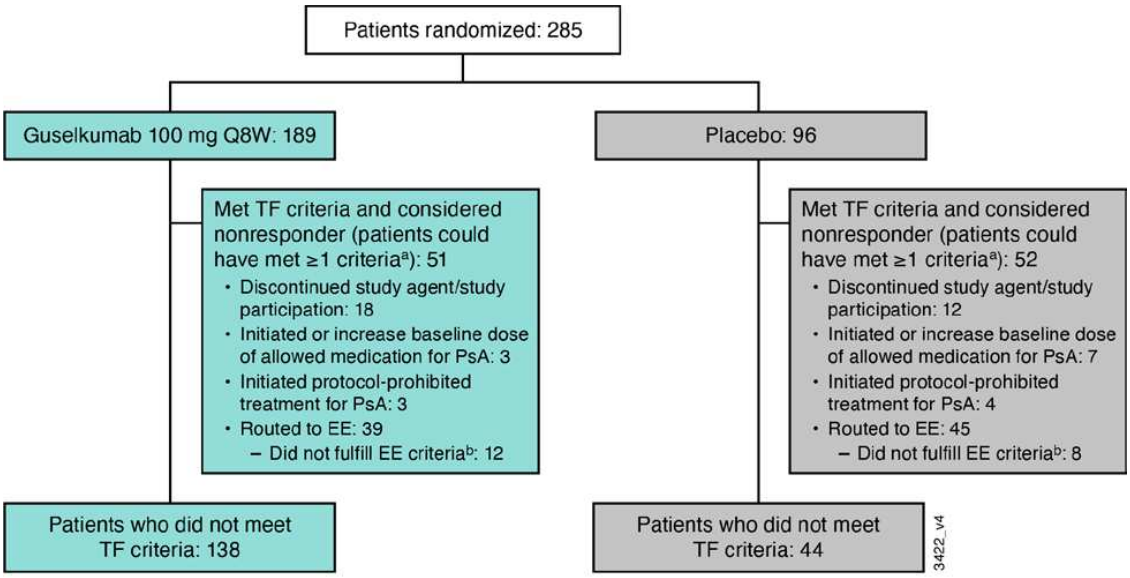

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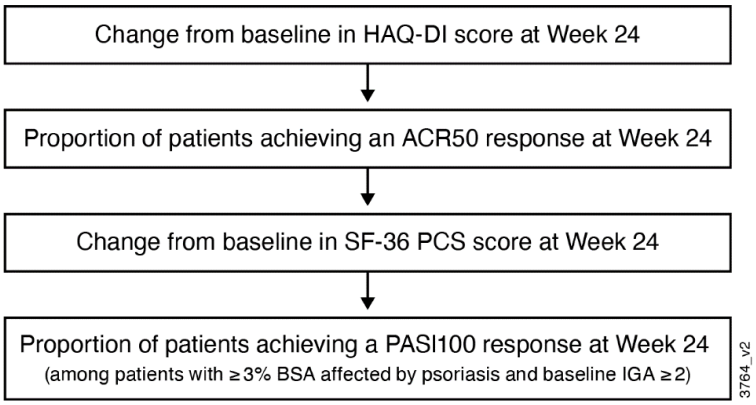

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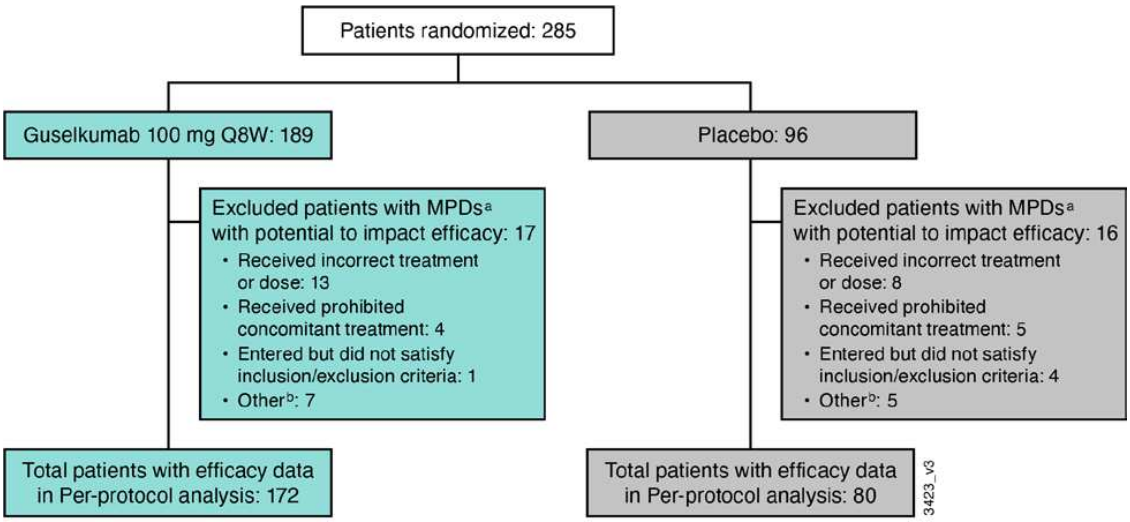

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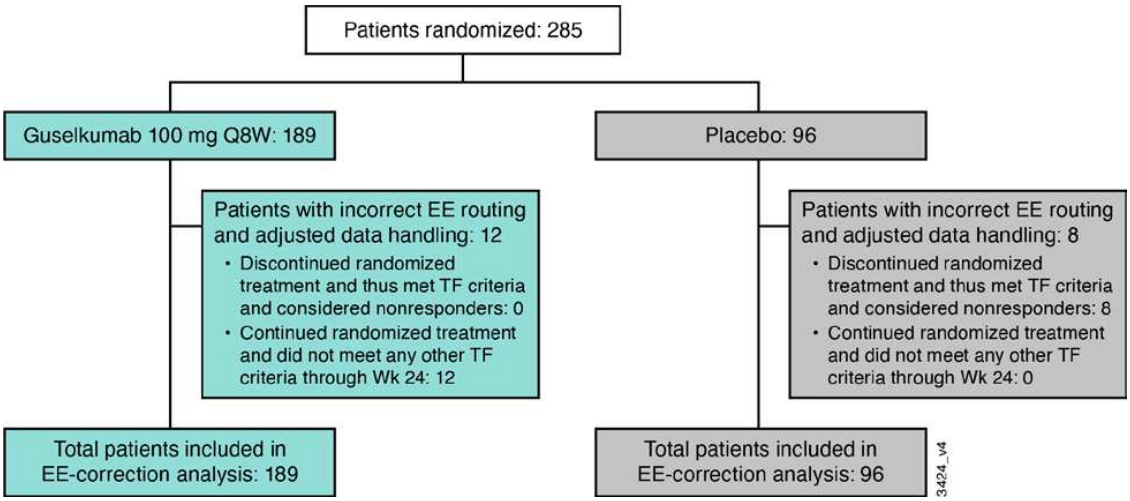
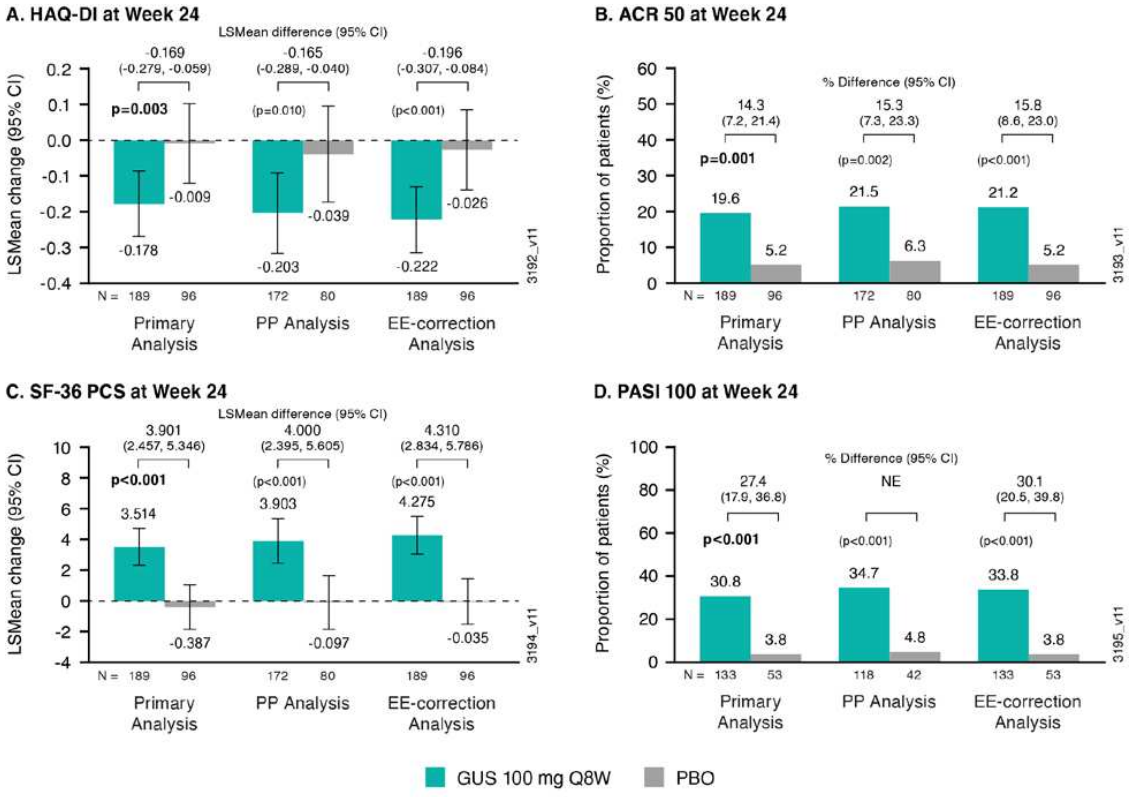
Supplemental Figure 4. Patients included in the EE-correction population. Treated participants analyzed by randomized group, adjusted for incorrect early escape (EE) assignment. Q8W, every 8 weeks; TF, treatment failure

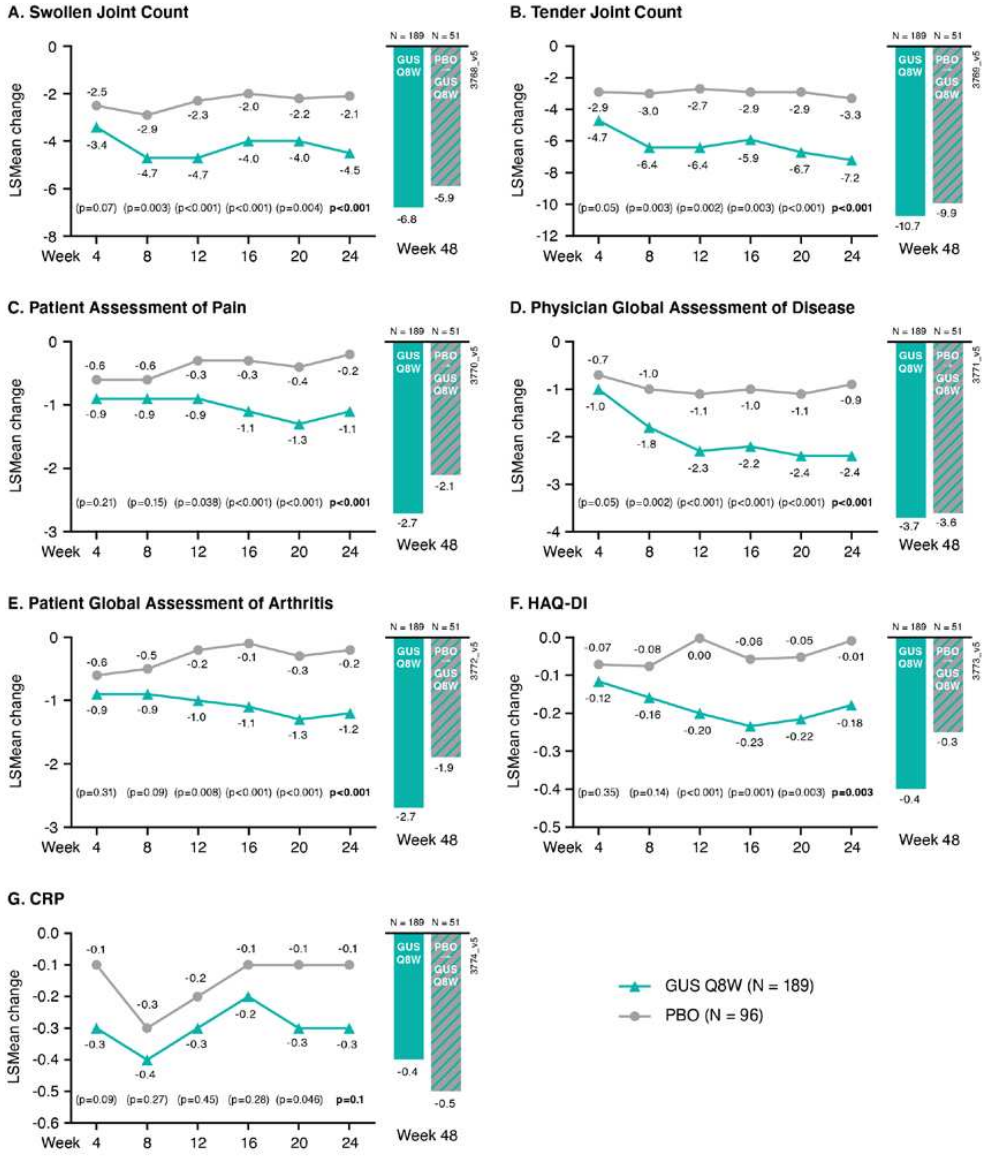


Supplemental Figure 5. Key secondary outcomes through week 24 of COSMOS. Results at week 24 across the Primary, PP, and EE-correction analyses for LSmean HAQ-DI change scores **(A),** ACR50 response (**B**), LSmean SF-36 PCS change scores (**C**), and PASI100 response (**D**). ACR50, ≥50% improvement in American College of Rheumatology criteria; CI, confidence interval; EE, early escape; GUS, guselkumab; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; PASI100, 100% improvement in Psoriasis Area and Severity Index; PBO, placebo; PP, per-protocol; Q8W, every 8 weeks; SF-36 PCS, 36-item Short-Form Health Survey Physical Component Summary



Bolded p values are adjusted for multiplicity of testing; p values shown in parentheses are not adjusted for multiplicity of testing
NE – not estimable

Supplemental Figure 6. Changes in ACR components through week 48 of COSMOS. Primary analysis through week24 and post hoc NRI analysis at week48 of LSmean change and mean change in swollen joint count **(A),** tender joint count **(B),** patient assessment of pain (VAS 0-100) **(C),** physician global assessment of disease (VAS 0-100) **(D),** patient assessment of arthritis (VAS 0-100) **(E),** HAQ-DI score **(F),** and CRP (mg/dL) **(G).** After week 24, analyses were performed using NRI (including imputation of EE patients as nonresponders in the guselkumab group; see Patients and Methods). Results for the placebo → guselkumab group at week 48 are reported for patients who did not enter EE and crossed over to guselkumab at week24. ACR, American College of Rheumatology; CRP, C-reactive protein; EE, early escape; GUS, guselkumab; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; NRI, nonresponder imputation; PBO, placebo; Q8W, every 8 weeks; VAS, visual analog scale



Bolded p values are adjusted for multiplicity of testing; p values shown in parentheses are not adjusted for multiplicity of testing