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Deodhar, A, Helliwell, PS, Boehncke, W-H et al. (9 more authors) (Cover date: 4-10 April 2020) Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. The Lancet, 395 (10230). pp. 1115-1125. ISSN 0140-6736

https://doi.org/10.1016/s0140-6736(20)30265-8

Words: 4467/4500

Summary (283/300 words)

Background: Many patients with psoriatic arthritis demonstrate inadequate response to tumor-necrosis-factor-inhibitors. The human anti-interleukin-23p19-subunit monoclonal antibody guselkumab safely and significantly improved psoriatic arthritis signs and symptoms in a Phase-2 trial.

Methods: This Phase-3, double-blind, placebo-controlled study (86 sites in 13 countries) enrolled adults with active psoriatic arthritis (≥3 swollen, ≥3 tender joints; C-reactive protein ≥0·3mg/dL) despite standard therapies. Approximately 30% of patients could have received 1-2 tumor-necrosis-factor-inhibitors. Patients were randomised (1:1:1, computer-generated permuted blocks; stratified by baseline disease-modifying antirheumatic drug and prior tumor-necrosis-factor-inhibitor use) to subcutaneous guselkumab 100mg every-4-weeks (q4w); guselkumab 100mg at Weeks 0, 4, every-8-weeks (q8w); or matching placebo. The primary endpoint was American College of Rheumatology 20% improvement (ACR20) at Week24 among randomised and treated patients using nonresponder imputation. Clinicaltrials.gov-identifier-NCT03162796 (active-not recruiting).

Findings: From 08/28/2017–03/14/2019, 381 patients received guselkumab q4w (N=128), q8w (N=127), or placebo (N=126); 362 patients continued study agent through Week24. Significantly greater proportions of patients receiving guselkumab q4w (76 [59·4%] of 128) and q8w (66 [52·0%] of 127) vs. placebo (28 [22·2%] of 126) achieved ACR20 at Week24 (%differences [95%confidence intervals]: 37·1 [26·1, 48·2] and 29·8 [18·6, 41·1], respectively; both $p \leq 0·001$). Consistent response rates were observed in patients irrespective of prior tumor-necrosis-factor-

inhibitor use, including those with inadequate response. Both guselkumab regimens significantly improved psoriasis, physical function, and quality-of-life vs. placebo at Week24. Serious adverse events through Week24 occurred in none of 128 patients receiving guselkumab q4w, four (3·1%) of 127 patients receiving guselkumab q8w, and five (4·0%) of 126 placebo-treated patients. No guselkumab-treated patient died or experienced serious infections through Week24.

Interpretation: Guselkumab demonstrated a favorable benefit-risk profile and is an effective treatment option in patients with active psoriatic arthritis.

Funding: Janssen Research & Development, LLC

Panel - Research in context

Evidence before this study – Psoriatic arthritis (PsA) is a heterogeneous inflammatory disorder that often requires targeted treatment. PsA patients with either inadequate response or inability to tolerate one biologic agent may benefit from switching to another biologic with a different mechanism of action. Guselkumab, a high-affinity, human, anti-interleukin-23p19-subunit monoclonal antibody that is approved to treat moderate-to-severe psoriasis, demonstrated efficacy in patients with active psoriatic arthritis in a Phase-2 study.

Added value of this study – Results from one of two trials comprising the first Phase-3 development program for an interleukin-23p19-subunit inhibitor in psoriatic arthritis provide pivotal evidence of guselkumab efficacy in this indication. Across patients with active disease, guselkumab 100mg significantly improved joint symptoms, physical function, skin symptoms of psoriasis, and quality of life when administered every 4 or 8 weeks. Improvements in disease activity were equally robust in patients who had received or demonstrated inadequate response to one or two tumor-necrosis-factor-inhibitors. For both guselkumab dose regimens, the safety profile through Week 24 in PsA patients was consistent with that observed in patients treated for psoriasis.

Implications of all the available evidence – Results of this confirmative Phase-3 study provide strong evidence that guselkumab provides a novel mechanism of action, via targeting the p19-subunit of interleukin-23, to treat the diverse peripheral clinical manifestations of psoriatic arthritis. Guselkumab may offer an additional treatment option for PsA patients with active disease uncontrolled by standard therapies, including tumor-necrosis-factor-inhibitors.

INTRODUCTION

As a heterogeneous inflammatory disorder, psoriatic arthritis (PsA) demands individualized and targeted treatment based on specific clinical manifestations, symptom severity, and comorbidities. For patients with moderate-to-severe disease activity, aggressive treatment with nonbiologic or biologic disease modifying antirheumatic drugs (DMARDs) can significantly improve joint and skin symptoms and/or prevent permanent structural damage.[1,2] When a patient has an inadequate response to, or is intolerant of, one biologic agent, switching to another biologic with a different mechanism of action can be a useful strategy.[3,4] Furthermore, patients often lose response over time, so new mechanisms to catalyze development of alternative treatments are needed.[5,6]

Current biologic treatment options for PsA include tumor-necrosis-factor-inhibitors (TNFi), an interleukin (IL)-12/23 inhibitor, and IL-17 inhibitors. These agents have been shown to significantly improve skin and joint responses in patients when used alone or with conventional DMARDs. Other biologics and targeted synthetic DMARDs are available to treat PsA but have not demonstrated inhibition of joint damage and appear to be less effective in resolving symptoms of skin disease.[7-9]

While TNFi are frequently chosen as the first biologic therapy for patients with PsA, a substantial proportion of patients evaluated in clinical trials do not achieve meaningful American College of Rheumatology (ACR)-defined responses. TNFi have a complicated safety profile, particularly with regard to infection risk,[10] and anti-IL-17 therapies carry warnings about new-onset or exacerbation of inflammatory bowel disease in addition to infection risk.[11-13]

Evidence from preclinical models and clinical trial data indicate that the IL-23/T-helper (Th)17 pathway is pivotal in the development of both the skin and joint manifestations of PsA.[14,15] IL-23 is a heterodimer composed of both p19- and p40-subunits. Guselkumab (Janssen Biotech, Inc., Horsham, PA, USA) is a novel human monoclonal antibody that binds to the p19-subunit of IL-23 with high specificity and affinity. In a Phase-2 proof-of-concept study, guselkumab 100 mg at Week0, Week4, and then every 8 weeks (q8w) demonstrated efficacy across all endpoints related to joint signs and symptoms, physical function, skin disease, enthesitis, dactylitis, and health-related quality of life.[16] In biomarker assessments from that study, guselkumab-treated patients demonstrated decreased serum concentrations of IL-17A and IL-17F and C-reactive protein (CRP), with IL-17A and IL-17F levels comparable to those of healthy controls by Week16. These changes were associated with achievement of ≥20% improvement in ACR response criteria (ACR20) and Psoriasis Area and Severity Index 75% improvement (PASI75) responses.[17] Such associations endorse the relevance of the IL-23/Th17 pathway in PsA and that of guselkumab treatment in suppressing the pathway common to both skin and joint pathologies.

Herein, we report results from one of two pivotal Phase-3 trials, i.e., DISCOVER-1, conducted to evaluate guselkumab in patients with active PsA, including those who were previously treated with one or two TNFi. Results from the other Phase 3 registrational trial of guselkumab in PsA (DISCOVER-2), which sought to enroll biologic-naïve PsA patients with higher levels of disease activity, are reported elsewhere (Lancet.org doi.xxxx).

METHODS

Study design

DISCOVER-1 is a Phase-3, randomised, double-blind, placebo-controlled, multicenter, 3-arm study of guselkumab in patients with active PsA despite standard therapies (non-biologic DMARDs, apremilast, nonsteroidal anti-inflammatory drugs [NSAIDs]). Approximately 30% of patients could have previously received one or two TNFi. The study was conducted at 86 sites in 13 countries (Australia, Canada, Czech Republic, Germany, Hungary, Malaysia, Poland, Republic of Korea, Russia, Spain, Taiwan, Ukraine, United States). Screening began on 08/28/2017, and the final Week24 visit occurred on 03/14/2019. Following a 6-week screening period, the study included a placebo-controlled period from Week0–Week24 and an active treatment period from Week24–Week52 (last dose administered at Week48). Patients were followed for safety for 12 weeks after the dose of study drug, i.e., through Week60. At Week16, all patients with <5% improvement in both swollen and tender joint counts were eligible for early escape, in which the investigator could initiate or increase the dose of NSAIDs or other analgesics (up to the regional marketed dose approved), oral corticosteroids (≤10 mg/day of prednisone or equivalent dose), or non-biologic DMARDs (limited to methotrexate ≤25 mg/week, sulfasalazine ≤3 g/day, hydroxychloroquine ≤400 mg/day, or leflunomide ≤20 mg/day). At Week24, all placebo patients began to receive guselkumab 100 mg every 4 weeks (q4w) through Week48. Herein we report results through Week24. This trial (NCT03162796) is being conducted per Declaration of Helsinki and Good Clinical Practice guidelines. The protocol (available at Lancet.org doi.xxxx) was approved by each site's governing ethical body.

Participants

The study planned to enroll approximately 360 adults with PsA for ≥6 months, fulfilling Classification Criteria for Psoriatic Arthritis (CASPAR)[18] and displaying ≥3 tender and ≥3 swollen joints and CRP ≥0·3 mg/dL. Eligible patients had a current or documented history of psoriasis and had demonstrated inadequate response to, or intolerance of, standard treatment including ≥4 months of apremilast, ≥3 months of non-biologic DMARDs, or ≥4 weeks of NSAIDs for PsA. Approximately 30% of enrolled patients could have been previously treated with one or two TNFi. Patients were permitted, but not required, to continue background use of stable doses of one selected non-biologic DMARD (as described above), oral corticosteroids (≤10 mg/day of prednisone or equivalent dose), and/or NSAIDs/other analgesics. Patients with other inflammatory diseases and those who had previously received biologic agents other than TNFi were excluded. Patients also had to meet criteria for screening laboratory test results and tuberculosis (TB) history and testing results (including treatment for latent TB if present). Full inclusion and exclusion criteria, and further details of permitted and prohibited therapies, are included in the protocol (available at Lancet.org doi.xxxx). All patients provided written informed consent.

Randomisation and masking

At Week0, patients were centrally randomised using an interactive web response system (with computer-generated permuted-block randomisation stratified by baseline non-biologic DMARD use [yes/no] and prior TNFi use [yes/no]) in a 1:1:1 ratio to receive guselkumab 100 mg q4w; guselkumab 100 mg at Week0, Week4, and then every 8 weeks (q8w); or placebo. Placebo and guselkumab were provided in identical prefilled syringes with non-identifying labels, and

patients in each treatment group received the same number of injections at the same time points, to ensure that patients and all study site personnel were masked to treatment assignment throughout the study.

Procedures

Guselkumab was administered as a 100-mg subcutaneous injection at Week0, Week4, and then q4w or q8w. The q8w dose regimen was chosen based on its robust efficacy and acceptable safety profile observed in the guselkumab Phase 3 psoriasis[19,20] and Phase 2 PsA[16] trials. The q4w dose regimen, which was predicted to provide an approximately 4-fold higher median steady-state trough concentration than the q8w regimen based on population pharmacokinetic analysis (data on file), was included to evaluate whether higher serum guselkumab concentrations could elicit greater efficacy, including inhibition of structural damage progression, in PsA. Through the Week24 primary outcome timepoint, patients in the q4w group received guselkumab at Weeks0, 4, 8, 12, 16, and 20; those in the q8w group received guselkumab at Weeks0, 4, 12, and 20 and placebo at Weeks8 and 16; and those in the placebo group received matching control at Weeks0, 4, 8, 12, 16, and 20.

Independent assessors evaluated joints for tenderness (N=68) and swelling (N=66, excluding hips), enthesitis, and dactylitis. Patients reported pain (0–10 cm visual analog scale [VAS]), global disease activity (0–10 cm VAS), and physical function (Health Assessment Questionnaire-Disability Index [HAQ-DI]). Investigators completed the global assessment of disease activity (0–10 cm VAS), and serum CRP (mg/dL) was determined.

The Investigator's Global Assessment of psoriasis (IGA) and PASI were used to assess skin disease severity and extent. The IGA averages induration, erythema, and scaling scores to

categorize the severity of psoriasis (0–cleared, 1–minimal, 2–mild, 3–moderate, 4–severe). The PASI, which takes into account the body surface area (BSA) affected by psoriasis, and also the degree of redness, scaling, and induration, ranges from 0–72. The 36-item Short-Form (SF-36) Health Survey physical and mental component summary (PCS and MCS) scores were used to assess health-related quality of life. Suicidal ideation or behavior or non-suicidal self-injurious behavior was assessed using electronic Columbia-Suicide Severity Rating Scale [eC-SSRS] questionnaires.

Clinical assessments were performed at screening, baseline, and q4w through Week24. Adverse events (AEs) were monitored, and routine haematology and chemistry evaluations were done throughout the study. See the Online Supplement for serum pharmacokinetic and immunogenicity testing methodology.

Outcomes

The primary endpoint was the proportion of patients with an ACR20 response at Week24. Major secondary endpoints included ACR50 and ACR70 response, change from baseline in the 28-joint Disease Activity Score employing C-reactive protein (DAS28-CRP); IGA skin response (score=0/1 and ≥2-grade improvement from baseline) among patients with ≥3% BSA of psoriasis and IGA≥2 (mild-to-severe psoriasis) at baseline; change from baseline in HAQ-DI score; resolution of, and mean changes from baseline in, enthesitis (in patients with enthesitis at baseline) and dactylitis (in patients with dactylitis at baseline) scores pooled across both DISCOVER trials (see Statistical analyses); changes in SF-36 PCS and MCS scores, all at Week24, and ACR20 and ACR50 responses at Week16. Other selected key secondary outcomes included clinically meaningful improvement (≥0.35) in HAQ-DI score among those with

baseline HAQ-DI ≥0·35, ≥75/90/100% improvement in the Psoriasis Area and Severity Index (PASI75/PASI90/PASI100) among patients with mild-to-severe psoriasis at baseline, and minimal disease activity (MDA), all at Week24. Patients were considered to have achieved MDA if fulfilling at least five of seven criteria: tender joint count ≤1, swollen joint count ≤1, PASI score ≤1, patient pain VAS score ≤15, patient global disease activity VAS score ≤20, HAQ-DI score ≤0·5, and tender entheseal points ≤1. Subgroup analyses of the primary endpoint determined the proportions of patients achieving ACR20 response at Week24 by prior TNFi use.

Safety outcomes included AEs, serious AEs, AEs resulting in discontinuation of study drug, infections, injection-site reactions, malignancies, major acute cardiovascular events (MACE), suicidal ideation or behavior (based on eC-SSRS questionnaire or reported AEs), and clinical laboratory abnormalities classified by National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) grades. A MACE was predefined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

Statistical analyses

Assuming Week24 ACR20 response rates of 40% with guselkumab vs. 20% with placebo, a sample size of 360 (120/treatment group) would provide >90% statistical power (α=0·05; 2-sided) to detect a treatment difference for the primary endpoint.

Efficacy analyses through Week24 included all randomised patients who received at least one administration of study agent analyzed by assigned treatment group (full analysis set). Treatment differences were assessed via Cochran-Mantel-Haenszel testing for binary, and analyses of covariance for continuous, endpoints.

Note that, to increase sample size, data for endpoints related to resolution of, and changes in, enthesitis and dactylitis among the smaller number of patients with those conditions at baseline were prespecified to be pooled with those from DISCOVER-2. Pooled data are reported in that companion manuscript (Lancet.org doi.xxxx).

Owing to differing health authority requirements for the multiplicity control of endpoints, two prespecified statistical testing procedures were employed. For both approaches, the primary endpoint was first tested for the q4w group and then for the q8w group (each at the 0·05 level). The first approach controlled the overall Type 1 error rate across both dose regimens at the 0·05 level with a graphical procedure (Figure S1A). The second approach controlled the overall Type 1 error rate by each dose at the 0·05 level with a different graphical procedure (Figure S1B). Results for the first approach are presented herein and those from the second approach are provided in the Online Supplement (Table S1). Note that unadjusted (nominal) p-values provided for endpoints not controlled for multiplicity should be interpreted only as supportive.

Data handling rules were applied to all efficacy analyses. Patients who met treatment-failure criteria (discontinued study agent, terminated study participation, initiated/increased DMARD or oral corticosteroid use, initiated protocol-prohibited PsA treatment) were considered nonresponders for binary, and as having no improvement from baseline for continuous, endpoints. Missing data were imputed as nonresponders for binary, and using multiple imputation for continuous, endpoints.

An independent data monitoring committee examined data on an ongoing basis through the Week24 database lock to ensure study participant safety. Statistical analyses were performed

using SAS version 9.4 with SAS/STAT version 14.2 (SAS Institute, Inc., Cary, NC, USA). This active (not recruiting) study was registered in Clinicaltrials.gov (NCT03162796).

Role of the funding source

Janssen Research & Development, LLC funded this trial. All authors, including Janssen employees (APK, ECH, RAS, XLX, SS, PA, BZ, YZ), were involved in data collection, analysis, and/or interpretation; trial design; manuscript preparation; and deciding to submit it for publication. Janssen funded a professional medical writer to help prepare and submit the manuscript. The corresponding author (AD) had full access to all study data and had final responsibility to submit for publication.

RESULTS

Among the 624 patients screened, 241 did not meet the study entrance criteria, most commonly because CRP was <0·3 mg/dL. As detailed in Figure 1, 381 randomised patients were treated and included in analyses (full analysis set). Three (2·3%) of 128 guselkumab q4w-, four (3·1%) of 127 guselkumab q8w-, and 24 (19·0%) of 126 placebo-treated patients had <5% improvement in both tender and swollen joint counts and were eligible to initiate or increase the dose of NSAIDs, oral corticosteroids, and/or permitted non-biologic DMARDs at Week16. Through Week24, more patients treated with placebo than guselkumab discontinued study agent, most commonly due to lack of efficacy. Overall, 362 (95·0%) of 381 patients continued study drug at Week24 (Figure 1).

Baseline characteristics were generally similar between randomised groups, although a few numerical imbalances were observed (Table 1). Baseline medication use was also consistent across randomised treatment groups; among the 381 treated patients, 247 (64·8%) were receiving non-biologic DMARDs, including 211 (55·4%) receiving MTX; 54 (14·2%) were receiving oral corticosteroids; and 217 (57·0%) were receiving NSAIDs for PsA. One hundred eighteen (31·0%) of 381 patients had previously received one (102 [26·8%]) or two (16 [4·2%]) TNFi; of these, 44 (37·3%) of 118 patients had discontinued TNFi use due to inadequate response (Table 1).

The study met its primary endpoint: significantly greater proportions of patients in both the guselkumab q4w (76 [59·4%] of 128) and q8w (66 [52·0%] of 127) groups than the placebo group (28 [22·2%] of 126) achieved an ACR20 response at Week24 (% differences vs. placebo [95% confidence interval (CI)]: 37·1 [26·1, 48·2] and 29·8 [18·6, 41·1], respectively; both

p<0·001; Table 2). ACR20 response was similar in patients with and without prior TNFi use for both the guselkumab q4w (22 [57·9%] of 38 and 54 [60·0%] of 90) and q8w (23 [56·1%] of 41 43 [50·0%] of 86) dosing regimens, as well as in the subgroups of these patients who previously had an inadequate response to TNFi (11 [64·7%] of 17 and nine [60·0%] of 15 patients, respectively) (Table 3). The q4w and q8w regimens of guselkumab elicited higher ACR20 response rates than placebo by Week4-Week8 (Figure 2A). Rates of ACR20 response at Week16 and ACR50 response at Week24 achieved with both guselkumab dose regimens were higher than those associated with placebo (Table 2, Figures 2A-C). Improvements in DAS28-CRP scores afforded by guselkumab q4w at Weeek24 (least squares [LS] mean change: -1·61) and q8w (-1·43) were larger than with placebo (-0·70) (Table 2).

Guselkumab q4w and q8w significantly improved skin disease as assessed by IGA response at Week24 vs. placebo (67 [75·3%] of 89 and 47 [57·3%] of 82 vs. 12 [15·4%] of 78; both p<0·001 (Table 2, Figure 2D). Higher PASI75, PASI90, and PASI100 response rates were also observed in guselkumab- than placebo-treated patients (Table 2).

Guselkumab q4w and q8w significantly improved physical function as assessed by change from baseline in the HAQ-DI score at Week24 (LSmean [95% CI]: -0·40 [-0·48, -0·31] and -0·32 [-0·41, -0·24] vs. -0·07 [-0·16, -0·01]; both p<0·001) (Table 2, Figure 2E). Further, in patients with baseline HAQ-DI ≥0·35, 63 (57·3%) of 110 (q4w) and 57 (50·9%) of 112 (q8w) guselkumab-treated patients vs. 32 (29·1%) of 110 placebo-treated patients achieved clinically meaningful improvement (≥0·35) from baseline in HAQ-DI scores (Table 2).

At study outset, patients presented with impaired quality of life related to physical (mean SF-36 PCS score: 33·8–35·9) and mental (mean SF-36 MCS score: 46·5–48·7) domains (United States

general population norm=50.0; Table 1). The LSmean changes in SF-36 PCS scores with guselkumab q4w and q8w were 6·87 and 6·10, respectively, vs. 1·96 with placebo (both p<0·001) (Table 2, Figure 2F). Smaller numerical differences between guselkumab q4w and q8w vs. placebo were observed for improvements in SF-36 MCS scores at Week24 (LSmean changes: 3·60 and 3·20, respectively, vs. 2·37 (Table 2).

Thirty-nine (30·5%) of 128 and 29 (22·8%) of 127 patients who received guselkumab q4w and q8w, respectively, achieved MDA at Week24 vs. 14 (11·1%) of 126 placebo-treated patients (Table 2).

Among the 254 patients with evaluable serum samples collected following subcutaneous administration of guselkumab 100 mg, the median steady-state trough serum guselkumab concentration was 3·90 µg/mL at Week12 and was maintained through Week24 (4·34 µg/mL). When guselkumab 100 mg was given at Week0, Week4 and then q8w, the median steady-state trough concentration was 0·95 µg/mL. Antibodies to guselkumab were detected in five (2·0%) of 254 guselkumab-treated patients through Week24 (see Online Supplement).

Guselkumab was generally well-tolerated. Among patients receiving guselkumab q4w, guselkumab q8w, and placebo, respectively, through Week24, AEs were reported by 71 (55·5%) of 128, 68 (53·5%) of 127, and 75 (59·5%) of 126 patients; SAEs were reported by none of 128, four (3·1%) of 127, and five (4·0%) of 126 patients; and AEs led to discontinuation of study agent for one (0·8%) of 128, three (2·4%) of 127, and three (2·4%) of 126 patients (Table 4). Among the guselkumab-treated patients, similar proportions of TNF-experienced (45 [57·0%] of 79) and TNFi-naïve (94 [53·4%] of 176) patients reported AEs.

The AEs reported by ≥5% of patients in any group were infections (nasopharyngitis, upper respiratory tract infection) and laboratory investigations (alanine aminotransferase [ALT] increased, aspartate aminotransferase [AST] increased) (Table 4). Serious infections occurred in no guselkumab-treated and two (1·6%) of 126 placebo-treated (limb abscess, upper respiratory tract infection) patients.

One patient, in the placebo group, died through Week24. The 50-year-old male succumbed to cardiac failure 166 days following the first dose of placebo (no receipt of guselkumab). This was the only MACE reported through Week24.

One patient was diagnosed with malignancy through Week24. Plasma cell myeloma was reported in a 73-year old female 15 days after the first administration of the guselkumab q8w dosing regimen. Clinical laboratory analysis of a serum sample collected prior to the first guselkumab dose indicated elevated levels of gamma globulin and M protein, excess free kappa light chain production, and a markedly abnormal kappa/lambda ratio. Follow-up testing indicated multiple bone metastases, and the patient's diagnosis was refined to Stage III multiple myeloma. The investigator did not consider the event to be related to guselkumab exposure.

No opportunistic infections or cases of active TB occurred. One patient reported a fungal skin infection (mycotic infection under right breast at Week16 in a patient receiving guselkumab q4w; the infection responded to topical therapy and the patient continued in the study). No AEs of inflammatory bowel disease were reported.

One patient receiving guselkumab 100 mg q8w reported suicidal ideation at Week16 and Week20. The patient had a history of depression/suicidal ideation and was using antidepressants at baseline. Suicidal ideation was also reported at Week8 in a placebo-treated patient with a

history of suicidal ideation. Both patients continued in the study. No suicidal behavior or self-injurious behavior without suicidal intent was reported through Week24.

Maximum NCI-CTCAE Grade-2 hematological abnormalities were uncommon and generally comparable between guselkumab- and placebo-treated patients. Among the two patients in the guselkumab q4w group and one patient in the guselkumab q8w group with Grade-2 neutrophil count decreases (<1·5–1·0 x 10^9/L), abnormalities were transient and reversible, resolved spontaneously without treatment, were not associated with infections, and did not result in discontinuation. Grade-2 lymphocyte count decreases were comparable between guselkumab- (five [2·0%] of 254) and placebo- (three [2·4%] of 124) treated patients. The only maximum CTCAE Grade-3 hematological abnormalities were lymphocyte decrease (<0·5–0·2 x 10^9/L) in three patients receiving guselkumab q8w; no Grade-4 abnormalities occurred. Two of the three patients with Grade-3 lymphocytopenia had Grade-2 abnormalities (<0·8–0·5 x 10^9/L) prior to the first guselkumab dose. All instances of Grade-3 lymphocytopenia were transient, with a return to pretreatment levels at the next visit. No hematological abnormality in guselkumab-treated patients led to guselkumab discontinuation, and only one Grade-2 decreased lymphocyte count was associated with infection (dental pulpitis/abscess, which resolved).

The proportions of patients with increased ALT or AST concentrations reported as AEs by the investigator appeared higher in the combined guselkumab than placebo groups, without evidence of a dose-response relationship (Table 4). However, maximum CTCAE Grade-2-4 ALT (>3·0x upper limit of normal [ULN]) or AST (>3·0 x ULN) increases, respectively, were comparable between guselkumab- (five [2·0%] of 254 and four [1·6%] of 254) and placebo- (two [1·6%] of 124 and four [3·2%] of 124) treated patients and also demonstrated no apparent relationship to dose regimen. No CTCAE Grade-3 (>5·0–20·0 x ULN) or Grade-4 (>20·0 x ULN) ALT

elevations were observed in guselkumab-treated patients. No Grade-4 AST elevations (>20·0 x ULN) were observed, and Grade-3 AST elevations (>5·0–20·0 x ULN) were comparable between guselkumab- (two [0·8%] of 254) and placebo- (two [1·6%] of 124) treated patients. These laboratory abnormalities were generally transient, and none resulted in study drug discontinuation.

DISCUSSION

The Phase-3, multicenter, randomised, double-blind, placebo-controlled, DISCOVER-1 study met its primary endpoint, with both guselkumab dose regimens eliciting significantly higher ACR20 response rates at Week24 than placebo. Robust treatment effects were also attained using the more stringent ACR50 response criteria.

Given the complex and variable disease presentation of PsA, discontinuation or switching of biological agents due to lack of efficacy or intolerance is common, as is loss of efficacy over time.[3,21] As a human monoclonal antibody directed against the p19-subunit of IL-23, guselkumab inhibits IL-23. Inhibition of upstream IL-23 signaling reduces production of cytokines with established (TNFα) or emerging (IL-17 family) roles in inflammatory conditions such as psoriasis.[22] It has also been postulated that IL-23 blockade, by transdifferentiating Th17 lymphocytes (likely central effector cells in psoriasis) into Treg or Th1 cell populations,[23] interrupts Th17 pathways that contribute to the chronic inflammation underlying the pathophysiology of many immune-mediated diseases, including inflammatory arthritis, PsA, and psoriasis.[24,25] Guselkumab was equally effective in patients who had previously received one or two TNFi, including in the subset of patients who inadequately responded to TNFi. Guselkumab's mechanism of action also differs from that of ustekinumab, which inhibits IL-23 by targeting the p40-subunit shared by IL-23 and IL-12. Given that IL-12 has been shown to have a protective role - by limiting the recruitment of IL-17-producing γδ T cells – in psoriasiform skin inflammation,[26] selective targeting of IL-23 via its p19-subunit will offer a novel mechanism of action to effectively treat the diverse manifestations of PsA.

Consistent with the robust efficacy demonstrated by guselkumab in the treatment of psoriasis,[19,20] both guselkumab dose regimens also elicited significant improvements in skin psoriasis in this study. Two-thirds of guselkumab-treated patients with ≥3% BSA involvement and IGA ≥2 at baseline achieved IGA response, >80% of such patients achieved PASI75 response, and more than half achieved clear or almost clear skin as assessed by a PASI90 response, all highlighting the suitability of guselkumab for PsA patients with significant skin disease. Guselkumab also significantly improved physical function as assessed by changes in HAQ-DI scores, and a majority of guselkumab-treated patients with impaired physical function at study outset experienced clinically meaningful improvement (≥0·35) in HAQ-DI scores at Week24. Improvements in psoriasis and physical function are particularly important given that these disease manifestations can lead to depression and diminished quality of life.[27]

Guselkumab treatment afforded a significantly improved physical component of health-related quality of life at Week24. Smaller numerical differences between both guselkumab regimens and placebo for improvements in the mental domain of quality of life likely derive from the milder impairment in mental than physical health at baseline in this study population.

Importantly, one-quarter of guselkumab-treated patients achieved MDA, which integrates independently-assessed joint, skin, and entheseal symptoms with patient-reported pain, global disease activity, and physical function,[28] at Week24. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis/Outcome Measures in Rheumatology consensus-based recommendations recently identified MDA as a preferred treatment target.[29]

This study was not powered to compare guselkumab dose regimens; however, numerically greater improvements were observed with q4w than q8w dosing for some of the clinical efficacy

endpoints. In the larger DISCOVER-2 study (Lancet.org doi.xxxx), clinical response rates were similar for the two guselkumab dose regimens. Further, the cumulative evidence derived from additional analyses, including exposure-response relationship analyses, covariate adjustment for the modest baseline imbalances across treatment groups, subgroup analyses, and comparisons within and across the guselkumab Phase-2 and Phase-3 PsA studies, did not indicate a difference between guselkumab q8w and q4w dose regimens in treating signs and symptoms of PsA (data on file).

Guselkumab was generally well tolerated by this PsA population. No clinically meaningful differences in safety were observed between the guselkumab q4w and q8w dose regimens or between patients with or without prior TNFi use. No opportunistic infections or cases of active TB, and no events of inflammatory bowel disease, occurred. The overall safety profile was generally consistent with that reported for patients with psoriasis.[19,20,30] Specifically, in an analysis of data from more than 1,800 patients enrolled in two Phase-3 psoriasis studies, guselkumab demonstrated a stable safety profile through 100 weeks of treatment, with no signals of concern with regard to serious infection, malignancy, MACE or suicidality,[30] and no new safety signals have been observed in psoriasis patients receiving guselkumab for up to 4 years in the Phase-3 VOYAGE-1 trial.[31] Thus, the guselkumab benefit-risk profile appears favorable for the treatment of patients with PsA.

Results reported through Week24 of the DISCOVER-1 study are limited by the relatively short duration of treatment in the context of a lifelong condition requiring chronic treatment. Results through 1 year of the DISCOVER-1 study and 2 years of the DISCOVER-2 study will be informative in assessing the maintenance of guselkumab efficacy. Findings related to patients who demonstrated an inadequate response to prior TNFi treatment should be interpreted with

caution due to the limited size of this study subgroup. While the DISCOVER-1 study did not include imaging evaluations, results of the larger DISCOVER-2 trial indicate that selective IL-23p19-subunit inhibition with guselkumab q4w inhibits progression of structural damage in patients with active PsA (Lancet.org doi.xxxx).

In conclusion, Week24 results of this confirmative Phase-3 study provide strong evidence that guselkumab provides a novel mechanism of action, via targeting the p19-subunit of IL-23, to treat the diverse clinical manifestations of PsA. Importantly, guselkumab offers an additional treatment option for patients with active disease uncontrolled by standard therapies, including TNFi.

CONTRIBUTORS

Authors

Substantial intellectual contribution to conception and design, or acquisition of data, or analysis and interpretation of data (AD, PH, W-HB, APK, ECH, RAS, XLX, SS, PA, BZ, YZ, CTR)

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DECLARATION OF INTERESTS

A Deodhar has received grants and research support paid to University from Bristol Myers Squibb, Eli Lilly, Glaxo Smith & Kline, Novartis, Pfizer, and UCB, as well as honoraria or

consultation fees paid to self from AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Glaxo Smith & Kline, Janssen, Novartis, Pfizer, and UCB.

P Helliwell has received grants/research support paid to charity (AbbVie, Janssen, Novartis) or honoraria/consultation fees paid to charity (AbbVie, Amgen, Pfizer, UCB) or himself (Celgene, Galapagos).

W-H Boehncke has received honoraria as a speaker and/or advisor from AbbVie, Almirall, Celgene, Janssen, Leo, Lilly, Novartis, and UCB. He has received a research grant from Pfizer to investigate the role of JAK inhibition in psoriasis.

AP Kollmeier, EC Hsia, RA Subramanian, XL Xu, S Sheng, P Agarwal, B Zhou, and Y Zhuang are employees of Janssen Research & Development, LLC (a subsidiary of Johnson & Johnson) and own Johnson & Johnson stock or stock options.

CT Ritchlin has received research funding from Amgen, AbbVie, and UCB and serves as a consultant for Amgen, AbbVie, UCB, Janssen, Lilly, Novartis, and Pfizer.

ACKNOWLEDGMENTS

None

DATA SHARING STATEMENT

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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FIGURE LEGENDS

Figure 1. DISCOVER-1 patient disposition through Week 24. CRP – C-reactive protein, q4/8w – every 4/8 weeks, TB – tuberculosis, W/D – withdrawal

Figure 2. DISCOVER-1 efficacy through Week 24 (FAS). Proportion of patients achieving ACR20 (**A**; Note: p=0.001 for q8w group at Week20), ACR50 (**B**) and ACR70 (**C**), and IGA (**D**) responses and mean changes from baseline in HAQ-DI (**E**) and SF-36 PCS (**F**) scores. ACR20/50/70 – American College of Rheumatology 20/50/70% improvement, FAS – full analyses set, HAQ-DI – Health Assessment Questionnaire-Disability Index, IGA – *Investigator's* Global Assessment, LS – least squares, SF-36 PCS – 36-item Short-Form physical component summary

TABLES

Table 1. Summary of DISCOVER-1 baseline patient characteristics (FAS)

	Guselkumab 100 mg		Placebo
	q4w	q8w	
Number of patients	128	127	126
Age (years)	47·4 (11·6)	48·9 (11·5)	49·0 (11·1)
Male, n (%)	66 (51·6%)	68 (53·5%)	61 (48·4%)
White, n (%)	121 (94·5%)	116 (91·3%)	112 (88·9%)
Body weight (kg)	86·7 (17·7)	86·3 (20·0)	85·2 (18·8)
PsA duration (years)	6·6 (6·3)	6·4 (5·9)	7·2 (7·6)
Number of swollen joints (0-66)	8·6 (5·8)	10·9 (9·3)	10·1 (7·1)
Number of tender joints (0-68)	17·7 (13·1)	20·2 (14·5)	19·8 (14·4)
Patient's assessment of pain (0-10 cm VAS)	5·9 (2·0)	6·0 (2·1)	5·8 (2·2)
Patient's global assessment (arthritis, 0-10 cm VAS)	6·1 (2·0)	6·5 (2·0)	6·1 (2·2)
Physician's global assessment (0-10 cm VAS)	6·2 (1·6)	6·2 (1·7)	6·3 (1·7)
HAQ-DI score (0-3)	1·1 (0·6)	1·2 (0·6)	1·1 (0·6)
CRP (mg/dL), median (IQR)	0·6 (0·29–1·28)	0·7 (0·38–1·86)	0·8 (0·34–1·51)
Psoriatic BSA, (%)	15·0 (18·3%)	13·1 (17·7%)	12·0 (16·0%)
IGA 3/4, n (%)	62 (48·4%)	57 (44·9%)	43 (34·1%)
PASI score (0-72)	9·5 (10·1)	8·4 (9·8)	7·7 (8·8)
Patients with enthesitis, n (%)	73 (57·0%)	72/126 (57·1%)	77 (61·1%)
Enthesitis (LEI) score (1-6)[a]	3·0 (1·5)	2·7 (1·6)	2·8 (1·6)
Patients with dactylitis, n (%)	38 (29·7%)	49 (38·9%)	55 (43·7%)
Dactylitis score (1-60)[b]	9·4 (12·5)	8·2 (10·0)	6·6 (7·4)
SF-36			
PCS score	35·9 (8·3)	34·1 (7·6)	33·8 (8·5)
MCS score	46·5 (9·8)	47·0 (11·1)	48·7 (9·6)

Table 1. Summary of DISCOVER-1 baseline patient characteristics (FAS)

	Guselkumab 100 mg		Placebo
	q4w	q8w	
Number of patients	128	127	126
Patients with prior TNFi use, n (%)	38 (29·7%)	41 (32·3%)	39 (31·0%)
1 prior TNFi	33/38 (86·8%)	34/41 (82·9%)	35/39 (89·7%)
2 prior TNFi	5/38 (13·2%)	7/41 (17·1%)	4/39 (10·3%)
Patients who failed prior TNFi	17 (13·3%)	15 (11·8%)	12 (9·5%)
Patients receiving at baseline, n (%)			
DMARDs	82 (64·1%)	83 (65·4%)	82 (65·1%)
Methotrexate	72 (56·3%)	68 (53·5%)	71 (56·3%)
Dose (mg/week)	15·6 (4·1)	16·7 (5·4)	15·9 (4·5)
Oral corticosteroids for PsA	16 (12·5%)	18 (14·2%)	20 (15·9%)
Dose equivalent to prednisone (mg/day)	6·4 (2·2)	6·0 (1·9)	6·4 (2·4)
NSAIDs for PsA	69 (53·9%)	71 (55·9%)	77 (61·1%)

Data presented are mean (SD) unless noted otherwise.

[a] Among patients with LEI enthesitis score at baseline (q4w, n=73; q8w, n=72; placebo, n=77).

[b] Among patients with dactylitis score at baseline (q4w, n=38; q8w, n=49; placebo, n=55).

BSA – body surface area, CRP – C-reactive protein, DMARDs – disease-modifying antirheumatic drugs, FAS – full analysis set (randomised and treated patients), HAQ-DI – Health Assessment Questionnaire- Disability Index, IGA – *Investigator's Global Assessment, IQR* - interquartile range, LEI – Leeds Enthesitis Index, MCS – mental component summary, NSAIDs – nonsteroidal anti-inflammatory drugs, PASI – Psoriasis Area and Severity Index, PCS – physical component summary, PsA – psoriatic arthritis, q4w/q8w – every 4/8 weeks, SD – standard deviation, SF-36 – 36-item Short-Form, TNFi – tumor necrosis factor inhibitor, VAS – visual analog scale

Table 2. Summary of DISCOVER-1 efficacy findings (FAS[a])

	Guselkumab 100 mg		Placebo
	q4w	q8w	
Number of patients	128	127	126
Primary endpoint			
ACR20 response at Week24, n (%)	76 (59.4%)	66 (52.0%)	28 (22.2%)
% difference vs. placebo (95% CI)	37.1 (26.1, 48.2)	29.8 (18.6, 41.1)	
US procedure[b]-adjusted p value	<0.001	<0.001	
Major secondary endpoints controlled by US procedure			
IGA 0/1+≥2-grade decrease response at Week24[c], n/N (%)	67/89 (75·3%)	47/82 (57·3%)	12/78 (15·4%)
% difference vs. placebo (95% CI)	60·0 (48·3, 71·8)	42·0 (28·9, 55·1)	
US procedure[b]-adjusted p value	<0·001	<0·001	
HAQ-DI, LSmean (95% CI) change at Week24	-0·40 (-0·48, -0·31)	-0·32 (-0·41, -0·24)	-0·07 (-0·16, 0·01)
LSmean difference vs. placebo (95% CI)	-0·32 (-0·44, -0·21)	-0·24 (-0·36, -0·13)	
US procedure[b]-adjusted p value	<0·001	<0·001	
SF-36 PCS, LSmean (95% CI) change at Week24	6·87 (5·60, 8·14)	6·10 (4·83, 7·37)	1·96 (0·69, 3·24)
LSmean difference vs. placebo (95% CI)	4·91 (3·19, 6·63)	4·14 (2·42, 5·85)	
US procedure[b]-adjusted p value	<0·001	<0·001	
Major secondary endpoints not controlled by US procedure			
ACR20 response at Week16, n (%)	77 (60·2%)	66 (52·0%)	32 (25·4%)
% difference vs. placebo (95% CI)	34·8 (23·5, 46·0)	26·7 (15·3, 38·1)	
Unadjusted p value[d]	<0·001	<0·001	
ACR50 response at Week24, n (%)	46 (35·9%)	38 (29·9%)	11 (8·7%)
% difference vs. placebo (95% CI)	27·2 (17·6, 36·8)	21·4 (12·1, 30·7)	
Unadjusted p value[d]	<0·001	<0·001	
ACR70 response at Week24, n (%)	26 (20·3%)	15 (11·8%)	7 (5·6%)
% difference vs. placebo (95% CI)	14·8 (6·9, 22·7)	6·4 (-0·3, 13·1)	
Unadjusted p value[d]	<0·001	0·069	

ACR50 response at Week16, n (%)	34 (26·6%)	29 (22·8%)	16 (12·7%)
% difference vs. placebo (95% CI)	13·9 (4·4, 23·4)	10·2 (1·0, 19·3)	
Unadjusted p value[d]	0·006	0·036	
Resolution of dactylitis at Week24s, n/N (%)	24/38 (63·2%)	32/49 (65·3%)	27/55 (49·1%)
% difference vs placebo (95% CI)	13·4 (-6·9, 33·7)	16·6 (-1·5, 34·8)	
Unadjusted p value[d]	0·212	0·088	
Resolution of enthesitis at Week24, n/N (%)	35/73 (47·9%)	29/72 (40·3%)	21/77 (27·3%)
% difference vs placebo (95% CI)	19·8 (4·9, 34·6)	13·0 (-1·6, 27·5)	
Unadjusted p value[d]	0·013	0·094	
DAS28-CRP, LSmean (95% CI) change at Week24	-1·61 (-1·80, -1·42)	-1·43 (-1·61, -1·24)	-0·70 (-0·89, -0·51)
LSmean difference vs. placebo (95% CI)	-0·91 (-1·16, -0·66)	-0·73 (-0·98, -0·48)	
Unadjusted p value[d]	<0·001	<0·001	
SF-36 MCS, LSmean (95% CI) change at Week 24	3·60 (2·17, 5·02)	3·20 (1·78, 4·63)	2·37 (0·93, 3·81)
LSmean difference vs. placebo (95% CI)	1·23 (-0·71, 3·16)	0·83 (-1·10, 2·77)	
US procedure[b]-adjusted p value	0·214	0·398	
Additional secondary endpoints not controlled by US procedure			
HAQ-DI improvement ≥0·35 at Week 24[e], n/N (%)	63/110 (57·3%)	57/112 (50·9%)	32/110 (29·1%)
% difference vs. placebo (95% CI)	28·0 (15·7, 40·3)	21·8 (9·3, 34·2)	
Unadjusted p value[d]	<0·001	0·001	
PASI75 response at Week 24[c], n/N (%)	77/89 (86·5%)	62/82 (75·6%)	11/78 (14·1%)
% difference vs. placebo (95% CI)	72·6 (62·3, 82·8)	61·7 (49·8, 73·7)	
Unadjusted p value[d]	<0·001	<0·001	
PASI90 response at Week 24[c], n/N (%)	56/89 (62·9%)	41/82 (50·0%)	9/78 (11·5%)
% difference vs. placebo (95% CI)	51·7 (39·7, 63·7)	38·6 (25·8, 51·4)	
Unadjusted p value[d]	<0·001	<0·001	
PASI100 response at Week 24[c], n/N (%)	40/89 (44·9%)	21/82 (25·6%)	5/78 (6·4%)
% difference vs. placebo (95% CI)	38·9 (27·5, 50·3)	19·9 (9·6, 30·2)	
Unadjusted p value[d]	<0·001	<0·001	

MDA at Week 24, n (%)	39 (30·5%)	29 (22·8%)	14 (11·1%)
% difference vs. placebo (95% CI)	19·3 (9·7, 28·9)	11·9 (2·9, 20·9)	
Unadjusted p value[d]	<0·001	0·012	

Patients meeting treatment-failure criteria were considered nonresponders for binary endpoints and as having no improvement from baseline for continuous endpoints. Missing data were imputed as nonresponders for binary endpoints; multiple imputation was used to impute missing data for continuous endpoints. Treatment differences for binary endpoints were assessed via Cochran-Mantel-Haenszel test, and those for continuous endpoints were assessed via an analysis of covariance model. All models included treatment group, baseline non-biologic DMARD use (yes/no), prior TNFi use (yes/no), and baseline value as independent variables.

[a] The FAS included all randomised and treated patients.

[b] See Figure S1A.

[c] Assessed in patients with ≥3% body surface area affected by psoriasis and IGA score ≥2 at Week0.

[d] Unadjusted (nominal) p values are not controlled for multiplicity and should be interpreted only as supportive.

[e] Assessed in patients with HAQ-DI ≥0·35 at Week 0.

ACR20/50/70 – American College of Rheumatology 20/50/70% improvement, CI – confidence interval, DAS28-CRP – 28-joint Disease Activity Score based on C-reactive protein, DMARDs – disease modifying antirheumatic drugs, FAS – full analysis set, HAQ-DI – Health Assessment Questionnaire-Disability Index, IGA – *Investigator's Global Assessment, LS* – least squares, MCS – mental component summary, MDA – minimal disease activity, PASI50/75/90/100 – Psoriasis Area and Severity Index 50/75/90/100% improvement, PCS – physical component summary, q4w/q8w – every 4/8 weeks, SF-36 – 36-item Short Form, TNFi – tumor necrosis factor inhibitor, US – United States

Table 3. Summary of DISCOVER-1 ACR response by prior TNFi use (FAS[a])

	Guselkumab 100 mg		Placebo
	q4w	q8w	
Number of patients	128	127	126
ACR20 response at Week24, n/N (%)			
Patients with prior TNFi use	22/38 (57·9%)	23/41 (56·1%)	7/39 (17·9%)
% difference vs. placebo (95% CI)	40·0 (20·8, 59·2)	38·5 (19·3, 57·7)	
Unadjusted p value[b]	<0.001	<0.001	
Patients with inadequate response to prior TNFi	11/17 (64·7%)	9/15 (60·0%)	3/12 (25·0%)
% difference vs. placebo (95% CI)	42·4 (11·0, 73·9)	35·9 (0·8, 71·0)	
Patients without prior TNFi use, n/N (%)	54/90 (60·0%)	43/86 (50·0%)	21/87 (24·1%)
% difference vs. placebo (95% CI)	35·9 (22·3, 49·4)	25·9 (12·0, 39·7)	
Unadjusted p value[b]	<0.001	<0.001	
ACR50 response at Week24, n/N (%)			
Patients with prior TNFi use	13/38 (34·2%)	11/41 (26·8%)	2/39 (5·1%)
% difference vs. placebo (95% CI)	29·1 (12·7, 45·4)	22·1 (7·3, 37·0)	
Unadjusted p value[b]	0.001	0.008	
Patients with inadequate response to prior TNFi	5/17 (29·4%)	2/15 (13·3%)	0/12 (0·0%)
% difference vs. placebo (95% CI)	n/a	n/a	
Patients without prior TNFi use, n/N (%)	33/90 (36·7%)	27/86 (31·4%)	9/87 (10·3%)
% difference vs. placebo (95% CI)	26·3 (14·5, 38·1)	21·1 (9·4, 32·8)	
Unadjusted p value[b]	<0.001	<0.001	
ACR70 response at Week24, n/N (%)			
Patients with prior TNFi use	8/38 (21·1%)	1/41 (2·4%)	1/39 (2·6%)
% difference vs. placebo (95% CI)	18·5 (4·9, 32·2)	-0·0 (-6·4, 6·4)	
Unadjusted p value[b]	0.014[c]	1.000[c]	
Patients with inadequate response to prior TNFi	3/17 (17·6%)	1/15 (6·7%)	0/12 (0.0%)
% difference vs. placebo (95% CI)	n/a	n/a	

Patients without prior TNFi use, n/N (%)	18/90 (20·0%)	14/86 (16·3%)	6/87 (6·9%)
% difference vs. placebo (95% CI)	13·2 (3·5, 22·9)	9·4 (0·0, 18·8)	
Unadjusted p value[b]	0.011	0.055	

See Table 2 for statistical methods.

[a] The FAS included all randomised and treated patients.

[b] Unadjusted (nominal) p values are not controlled for multiplicity and should be interpreted only as supportive.

[c] Comparison vs. placebo employed Fisher's exact test due to not meeting the Mantel Fleiss criterion for Cochran-Mantel-Haenszel testing,

ACR20/50/70 – American College of Rheumatology 20/50/70% improvement, CI – confidence interval, FAS – full analysis set, n/a – not applicable, q4w/q8w – every 4/8 weeks, TNFi – tumor necrosis factor inhibitor

Table 4. Summary of DISCOVER-1 safety results through Week 24 (SAS)

	Guselkumab 100 mg			Placebo
	q4w	q8w	Combined	
Number of patients	128	127	255	126
Mean length of follow up (weeks)	23·9	23·9	23·9	23·7
Mean number of administrations	5·9	5·9	5·9	5·8
Patients with 1 or more AE, n (%)	71 (55·5%)	68 (53·5%)	139 (54·5%)	75 (59·5%)
AEs occurring in ≥5% of patients in any group (in alphabetical order)				
Alanine aminotransferase increased	5 (3·9%)	8 (6·3%)	13 (5·1%)	3 (2·4%)
Aspartate aminotransferase increased	3 (2·3%)	9 (7·1%)	12 (4·7%)	3 (2·4%)
Nasopharyngitis	7 (5·5%)	16 (12·6%)	23 (9·0%)	8 (6·3%)
Upper respiratory tract infection	11 (8·6%)	7 (5·5%)	18 (7·1%)	8 (6·3%)
Patient death	0	0	0	1 (0·8%)
Patients with 1 or more SAE, n (%)	0	4 (3.1%)[a]	4 (1·6%)	5 (4.0%)[b]
Patients with AE resulting in study drug d/c, n (%)	1 (0·8%)[c]	3 (2·4%)[d]	4 (1·6%)	3 (2·4%)[e]
Patients with MACE	0	0	0	1 (0·8%)
Patients with malignancy	0	1 (0·8%)	1 (0·4%)	0
Patients with infections[f], n (%)	31 (24·2%)	33 (26·0%)	64 (25·1%)	32 (25·4%)
Serious infections	0	0	0	2 (1·6%)
Patients with injection-site reactions, n (%)	1 (0·8%)	2 (1·6%)	3 (1·2%)	0
Patients with suicidal ideation, n (%)	0	1 (0·8%)	1 (0·4%)	1 (0·8%)

[a] 1 patient each with cervical dysplasia, ileus, plasma cell myeloma, supraventricular arrhythmia

[b] 1 patient each with cardiac failure, chronic obstructive pulmonary disease, limb abscess, pain, upper respiratory tract infection

[c] 1 patient with dyspepsia, gastritis, and hiatus hernia.

[d] 1 patient each with bronchitis, plasma cell myeloma, and worsened psoriatic arthropathy

[e] 1 patient with cardiac failure and 2 patients with worsened psoriasis

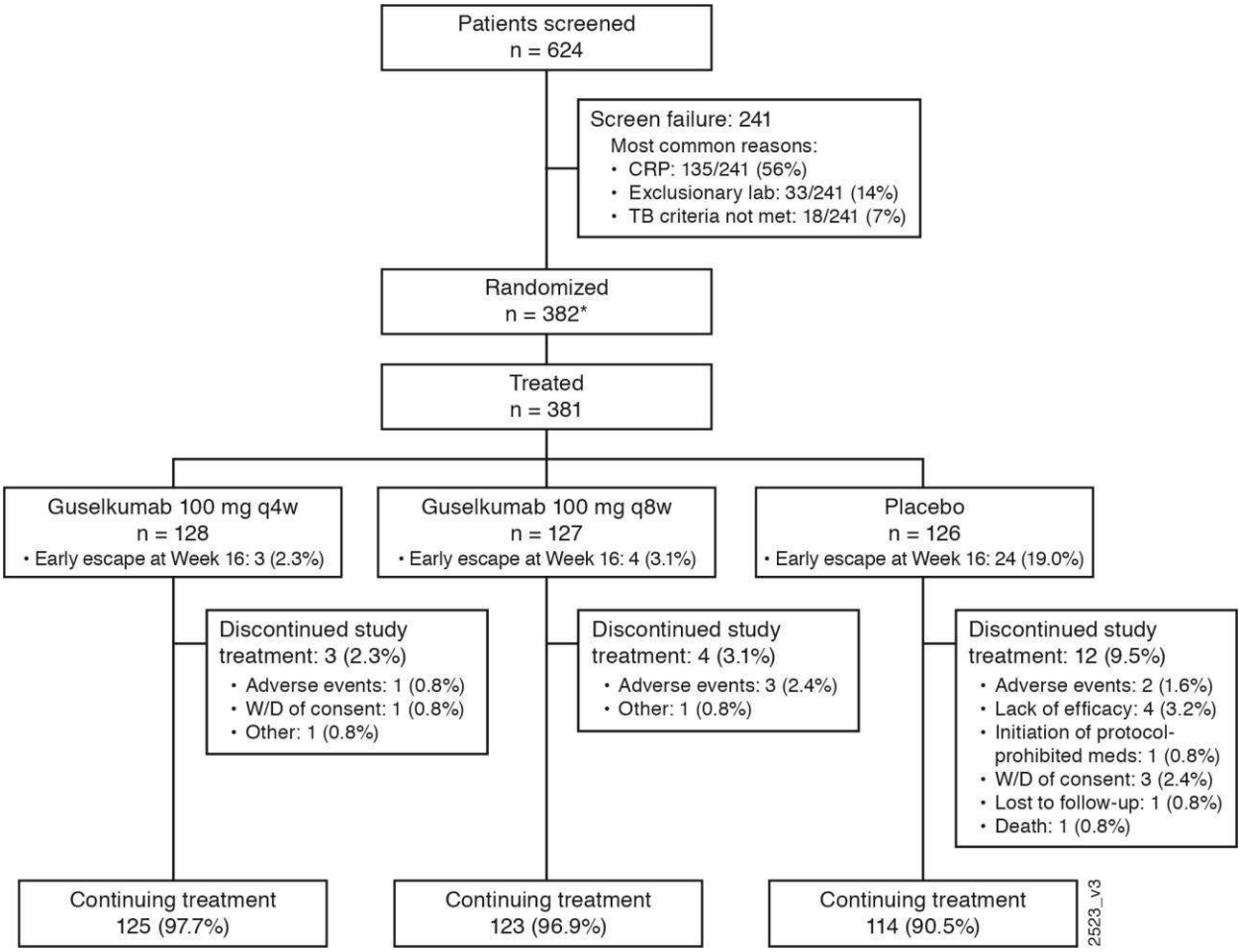
[f] AEs identified by investigators as infections.

Table 4. Summary of DISCOVER-1 safety results through Week 24 (SAS)

	Guselkumab 100 mg			Placebo
	q4w	q8w	Combined	

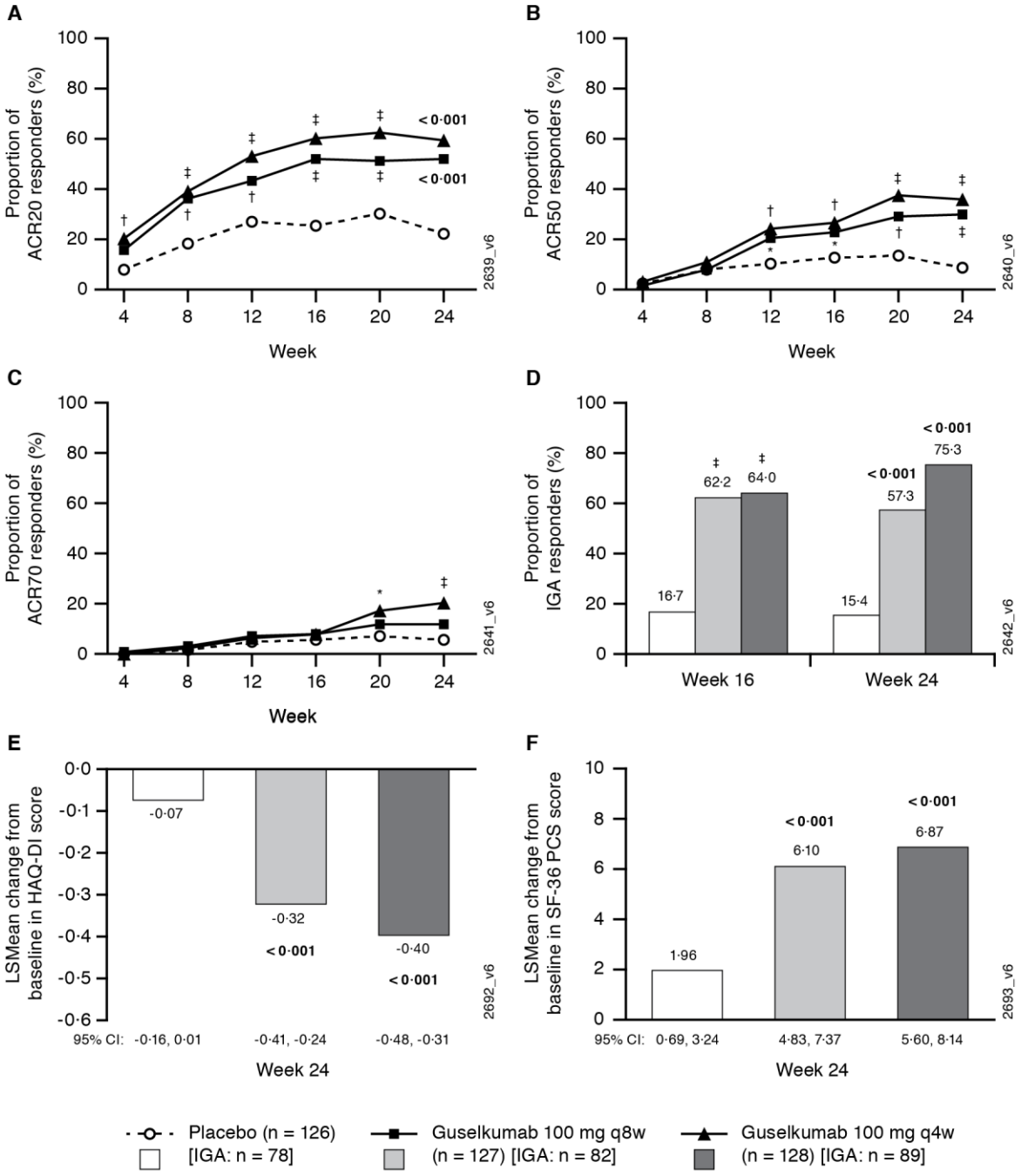
AE – adverse event, d/c – discontinuation, MACE – major adverse cardiovascular event, q4w/q8w – every 4/8 weeks, SAE – serious adverse event, SAS – safety analysis set (treated patients)

Figure 1.



* One patient was accidentally randomized before completion of the screening assessments. Subsequently, this patient screening failed and was later re-screened and randomized using a new patient number. Therefore, this patient was counted twice in the number of patients screened, but only once in the number of patients randomized. All data collected under the patient's initial patient number were excluded from subsequent analyses.

Figure 2.



unadjusted *p<0·05, †p<0·01, and ‡p<0·001
bolded p values are adjusted

Figure 1

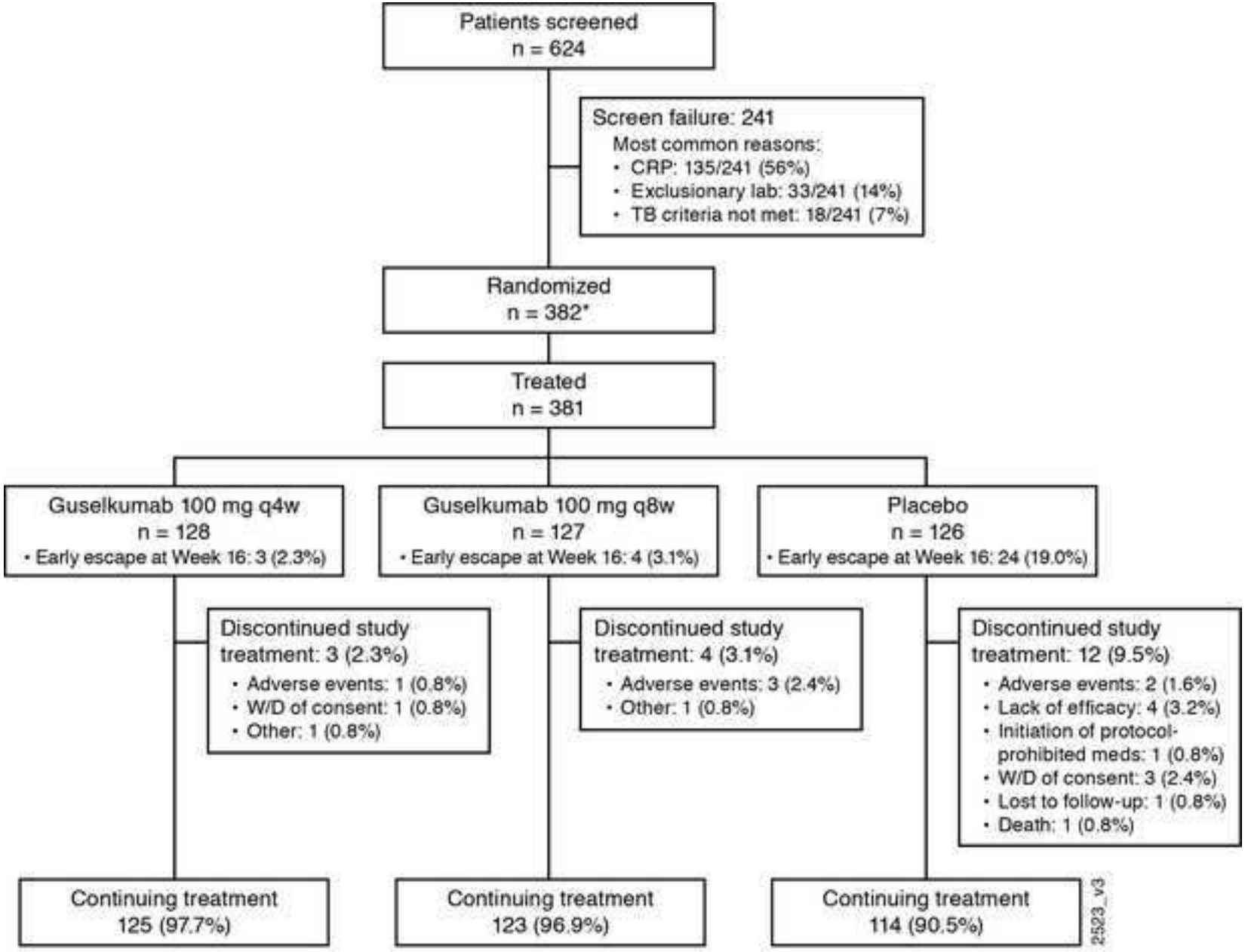


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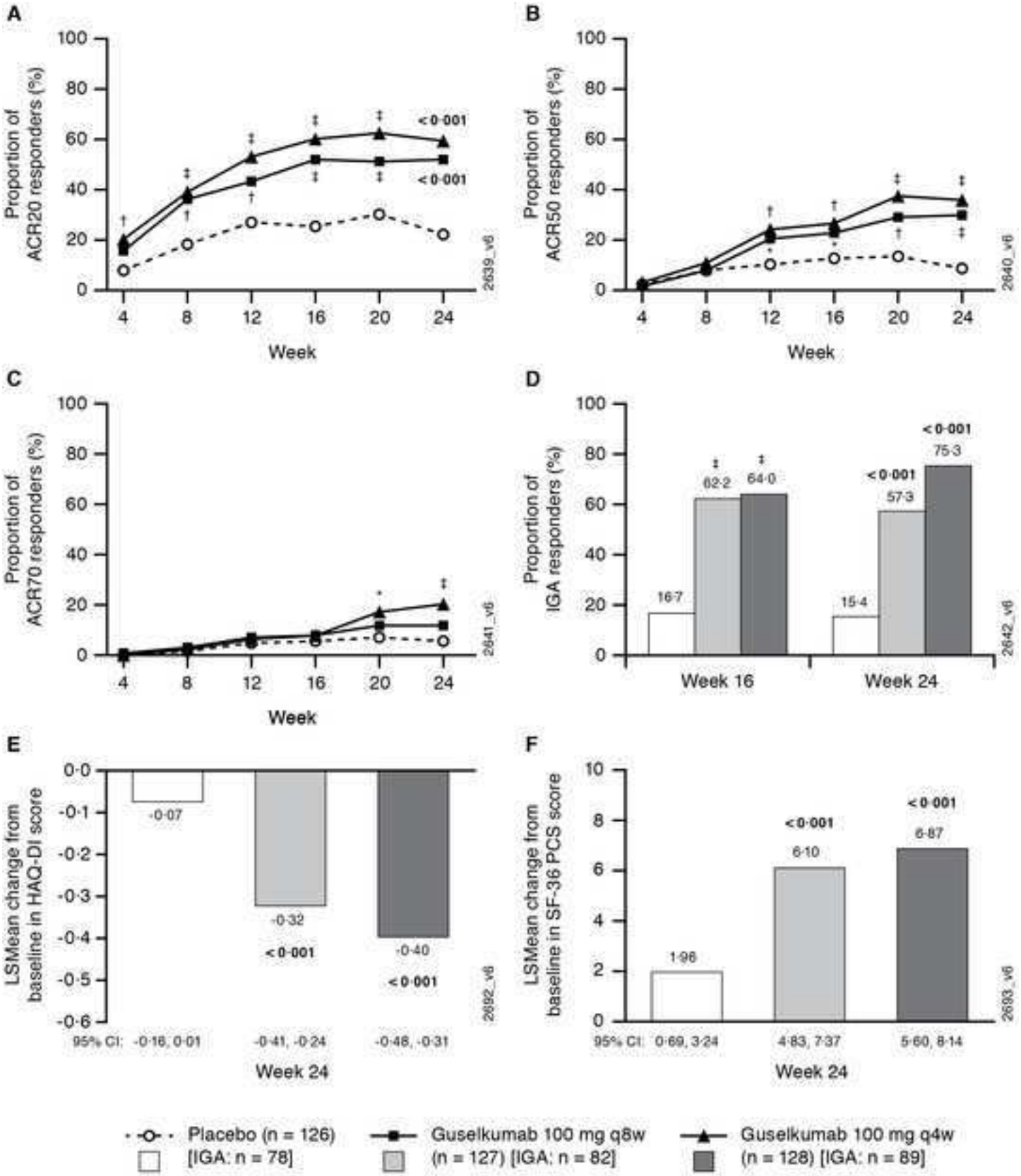
Figure 2



unadjusted *p<0·05, †p<0·01, and ‡p<0·001
bolded p values are adjusted

Figure S1