Guselkumab, an Interleukin-23-Inhibitor That Specifically Binds the IL-23p19-Subunit,~~an Anti-interleukin-23p19-subunit Monoclonal Antibody~~, in Biologic-naïve Patients with Active Psoriatic Arthritis

Week 24 Clinical and Radiographic Results of a Phase 3, Randomized, Double-blind, Placebo-controlled Study

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Summary (~~298~~282/300 words)

Background: The interleukin-23/Th17 pathway is implicated in psoriatic arthritis pathogenesis. Guselkumab, ~~a~~ an interleukin-23-inhibitor that specifically binds the IL23p19-subunit, ~~human anti-interleukin-23p19-subunit monoclonal antibody~~, significantly and safely improved psoriatic arthritis in a Phase-2 study.

Methods: This Phase-3, double-blind, placebo-controlled study (118 sites in 13 countries) enrolled biologic-naïve patients with active psoriatic arthritis (≥5 swollen, ≥5 tender joints, C-reactive-protein ≥0·6mg/dL) despite standard therapies. Patients were randomised (1:1:1; computer-generated permuted blocks; stratified by baseline disease-modifying antirheumatic drug use and C-reactive-protein) to subcutaneous guselkumab 100mg every-4-weeks (q4w); guselkumab 100mg at Weeks 0, 4, every-8-weeks (q8w); or placebo. The primary endpoint was ACR20 response at Week24 among randomized and treated patients. Clinicaltrials.gov identifier-NCT03158285 (active-not recruiting).

Findings: From 07/13/2017–03/06/2019, 739 randomised patients received guselkumab q4w (N=245), q8w (N=248), or placebo (N=246); 716 patients continued treatment through Week24. Significantly greater proportions of guselkumab q4w- (156 [6~~3·74~~%] of 245; 95% confidence interval: 57%, 70%) and q8w- (159 [64~~·1~~%] of 248; 95% confidence interval: 58%, 70%) than placebo- (81 [3~~2·93~~%] of 246; 95% confidence interval: 27%, 39%) treated patients achieved Week24 ACR20 response (% differences [95% confidence intervals]: 3~~0·81~~ (22~~·4~~, 39~~·1~~) and 31~~·2~~ (2~~2·93~~, ~~39·5~~40), respectively; both p<0·00~~0~~1). ~~Both guselkumab regimens significantly improved psoriasis, enthesitis, dactylitis, physical function, and quality-of-life vs. placebo at Week24. Mean changes in total modified van der Heijde-Sharp scores at Week24 were~~

~~significantly (0·29) and numerically (0·52) lower with guselkumab q4w and q8w, respectively, than placebo (0·95; p=0.011 and p=0.07).~~ Through Week24, serious adverse events, and specifically serious infections, occurred in eight (3~~·3~~%) and three (1~~·2~~%) of 245 patients receiving guselkumab q4w, three (1~~·2~~%) and one (~~0·4~~<1%) of 248 receiving guselkumab q8w, and seven (~~2·8~~3%) and one (~~0·4~~<1%) of 246 receiving placebo, respectively. No deaths occurred.

Interpretation: Guselkumab, a human ~~anti-interleukin-23p19-subunit~~ monoclonal antibody that specifically inhibits interleukin-23 by binding the cytokine's p19-subunit, was efficacious and well tolerated in patients with active psoriatic arthritis who were biologic naive. These data support the further development of guselkumab for treating psoriatic arthritis.

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Panel - Research in context

Evidence before this study – Current literature indicates that interleukin-23 is instrumental in driving the chronic inflammation associated with several immune-mediated diseases, including psoriasis and psoriatic arthritis. Guselkumab is a high-affinity, anti-interleukin-23~~p19-subunit specific~~ human monoclonal antibody that specifically bind's the cytokine's p19-subunit and is approved to treat moderate-to-severe psoriasis. In a Phase-2 study, selective blockade of interleukin-23 by guselkumab significantly improved signs and symptoms of active psoriatic arthritis and was well tolerated during 1 year of exposure.

Added value of this study – Results of this pivotal study, the larger of two comprising the first Phase-3 program investigating a novel mechanism of action to treat psoriatic arthritis, confirm that targeting the p19-subunit of interleukin-23 effectively treats the diverse domain manifestations of psoriatic arthritis. Specifically, in patients with active disease despite non-biologic disease-modifying antirheumatic, apremilast, and/or nonsteroidal anti-inflammatory drug treatment, but no prior exposure to biologics, subcutaneous guselkumab 100 mg significantly improved joint symptoms, dactylitis, enthesitis, psoriasis, physical function, and quality of life when administered every 4 or 8 weeks. Progression of structural damage through Week24 was significantly lower with guselkumab q4w, and numerically lower with q8w, dosing vs. placebo, providing initial evidence of inhibition of radiographic progression by an interleukin-23 inhibitor that target its p19-subunit ~~inhibitor~~. The guselkumab safety profile in psoriatic arthritis patients was comparable to profiles observed in placebo-treated psoriatic arthritis patients and guselkumab-treated patients with psoriasis.

Implications of all the available evidence – Consistent with previous findings of a proof-of-concept study confirming that interleukin-23 plays a critical role in the pathogenesis of psoriatic arthritis, these Phase-3 trial data provide pivotal evidence that guselkumab offers a novel mechanism of action to treat the diverse clinical manifestations of psoriatic arthritis and inhibit structural damage progression.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with peripheral joint inflammation, enthesitis, dactylitis, axial disease, and cutaneous and nail involvement, all of which can significantly limit physical function and impair quality of life. While the introduction of biologic (e.g., tumor necrosis factor-α inhibitors [TNFi], ustekinumab, interleukin [IL]-17A inhibitors, abatacept) and oral (e.g., apremilast, tofacitinib) agents has increased the extent and duration of achievable clinical responses, ~~there remains a need for~~ new therapies are needed ~~that can~~to treat the diverse manifestations of PsA while maintaining a favorable risk-benefit profile.[1]

The origins of the varying clinical manifestations of PsA remain under study. The IL-23/T-helper cell 17 (Th17) pathway – via downstream IL-17 expression - appears critical to skin manifestations. IL-23 can also induce IL-22, a cytokine implicated in enthesitis and bone formation,[2] and, in part via IL-17A and TNF induction, elicit the joint symptoms and damage that are hallmarks of PsA. IL-23 is a heterodimer formed by pairing ~~of the~~ p19-~~subunit with a~~ and p40-subunits, the latter of which is shared with IL-12. Although IL-12 and IL-23 share the p40-subunit, they also encompass unique p35- (for IL-12) and p19- (for IL-23) subunits.[3,4] Whereas IL-23 has been determined to be a predominant promoter of autoimmune-mediated articular inflammation, IL-12 more likely facilitates protection from autoimmune inflammation and T-cell exhaustion.[4-7] The divergent roles of these closely related cytokines are highlighted by differential skin effects, whereby abnormal differentiation of keratinocytes is triggered by IL-23, but not IL-12,[6] and differing roles in the body's response to bacterial and viral infections, as well as tumour control via their regulation of T-cell function.[5] Targeting the p19-subunit of IL-23, and thus sparing IL-12, has demonstrated robust efficacy in psoriasis,[~~3~~7-~~6~~-10] suggesting a prominent

upstream position in the inflammatory hierarchy across the psoriatic disease spectrum, which thereby merits evaluation of selective IL-23~~p19 subunit~~ inhibition via IL23-p19 binding in PsA.

Guselkumab (Janssen Biotech, Inc., Horsham, PA, USA), a high-affinity, human monoclonal antibody that binds specifically to the p19-subunit of IL-23, is approved to treat patients with moderate-to-severe psoriasis who are candidates for systemic and/or phototherapy. In a randomised, placebo-controlled, Phase-2 study evaluating ~~the efficacy and safety of~~ subcutaneous guselkumab 100 mg at Weeks 0, 4 and every 8 weeks (q8w) in 149 patients with active PsA, including ≥3% body surface area (BSA) of psoriasis, guselkumab demonstrated efficacy across all endpoints related to joint signs and symptoms, physical function, skin disease, enthesitis, dactylitis, and health-related quality of life.[~~7~~11]

Herein, we report 24-week results from one of two Phase-3 trials, i.e., DISCOVER-2, conducted to evaluate guselkumab in ~~the treatment of~~ biologic-naïve patients with active PsA. DISCOVER-2 evaluations included joint and skin manifestations, as well as structural damage. Results from the other registrational trial of guselkumab in PsA (DISCOVER-1), which aimed to enroll patients with a broader range of baseline levels of disease activity, some of whom were previously treated with one or two TNFi, are reported elsewhere (Lancet.org doi.xxxx).

METHODS

Study design

This Phase-3, randomised, double-blind, placebo-controlled, multicenter, 3-arm study of guselkumab in patients with active PsA, who were biologic-naïve and demonstrated inadequate response to standard therapies (non-biologic disease-modifying antirheumatic drugs [DMARDs], apremilast, and/or nonsteroidal anti-inflammatory drugs [NSAIDs]), was conducted at 118 sites ~~in 13 countries~~ worldwide (see Online Supplement)~~Bulgaria, Czech Republic, Estonia, Latvia, Lithuania, Malaysia, Poland, Russia, Spain, Taiwan, Turkey, Ukraine, USA)~~. Screening began ~~on~~ 07/13/2017~~, and~~; the final Week-24 visit occurred on 02/25/2019. The trial design includes a 6-week screening period; a 100-week treatment phase, with a placebo-controlled period from Week0–Week24 and an active treatment period from Week24–Week100; and 12-weeks of safety follow-up after the last administration of study agent. 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 ≤3g/day, hydroxychloroquine ≤400 mg/day, or leflunomide ≤20 mg/day). Study results through Week24 are reported. This trial (NCT03158285) is being conducted per Declaration of Helsinki and Good Clinical Practice guidelines. The protocol (available at Lancet.org) was approved by each site's governing ethical body.

Participants

Approximately 684 eligible patients were planned for this study. Adults with PsA for ≥6 months, fulfilling the Classification Criteria for Psoriatic Arthritis ~~(CASPAR)~~[8-12] and with ≥5 tender and ≥5 swollen joints; C-reactive protein (CRP) ≥0·6 mg/dL; current or documented history of psoriasis; and either inadequate response to, or intolerance of, standard non-biologic treatment were eligible. Standard treatment included ≥3 months of non-biologic DMARDs, ≥4 months of apremilast at the approved dose (if discontinued >4 weeks before receiving study agent), or ≥4 weeks of NSAIDs for PsA. Previous exposure to biologic agents or Janus kinase inhibitors precluded ~~study entry~~participation. Patients were permitted, but not required, to continue stable ~~baseline~~ use of ~~stable doses of~~ selected non-biologic DMARDs (limited to those allowed for early escape ~~as detailed above~~), and NSAIDs/other analgesics. Only one DMARD was permitted through Week52. Patients also had to meet screening criteria for ~~screening~~ laboratory ~~test results~~evaluations 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 (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 the most recent high-sensitivity serum CRP value prior to randomization [<2·0/≥2·0 mg/dL]) in a 1:1:1 ratio to receive guselkumab 100 mg every 4 weeks (q4w); guselkumab 100 mg at Week0, Week4, and every 8 weeks (q8w); or placebo. ~~Patients,~~

~~investigators, and study site staff were blinded to treatment assignment. Placebo and guselkumab were provided in identical prefilled syringes with non-identifying labels. Patients in each treatment group received the same number of injections at the same time points~~Blinding was accomplished as reported for DISCOVER-1 (Lancet.org doi.xxxx).

Procedures

Guselkumab was administered as a 100-mg subcutaneous injection at Week0, Week4, and then q4w or q8w. Dose selection for DISCOVER-2 was as described for DISCOVER-1 (Lancet.org doi.xxxx). Clinical efficacy and safety assessments were performed at screening, baseline, Week2, Week4, and q4w through Week24. An independent joint assessor evaluated 66 joints for swelling, 68 joints for tenderness, and determined the presence/severity of enthesitis (Leeds Enthesitis Index [LEI]) and dactylitis. Dactylitis severity for each ~~finger and toe~~digit was scored ~~on a scale of 0–3 (~~as 0–no dactylitis, 1–mild dactylitis, 2–moderate dactylitis, or 3–severe dactylitis~~; (~~total score 0–60). Serum pharmacokinetic and immunogenicity assessments are as reported for DISCOVER-1 (Lancet.org doi.xxxx). As well, details of joint (American College of Rheumatology [ACR] response, 28-joint Disease Activity Score incorporating CRP [DAS28-CRP]), skin (Investigator's Global Assessment of psoriasis [IGA], Psoriasis Area and Severity Index [PASI]), physical function (Health Assessment Questionnaire-Disability Index [HAQ-DI]), health-related quality of life (36-item Short-Form [SF-36] Health Survey), and safety (adverse events [AEs], routine haematology and chemistry assessment, electronic Columbia-Suicide Severity Rating Scale [eC-SSRS] questionnaires) assessments are as reported for DISCOVER-1 (Lancet.org doi.xxxx).

In DISCOVER-2, single radiographs of the hands (posteroanterior) and feet (anteroposterior) were obtained at screening and Week24. ~~The r~~Radiographs were evaluated independently by two central readers (~~, who were~~ blinded to ~~the~~ order of ~~the~~ radiographs and clinical data), with the van der Heijde-Sharp (vdH-S) score modified for PsA (~~, i.e., with the addition of~~ distal interphalangeal joints of ~~the~~ hands added).[9-13] Adjudication was employed as mandated by primary reader disagreement. The total PsA-modified vdH-S score (0–528) sums the joint erosion score (0–320; 0–no erosions, 5–extensive loss of bone from >50% of the articulating bone) and the joint space narrowing (JSN) score (0–208; 0–no JSN, 4–complete loss of joint space, bony ankylosis, or complete luxation). The average score of the two readers was ~~used~~ employed in ~~the~~ analyses.

Outcomes

The primary endpoint was the ~~proportion of patients achieving~~ ACR20 response rate at Week24. Major secondary endpoints included ACR50 and ACR70 responses, changes from baseline in ~~the~~ DAS28-CRP scores, 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, changes from baseline in HAQ-DI and PsA-modified vdH-S scores, changes from baseline in, and resolution of, enthesitis and dactylitis pooled across ~~both~~ DISCOVER-1&2 ~~trials~~ (~~see~~ *Statistical analyses*), changes in the SF-36 physical/mental component summary (PCS/MCS) ~~and mental component summary (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 scores in patients with baseline HAQ-DI scores ≥0·35, ≥75/90/100% improvement in the PASI (PASI75/PASI90/PASI100) in patients with mild-to-severe psoriasis at baseline, and minimal disease activity (MDA; see Lancet.org doi.xxxx), all at Week24. Safety

outcomes were as reported for DISCOVER-1 (Lancet.org doi.xxxx). ~~included AEs, serious AEs (SAEs), AEs resulting in discontinuation of study drug, infections, injection-site reactions, malignancies, major adverse cardiovascular events (MACE; i.e., cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), 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.~~

Statistical analyses

Assuming Week24 ACR20 response rates of 45% with guselkumab versus 25% with placebo, 684 patients (228/treatment group) were required to provide ~99% statistical power (α=0·05; 2-sided). With 684 patients, the study was estimated to have 90% power to detect a treatment difference in change from baseline in total PsA-modified vdH-S scores, assuming mean changes from baseline at Week24 of 0·9 and 0·3, respectively, in placebo- and across all guselkumab-treated patients~~with placebo and guselkumab~~ and a standard deviation of 2·5 for each treatment. Strategies employed to control the overall Type 1 error rate are described below.

Efficacy analyses through Week24 included all randomised patients who received ≥1 administration of study treatment and were conducted according to assigned treatment groups (full analysis set). Treatment differences for binary endpoints were assessed via a Cochran-Mantel-Haenszel test; those for continuous endpoints employed an analysis of covariance model.

To increase sample size, endpoints related to enthesitis and dactylitis among the smaller number of patients with those conditions at baseline were prespecified to be tested by pooling data from this study with those from DISCOVER-1 (Lancet.org doi.xxxx). Results of these pooled analyses are presented herein.

Owing to differences in health authority requirements for multiplicity control between the United States (US) and other countries, two graphical testing procedures were prespecified to control overall Type I error at α=0·05 (2-sided). For both approaches, the primary endpoint (ACR20 response at Week24) was first tested for the q4w group and then for the q8w group (each at 0·05 level). The first graphical procedure (Figure S1A) controlled the overall Type 1 error rate across both dosing regimens at the 0·05 level for the primary and the following major secondary endpoints at Week24: IGA skin response among patients with mild-to-severe psoriasis; changes in HAQ-DI, PsA-modified vdH-S, and SF-36 PCS scores; resolution of dactylitis and enthesitis among patients with the respective condition at baseline pooled across both DISCOVER trials, and changes in SF-36 MCS scores. Results of this testing procedure are presented in the main manuscript text and those from the second graphical procedure (Figure S1B), which controlled the overall Type 1 error rate for each dosing regimen at the 0·05 level for all major secondary endpoints, except changes from baseline in enthesitis and dactylitis scores at Week24, with two parallel procedures, are provided online (Table S1). For endpoints not controlled for multiplicity, unadjusted (nominal) p values provided should be interpreted only as supportive.

Data handling rules were applied to all clinical efficacy analyses. Patients who met treatment-failure criteria (discontinued study agent, terminated study participation, initiated or increased DMARD or oral corticosteroid doses, initiated protocol-prohibited PsA treatment) 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 and using multiple imputation for continuous endpoints. For radiographic endpoints, treatment failure rules were not applied, and missing data (five in guselkumab q4w group, one in guselkumab q8w group, one in placebo group) were imputed using multiple imputation.

An independent data monitoring committee examined data on an ongoing basis through the Week24 database lock to ensure the safety of the study participants. 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 (NCT03158285).

Role of the funding source

Janssen Research and Development, LLC funded this trial. All authors, including employees of Janssen (APK, ECH, XLX, SS, PA, BZ, YZ), were involved in data collection, analysis, and/or interpretation; trial design; manuscript preparation; and the decision to submit the paper for publication. Janssen provided funding to a professional medical writer who assisted with manuscript preparation and submission. The corresponding author (PJM) had full access to all study data and final responsibility to submit for publication.

RESULTS

From 1,153 screened patients, 741 were randomised. Patients failed screening most often for serum CRP levels <0·6 mg/dL. Overall, 739 randomised patients were treated with guselkumab q4w (N=245), guselkumab q8w (N=248), or placebo (N=246) and included in the full analysis set. At Week16, 12 (4·95%) of 245 guselkumab q4w-, 13 (5·2%) of 248 guselkumab q8w-, and 38 (15·4%) of 246 placebo-treated patients had <5% improvement in both tender and swollen joint counts and qualified for early escape, of which seven (2·93%) of 245 guselkumab q4w-, six (2·4%) of 248 guselkumab q8w-, and 14 (5·76%) of 246 placebo-treated patients initiated or increased the dose of NSAIDs, oral corticosteroids, and/or permitted non-biologic DMARDs. Overall, 23 (3·1%) of 739 treated patients discontinued study agent, most commonly due to AEs, resulting in robust patient retention through Week24 (Figure 1).

Baseline characteristics were generally well balanced across randomised groups. Modest numerical differences were observed between the guselkumab and placebo groups for the proportions of males, severity of psoriasis assessed by the PASI score, and presence of dactylitis and enthesitis at study outset. Background medication use was consistent across randomised treatment groups; among the 739 treated patients, 512 (69·3%) were receiving non-biologic DMARDs, including 443 (59·960%) receiving MTX, 145 (19·620%) were receiving oral corticosteroids for PsA, and 504 (68·2%) reported NSAID use at baseline (Table 1).

Major protocol deviations were evenly distributed between guselkumab- (35 [7%] of 493) and placebo- (23 [9%] of 246) treated patients. Overall, 11 patients (five guselkumab, six placebo) entered the study without satisfying all criteria, six (four guselkumab, two placebo) received the incorrect treatment/dose), six received a disallowed medication (three guselkumab, three

placebo), and one (guselkumab) met a withdrawal criterion but was not withdrawn. No deviation was considered to impact overall results.

For the study's primary endpoint, significantly greater proportions of patients in the guselkumab q4w (156 [63·74%] of 245; 95% confidence interval [CI]: 57%, 70%) and q8w (159 [64·1%] of 248; 95% CI: 58%, 70%) groups than in the placebo group (81 [32·93%] of 246; 95% CI: 27%, 39%) groups achieved an ACR20 response at Week24 (% differences [95% confidence interval (CIs): 30·81 [22·4, 39·1] and 31·2 [22·93, 39·540], respectively; both p<0·00001; Table 2). Results of all prespecified sensitivity analyses were consistent with the primary analysis (data on file).

A consistent treatment benefit was observed for the primary efficacy endpoint for both guselkumab dosing regimens across patient subgroups defined by demography, baseline disease characteristics, and prior and baseline medication use. In particular, ACR20 response at Week24 was consistent in the subgroup of patients with MTX use at baseline (q4w: 92 [63%] of 146 and q8w: 85 [60%] of 141),

With both guselkumab dosing regimens, more patients achieved ACR20 response vs. placebo by Week4 (following one injection of guselkumab); response rates continued to increase through Week24 (Figure 2A). ACR50 and ACR70 response rates were also consistently higher with both guselkumab dosing regimens vs. placebo (Figures 2B, 2C). Higher rates of ACR20 response at Week16, ACR50 response at Week16 and Week24, and ACR70 response at Week24 were observed among guselkumab q4w- and q8w-treated than placebo-treated patients. Further, greater improvements in DAS28-CRP scores at Week24 were observed with guselkumab q4w (LS mean change: -1·62) and q8w (-1·59) vs. placebo (-0·97; Table 2).

Among DISCOVER-1 (Lancet.org doi.xxxx) and DISCOVER-2 patients with the respective manifestations at baseline, dactylitis resolved at Week24 in significantly higher proportions of guselkumab q4w- (101 [63·54%] of 159) and q8w- (95 [59·4%] of 160) than placebo- (65 [42·2%] of 154) treated patients (p=0·0110 and p=0·0301, respectively). Resolution of enthesitis was also observed in significantly higher proportions of guselkumab q4w- (109 [44·95%] of 243) and q8w- (114 [49·650%] of 230) than placebo- (75 [29·4%] of 255) treated patients (both p=0·0301) when combined across both trials. Improvements from baseline in the enthesitis LEI and dactylitis scores at Week24 were also numerically greater with both guselkumab dosing regimens than placebo when pooled across DISCOVER-1 and DISCOVER-2 (Table 3), and consistent trends were observed in the individual trials (Table 3S2).

Patients treated with guselkumab q4w demonstrated significantly less progression of structural damage, as reflected by smaller changes from baseline in the PsA-modified vdH-S score at Week24, than placebo-treated patients (LS mean [95% CI]: 0·29 [-0·05, 0·63] vs. 0·95 [0·61, 1·29], respectively; p=0·0110). Guselkumab administered q8w resulted in numerically less radiographic progression (LS mean [95% CI]: 0·52 [0·18, 0·86]) than placebo, but the treatment difference did not achieve statistical significance (p=0·07; Table 2). A probability plot of changes in modified vdH-S scores from baseline at Week24 is provided in Figure S2.

In patients with mild-to-severe psoriasis at baseline, guselkumab q4w and q8w significantly improved skin disease, as assessed by IGA response rates, at Week24 vs. placebo (126 [68·5%] of 184 and 124 [70·5%] of 176, respectively vs. 35 [19·1%] of 183; both p<0·0001; Table 2, Figure 2D). PASI75, PASI90, and PASI100 response rates were also higher among guselkumab- than placebo-treated patients (Table 2).

Guselkumab q4w and q8w significantly improved HAQ-DI scores from baseline at Week24 vs. placebo (LSmean [95% CI] changes: -0·40 [-0·46, -0·34] and -0·37 [-0·43, -0·31], respectively, vs. -0·13 [-0·19, -0·07]; both p<0·0001). The proportions of patients with improvement in the HAQ-DI score ≥0·35 at Week24, among those with baseline HAQ-DI ≥0·35, also indicated that guselkumab q4w (128 [56·1%] of 228) and q8w (114 [50·0%] of 228) improved physical function to a greater extent than placebo (74 [31·4%] of 236; Table 2).

Patients started the study with impaired health-related quality-of-life as assessed by mean SF-36 PCS (32·4–33·3) and MCS (47·2–48·4) scores (US general population norm=50.0). Significant improvements in SF-36 PCS scores from baseline at Week24 were demonstrated by guselkumab q4w and q8w, respectively, vs. placebo (LSmean changes: 7·04 and 7·39 vs. 3·42; both p=0·0110). Numerical improvements in SF-36 MCS scores (4·22 and 4·17 vs. 2·14; both p=0·07) were also observed for both guselkumab dosing regimens vs. placebo; although the lower bounds of the 95% CIs of the differences from placebo exceeded 0, differences were not significant after multiplicity adjustment (Table 2). At Week24, MDA was achieved by 46 (18·89%) of 245 and 62 (25·0%) of 248 patients receiving guselkumab q4w and q8w, respectively, vs. 15 (6·1%) of 246 placebo-treated patients (Table 2).

An overview of guselkumab pharmacokinetic and immunogenicity findings can be found in the Online Supplement.~~Four hundred ninety-two patients who had serum samples collected following subcutaneous administration of guselkumab were evaluable for pharmacokinetic analysis. The median steady-state trough serum guselkumab concentration was 3·35 µg/mL at Week12, which was maintained through Week24 (3·98 µg/mL) with guselkumab 100 mg q4w~~

~~dosing. The median steady-state trough serum guselkumab concentration was 1·05 μg/mL when guselkumab 100 mg was given at Week0, Week4, and then q8w.~~

~~Antibodies to guselkumab were detected in 10 (2·0%) of 490 guselkumab-treated patients with evaluable samples through Week24. None of these patients tested positive for neutralizing antibodies to guselkumab. Additional findings related to anti-drug antibodies are reported in the Online Supplement.~~

Guselkumab was generally well-tolerated. Through Week24, AEs were reported by 113 (46~~·1~~%) of 245, 114 (46~~·0~~%) of 248, and 100 (4~~0·7~~1%) of 246 patients receiving guselkumab q4w, guselkumab q8w, and placebo, respectively. Serious AEs (SAEs) were reported by eight (3~~·3~~%) of 245, three (1~~·2~~%) of 248, and seven (~~2·8~~3%) of 246 patients, and AEs led to discontinuation of study agent for six (2~~·4~~%) of 245, two (~~0·8~~1%) of 248, and four (~~1·6~~2%) of 246 patients receiving guselkumab q4w, guselkumab q8w, and placebo, respectively (Table 4).

The AEs reported by ≥3% of patients in any treatment group were infections (upper respiratory tract infection, nasopharyngitis, bronchitis) and laboratory investigations (alanine aminotransferase [ALT] increased, aspartate aminotransferase [AST] increased; Table 4). Serious infections occurred in three (1~~·2~~%) of 245 patients receiving guselkumab q4w (acute hepatitis B [*de novo*], influenza pneumonia, oophoritis), one (<1~~0·4~~%) of 248 patients receiving guselkumab q8w (pyrexia [likely of urinary origin]), and one (~~0·4~~<1%) of 246 placebo-treated patients (post-procedural fistula). No *Candida* or opportunistic infections, or cases of active TB, occurred through Week24. No AEs of inflammatory bowel disease were reported in guselkumab-treated patients, whereas there was one suspected case in the placebo group through Week24.

No deaths were reported through Week24. One patient in each of the guselkumab q4w (at Week2 only) and placebo (pre-existing and at Week12) groups experienced suicidal ideation (Level 1 – wish to be dead); no patient reported suicidal or self-injurious behavior without suicidal intent through Week24. Two patients were diagnosed with a malignancy through Week24 (guselkumab q8w: melanoma *in situ* at Week4; placebo: clear-cell renal cell carcinoma at Week12). One patient had a major acute cardiovascular event: a 58-year-old female with a history of hypertension, hyperlipidemia, and diabetes and who was receiving guselkumab 100 mg q4w had an ischaemic stroke at Week20. The patient recovered, and study drug was discontinued.

Two patients demonstrated maximum National Cancer Institute Common Terminology Criteria for AEs (~~CTCAE~~NCI-CTCAE) Grade-3 or 4 neutropenia, one in the placebo group (Grade-3 [<1·0–0·5 x 10^9/L] at Week 8 only) and one in the guselkumab q4w group (did not recur upon retest the following week, not associated with infections or study drug interruptions). No other NCI-CTCAE Grade-3 or higher hematology abnormalities were observed in guselkumab-treated patients, except a case of anemia in one guselkumab q8w-treated patient (Grade-3 hemoglobin [<80·0 g/L] of 69 g/L at Week16 only).

The proportions of patients with increased ALT or AST levels reported as AEs appeared slightly higher in the guselkumab than placebo groups (Table 4). The overall incidences of maximum NCI-CTCAE Grade-2 (>3.0–5.0 x upper limit of normal [ULN]) ALT and AST increases were low and slightly more common in guselkumab- (nine [~~1·8~~2%] and 11 [2~~·2~~%] of 490 patients, respectively) than placebo- (four [~~1·6~~2%] and none of 246 patients, respectively) treated patients. Maximum NCI-CTCAE Grade-3 (>5·0–20·0 x ULN) or Grade-4 (>20·0 x ULN) ALT values were observed in four (~~1·6~~2%) of 243 patients receiving guselkumab q4w (all Grade-3), three (1~~·2~~%) of 247 patients receiving guselkumab q8w (all Grade-3), and two (~~0·8~~1%) of 246

placebo-treated patients (one patient each with Grade-3 and Grade-4 values). For AST, maximum NCI-CTCAE Grade-3 (>5·0–20·0 x ULN) or Grade-4 (>20·0 x ULN) values were observed in five (2~~·1~~%) of 243 patients receiving guselkumab q4w (all Grade-3), one (~~0·4~~<1%) of 247 patients receiving guselkumab q8w (Grade-3), and two (~~0·81~~%) of 246 placebo-treated patients (all Grade-3). These laboratory abnormalities resulted in study drug discontinuation in one placebo-treated patient (Week8 ALT/AST of 1053/665 U/L related to serious isoniazid-induced hepatitis that resolved by Week12) and two patients receiving guselkumab q4w (one with Week4 ALT/AST of 479/484 U/L related to non-serious AE of isoniazid-induced hepatitis that resolved by Week16 and one with Week20 ALT/AST of 373/238 U/L related to an SAE of acute hepatitis B with no clinically significant increase in bilirubin; AEs were resolving at the last contact).

DISCUSSION

Results of the Phase-3, multicenter, randomised, double-blind, placebo-controlled, DISCOVER-2 study through Week24 indicate that guselkumab, a selective IL-23 inhibitor that binds the cytokine's p19-subunit, effected robust improvements in signs and symptoms of joint disease in patients with PsA. The study met its primary endpoint for both guselkumab 100 mg q4w and q8w, with 63~~-74~~% and 64~~-1~~% of these patients, respectively, achieving an ACR20 response at Week24, compared with 32~~-93~~% of placebo-treated patients. Similarly, ACR50 and ACR70 response rates demonstrated that treatment with guselkumab results in clinically meaningful reductions in the joint signs and symptoms of PsA. Improvement occurred at early timepoints and increased over time through Week24.

Guselkumab, whether administered q4w or q8w, also elicited significant improvements in skin psoriasis, physical function, and health-related quality of life, all of which significantly impact mental health, work productivity, and the economic burden of PsA.[13,14,15] Of particular note, >60% of guselkumab-treated patients achieved PASI90 and 45% achieved PASI100 responses at Week24. These findings are consistent with the established efficacy of guselkumab in treating moderate-to-severe plaque psoriasis.[~~3~~7,~~5~~9,~~6~~10] Guselkumab q4w inhibited progression of structural damage vs. placebo at Week24, based on changes in the PsA-modified vdH-S score. Guselkumab q8w dosing also reduced structural damage progression, but the difference from placebo was not statistically significant. This observation could derive from differences in total guselkumab exposure between q4w and q8w dosing from Weeks0-24. Radiographic data being collected through 1 year will provide additional data with which to evaluate the ability of the q8w dosing regimen to limit progression of structural damage.

Inflammation of periarticular tissues~~, i.e.,~~ such as dactylitis and enthesitis, is a hallmark of PsA that can present a treatment challenge.~~10~~ 16 IL-23 is essential for both activating Th17 cells, which produce IL-17A, and maintaining IL-17A production thereafter. ~~IL-17A has been implicated mechanistically in both inflammation and bone remodeling in a murine model of rheumatoid arthritis by stimulating osteoclastogenesis; promoting bone resorption in fetal mouse long bones; and inducing expression of the receptor activator of nuclear factor kappa-B ligand (RANKL), an osteoclast differentiation factor, in osteoclast-supporting cells.~~11 ~~In addition, IL-23 can induce IL-22, a cytokine implicated in enthesitis and bone formation.~~[2] IL-23 also regulates innate cells (e.g., γδ T, natural killer T, and innate lymphoid cell subsets), which are predominantly located in non-lymphoid tissue and, upon stimulation by IL-23, produce pro-inflammatory cytokines (IL-17, IL-22, and interferon-γ), thereby inducing local tissue inflammation.[17-20] Given that guselkumab 100 mg q8w has been shown to decrease serum IL-17A concentrations of PsA patients to levels observed in healthy controls by Week16,~~12~~ 21 it is not unexpected that both guselkumab ~~dosing~~ regimens afforded significantly higher proportions of patients with clinically resolved dactylitis and enthesitis at Week24 when data were pooled across ~~the~~ DISCOVER-1 and DISCOVER-2 ~~trials~~.

As a downstream effector cytokine of IL-23, IL-17A has been implicated mechanistically in both inflammation and bone remodeling in a murine rheumatoid arthritis model by stimulating osteoclastogenesis; promoting bone resorption in fetal mouse long bones; and inducing expression of the receptor activator of nuclear factor kappa-B-ligand, an osteoclast differentiation factor, in osteoclast-supporting cells.[22] IL-23 can also induce IL-22, a cytokine implicated in bone formation.[2] Because IL-23 regulates several effector cytokines that are thought to contribute to PsA disease pathology, inhibition of multiple effector cytokines through

IL-23 targeting may provide more effective modulation of these processes than single cytokine inhibition. ~~Selective IL-23p19 subunit inhibition with guselkumab q4w also inhibited progression of structural damage relative to placebo at Week24, as evidenced by changes from baseline in the PsA-modified vdH-S score. Guselkumab q8w dosing also reduced structural damage progression relative to placebo, but this difference did not achieve statistical significance. Radiographic data being collected through 1 year differences between the two guselkumab dosing regimens in their ability to limit progression of structural damage.~~

~~Guselkumab, whether administered q4w or q8w, also elicited significant improvements in skin psoriasis, physical function, and health-related quality of life, all of which significantly impact mental health, work productivity, and the economic burden of PsA.[13,14] Of particular note, >60% of guselkumab-treated patients achieved PASI90 and 45% achieved PASI100 responses at Week24. These findings are consistent with the established efficacy of guselkumab in treating moderate-to-severe plaque psoriasis.[3,5,6]~~

~~Both regimens of g~~Guselkumab 100 mg was~~were~~ generally well tolerated in this PsA population, with~~out any~~ no clinically meaningful differences ~~in safety~~ between q4w and q8w dosing through Week24. No *Candida* or opportunistic infections or cases of active TB occurred. One suspected case of inflammatory bowel disease was reported in a placebo-treated patient. There was no apparent association between the development of antibodies to guselkumab and the occurrence of injection-site reactions (see Online Supplement). The overall safety profile was generally consistent with that reported for patients with psoriasis.[~~3~~7,~~5~~9,~~15~~ 23] Specifically, guselkumab 100 mg q8w demonstrated a stable safety profile through 100 weeks of treatment, with no safety signals with regard to serious infection, malignancy, MACE, or suicidality, in an analysis of data from more than 1,800 patients enrolled in two Phase-3 psoriasis studies.[~~15~~ 23] Further, in ~~more~~

than >800 patients with psoriasis who participated in the VOYAGE-1 study, no new safety signals were observed through up to 4 years of guselkumab 100 mg when given q8w.[16][24]

IL-12 and IL-23 are proinflammatory cytokines known to facilitate autoimmunity and associated inflammation.[17] Although IL-12 and IL-23 share a common p40 subunit, they also encompass unique p35- (in the case of IL-12) and p19- (in the case of IL-23) subunits.[18,19] Whereas IL-23 has been determined to be a predominant promoter of autoimmune-mediated articular inflammation, IL-12 more likely facilitates protection from autoimmune inflammation and T-cell exhaustion.[17,19] The divergent roles of these closely related cytokines are highlighted by differential skin effects, whereby abnormal differentiation of keratinocytes is triggered by IL-23, but not IL-12,[20] and differing roles in the body's response to bacterial and viral infections, as well as tumour control via their regulation of T-cell function.[17] In DISCOVER-2, inhibition of IL-23 by selectively targeting its p19 subunit was well tolerated and demonstrated robust efficacy across clinical domains that have been identified as crucial to achieving PsA remission (e.g., synovitis, enthesitis, dactylitis, psoriasis).[21] As such, it appears that inhibiting the p19 subunit of IL-23, but not the p40 subunit it shares with IL-12, is a novel mechanism by which to safely and effectively treat the diverse manifestations of PsA.

The biologic-naïve patients enrolled into DISCOVER-2 patients presented with an average of 12–13 swollen and 20–22 tender joints, along with substantial systemic inflammation (median serum CRP: 1·2–1·3 mg/dL), possibly limiting the applicability of findings to patients with less active disease. The relatively high placebo response rates observed for joint (ACR20-33%) and skin (IGA-19%) outcomes may also affect data interpretation. However, these response rates are consistent with other recently reported findings in biologic-naïve PsA populations,[25,26] and likely reflect higher expectations for efficacy as more potent therapies have become available for PsA.

It will be important to evaluate whether the favourable responses and safety profile through Week24 are maintained; such data are being collected throughout this 2-year study.

Thus, guselkumab was well tolerated and demonstrated robust efficacy in DISCOVER-2 across clinical domains crucial to achieving PsA remission (e.g., synovitis, enthesitis, dactylitis, psoriasis), including reducing structural damage progression.[27] By binding to IL-23's p19-subunit, but not the p40-subunit it shares with IL-12, guselkumab targets the key upstream regulatory cytokine responsible for the Th17 pathway implicated in PsA, thereby providing a targeted yet comprehensive means of controlling the downstream inflammatory cascade and thus safely and effectively treating PsA's diverse manifestations.

~~In conclusion, these Phase 3 trial data provide pivotal evidence that the high-affinity, human, anti-IL-23p19-subunit monoclonal antibody guselkumab offers a novel mechanism of action to treat the diverse manifestations of active PsA, including reducing structural damage progression~~.

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Authors

Substantial intellectual contribution to conception and design, or acquisition of data, or analysis and interpretation of data (PJM, PR, ABG, APK, ECH, XLX, SS, PA, BZ, YZ, DvdH, IBM)

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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. Patient disposition through Week 24. Two patients (1-guselkumab q4w, 1-placebo were randomized in error and never treated). *CRP – C-reactive protein, q4/8w – every 4/8 weeks, TB – tuberculosis, W/D – withdrawal*

Figure 2. Proportions of patients achieving ACR20 (A), ACR50 (B), ACR70 (C), and Psoriasis IGA (D) responses over time (FAS). *ACR20/50/70 – American College of Rheumatology 20/50/70% improvement, FAS – full analyses set, IGA – Investigator's Global Assessment, q4/8w – every 4/8 weeks*

TABLES

Table 1. Summary of baseline patient characteristics (FAS)

	Guselkumab 100 mg		Placebo
	q4w	q8w	
Number of patients	245	248	246
Age (years)	45·9 (11·5)	44·9 (11·9)	46·3 (11·7)
Male, n (%)	142 (58·0%)	129 (52·0%)	117 (47·68%)
White, n (%)	242 (98·89%)	240 (96·87%)	242 (98·4%)
Body weight (kg)	85·8 (19·5)	83·0 (19·31)	84·0 (19·7)
PsA duration (years)	5·53 (5·9)	5·11 (5·5)	5·75 (5·6)
Number of swollen joints (0-66)	12·9 (7·8)	11·7 (6·8)	12·3 (6·9)
Number of tender joints (0-68)	22·4 (13·5)	19·8 (11·9)	21·6 (13·06)
Patient's assessment of pain (0-10 cm VAS)	6·2 (2·0)	6·3 (2·0)	6·3 (1·8)
Patient's global assessment (arthritis, 0-10 cm VAS)	6·4 (1·9)	6·5 (1·9)	6·5 (1·8)
Physician's global assessment (0-10 cm VAS)	6·6 (1·5)	6·6 (1·6)	6·6 (1·5)
HAQ-DI score (0-3)	1·2 (0·6)	1.3 (0.6)	1·3 (0·6)
CRP (mg/dL), median (IQR)	1·2 (0·6–2·3)	1·3 (0·7–2·5)	1·2 (0·5–2·6)
Psoriatic BSA, %	18·2 (20·4%)	17·0 (21·0%)	17·1 (20·0%)
IGA score=3/4, n (%)	117 (47·8%)	108 (43·54%)	115 (46·97%)
PASI score (0-72)	10·8 (11·7)	9·7 (11·7)	9·3 (9·8)
PsA-modified vdH-S score (0-528)	27·2 (42·2)	23·0 (37·8)	23·8 (37·8)
Patients with enthesitis, n (%)	170 (69·4%)	158 (63·74%)	178 (72·4%)
Enthesitis (LEI) score (1-6)[a]	3·0 (1·7)	2·6 (1·5)	2·8 (1·6)
Patients with dactylitis, n (%)	121 (49·4%)	111 (44·85%)	99 (40·2%)
Dactylitis score (1-60)[b]	8·6 (9·6)	8·0 (9·6)	8·4 (9·3)
SF-36			
PCS score	33·3 (7·1)	32·6 (7·9)	32·4 (7·0)

Table 1. Summary of baseline patient characteristics (FAS)

	Guselkumab 100 mg		Placebo
	q4w	q8w	
MCS score	48·4 (11·0)	47·4 (10·8)	47·2 (12·0)
Patients with prior apremilast use, n (%)	5 (2%)	4 (2%)	4 (2%)
Patients receiving at baseline, n (%)			
DMARDs	170 (69~~·4~~%)	170 (68~~·5~~%)	172 (~~69·9~~70%)
Methotrexate	146 (~~59·~~60%)	141 (~~56·9~~60%)	156 (63~~·4~~%)
Dose (mg/week)	15·6 (5·0)	15·3 (5·2)	15·2 (4·6)
Oral corticosteroids for PsA	46 (1~~8·89~~%)	50 (20~~·2~~%)	49 (~~19·9~~20%)
Dose equivalent to prednisone (mg/day)	7·0 (2·4)	6·8 (2·5)	7·8 (2·5)
NSAIDs for PsA	171 (~~69·8~~70%)	165 (66~~·5~~%)	168 (68~~·3~~%)

Data presented are mean (SD) unless noted otherwise.

[a] Among patients with LEI enthesitis score at baseline (q4w, n=166; q8w, n=157; placebo, n=175)

[b] Among patients with dactylitis score at baseline (q4w, n=121; q8w, n=111; placebo, n=99)

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, TNF – tumor necrosis factor, VAS – visual analog scale, vdH-S - van der Heijde-Sharp

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Table 2. Summary of efficacy findings through Week24 (FAS[a])

	Guselkumab 100 mg		Placebo
	q4w	q8w	
Number of patients	245	248	246
Primary endpoint			
ACR20 response at Week24, n (%)	156 (63·74%)	159 (64·1%)	81 (32·93%)
% difference vs placebo (95% CI)	*30·81 (22·4, 39·1)*	*31·2 (22·93, 39·540)*	
US procedure[b]-adjusted p value	*<0·0001*	*<0·0001*	
Major secondary endpoints controlled by US procedure			
Psoriasis IGA response at Week24[c], n/N (%)	126/184 (68·5%)	124/176 (70·5%)	35/183 (19·1%)
% difference vs placebo (95% CI)	*49·850 (41·2, 58·4)*	*50·951 (42·2, 59·760)*	
US procedure[b]-adjusted p value	*<0·0001*	*<0·0001*	
HAQ-DI, LSmean (95% CI) change at Week24	-0·40 (-0·46, -0·34)	-0·37 (-0·43, -0·31)	-0·13 (-0·19, -0·07)
LSmean difference vs placebo (95% CI)	-0·27 (-0·35, -0·19)	*-0·24 (-0·32, -0·15)*	
US procedure[b]-adjusted p value	*<0·0001*	*<0·0001*	
PsA-modified vdH-S, Median (IQR) change at Week24LSmean (95% CI) change at Week24	0.29 (-0.05, 0.63) 0·00 (-0·50–0·50)	0·52 (0·18, 0·86) 0.00 (-0.50–1.00)	0·95 (0·61, 1·29)0·00 (0·00– 1·00)
LSmean (95% CI) change at Week24	0·29 (-0·05, 0·63)	0·52 (0·18, 0·86)	0·95 (0·61, 1·29)
LSmean difference vs placebo (95% CI)	*-0.66 (-1.13, -0.19)*	*-0·43 (-0·90, 0·03)*	
US procedure[b]-adjusted p value	*0·010*	*0·07*	
SF-36 PCS, LSmean (95% CI) change at Week24	7·04 (6·14, 7·94)	7·39 (6·50, 8·29)	3·42 (2·53, 4·32)
LSmean difference vs placebo (95% CI)	*3·62 (2·39, 4·85)*	*3·97 (2·7475, 5·20)*	
US procedure[b]-adjusted p value	*0·010*	*0·010*	
SF-36 MCS, LSmean (95% CI) change at Week24	4·22 (3·14, 5·29)	4·17 (3·10, 5·23)	2·14 (1·07, 3·2122)
LSmean difference vs placebo (95% CI)	*2·07 (0·60, 3·54)*	*2·02 (0·56, 3·49)*	
US procedure[b]-adjusted p value	*0·07*	*0·07*	

Major secondary endpoints not controlled by US procedure

ACR20 response at Week16, n (%)	137 (55·96%)	137 (55·2%)	83 (33·74%)
% difference vs placebo (95% CI)	*22·2 (13·74, 30·71)*	*21·52 (13·1, 30·0)*	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	
ACR50 response at Week24, n (%)	81 (33·1%)	78 (31·52%)	35 (14·2%)
% difference vs placebo (95% CI)	*18·89 (11·52, 26·1)*	*17·2 (10·0, 24·4)*	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	
ACR50 response at Week16, n (%)	51 (20·81%)	71 (28·69%)	23 (9·3%)
% difference vs placebo (95% CI)	*11·52 (5·2, 17·78)*	*19·3 (12·63, 25·96)*	
Unadjusted p value[d]	*<0·0010004*	*<0·0001*	
ACR70 response at Week24, n (%)	32 (13·1%)	46 (18·5%)	10 (4·1%)
% difference vs placebo (95% CI)	*9·0 (4·1, 13·84)*	*14·5 (9·1, 19·920)*	
Unadjusted p value[d]	*<0·0010004*	*<0·0001*	
DAS28-CRP, LSmean (95% CI) change at Week24	-1·62 (-1·76, -1·49)	-1·59 (-1·72, -1·45)	-0·97 (-1·11, -0·84)
LSmean difference vs placebo (95% CI)	*-0·65 (-0·83, -0·47)*	*-0·61 (-0·80, -0·43)*	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	

Additional secondary endpoints not controlled by US procedure

HAQ-DI improvement ≥0.35[e] **at Week24**, n/N (%)	128/228 (56·1%)	114/228 (50·0%)	74/236 (31·4%)
% difference vs placebo (95% CI)	24·4 (15·86, 33·0)	18·79 (10·0, 27·3)	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	
PASI75 response at Week24[c], n/N (%)	144/184 (78·3%)	139/176 (79·0%)	42/183 (23·0%)
% difference vs placebo (95% CI)	*55·4 (47·0, 63·84)*	*55·76 (47·2, 64·2)*	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	
PASI90 response at Week24[c]**,** n/N (%)	112/184 (60·91%)	121/176 (68·89%)	18/183 (9·810%)
% difference vs placebo (95% CI)	*51·3 (43·2, 59·3)*	*58·69 (50·61, 66·67)*	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	
PASI100 response at Week24[c], n/N (%)	82/184 (44·65%)	80/176 (45·56%)	5/183 (2·73%)
% difference vs placebo (95% CI)	*42·2 (34·95, 49·650)*	*42·4 (34·85, 50·1)*	

Unadjusted p value[d]	*<0·0001*	*<0·0001*	
MDA response at Week24, n (%)	46 (18·89%)	62 (25·0%)	15 (6·1%)
% difference vs placebo (95% CI)	12·73 (7·0, 18·4)	18·99 (12·83, 25·0)	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	

Patients meeting treatment-failure criteria (13 [5%] q4w, 12 [5%] q8w, and 17 [7%] placebo patients) were considered nonresponders for binary clinical endpoints and as having no improvement from baseline for continuous clinical endpoints. After application of treatment failure rules, there were limited instances of patients with missing data (ACR20: 2 q8w, 1 placebo; DAS28-CRP: 2 q8w, 3 placebo; IGA: 1 per group; HAQ-DI: 2 q8w, 2 placebo; vdH-S: 5 q4w, 1 q8w, 1 placebo; PCS/MCS: 2 q8w, 2 placebo; PASI: 1 per group; enthesitis/dactylitis resolution: 1 q8w, 1 placebo). Missing data were imputed as nonresponders for binary clinical endpoints; multiple imputation was used to impute missing data for continuous clinical endpoints assuming missing at random and using the predicted value from the Full Conditional Specification regression method (requiring 200 successful imputations) for any missing pattern. Each variable eligible for imputation was to be restricted to only impute within its possible range of values. 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), most current CRP value prior to randomization (<2·0/≥2·0 mg/dL), and baseline value as explanatory factors. Continuous radiographic endpoints were compared using an analysis of covariance test; missing data were assumed to be missing at random and were imputed using multiple imputation. The 95% CIs surrounding the % differences vs. placebo were determined based on the Wald statistic.

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

[b] See Figure S1A.

[c] Assessed in patients with ≥3% BSA 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 Week0.

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, 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, PASI/75/90/100 – Psoriasis Area and Severity Index 50/75/90/100% improvement, PCS – physical

component summary, q4/8w – every 4/8 weeks, SF-36 – 36-item Short Form, PsA – psoriatic arthritis, US – United States, vdH-S – van der Heijde-Sharp

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Table 3. Summary of Dactylitis and Enthesitis Results at Week 24 (FAS[a])

	Guselkumab 100 mg q4w	Guselkumab 100 mg q8w	Placebo
Major secondary endpoints controlled by US procedure[b]			
DISCOVER-1 + DISCOVER-2 Pooled			
Resolution of dactylitis, n/N (%)	101/159 (63·54%)	95/160 (59·4%)	65/154 (42·2%)
% difference vs placebo (95% CI)	*21·3 (10·5, 32·0)*	*18·0 (7·4, 28·69)*	
US procedure-adjusted p value	*0·0110*	*0·0301*	
Resolution of enthesitis, n/N (%)	109/243 (44·95%)	114/230 (49·650%)	75/255 (29·4%)
% difference vs placebo (95% CI)	*14·65 (6·4, 22·73)*	*20·1 (11·82, 28·5)*	
US procedure-adjusted p value	*0·0301*	*0·0301*	
Major secondary endpoints not controlled by US procedure[c]			
DISCOVER-1 + DISCOVER-2 Pooled			
Dactylitis score, LSmean (95% CI) change	-5·97 (-6·84, -5·11)	-6·10 (-6·92, -5·27)	-4·21 (-5·05, -3·36)
LSmean difference vs placebo (95% CI)	*-1·77 (-2·87, -0·66)*	*-1·89 (-2·99, -0·79)*	
Unadjusted p value	*0·0025*	*<0·0010020*	
Enthesitis LEI score, LSmean (95% CI) change	-1·59 (-1·79, -1·38)	-1·52 (-1·73, -1·31)	-1·02 (-1·22, -0·82)
LSmean difference vs placebo (95% CI)	*-0·57 (-0·83, -0·31)*	*-0·50 (-0·77, -0·23)*	
Unadjusted p value	*<0·0017*	*<0·0010003*	
Dactylitis			
DISCOVER-1 resolution, 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	*0·212*	*0·088*	

Table 3. Summary of Dactylitis and Enthesitis Results at Week 24 (FAS[a])

	Guselkumab 100 mg		Placebo
	q4w	q8w	
DISCOVER-1 change from baseline, LSmean (95% CI)	-5·82 (-7·82, -3·83)	-6·11 (-7·81, -4·41)	-4·30 (-5·96, -2·63)
LSmean difference vs placebo (95% CI)	*-1·53 (-4·00, 0·95)*	*-1·82 (-4·12, 0·49)*	
Unadjusted p value	*0·225*	*0·121*	
DISCOVER-2 resolution, n/N (%)	77/121 (63·6%)	63/111 (56·8%)	38/99 (38·4%)
% difference vs placebo (95% CI)	*24·5 (11·8, 37·1)*	*18·7 (5·7, 31·7)*	
Unadjusted p value	*<0.001*	*0.007*	
DISCOVER-2, change from baseline, LSmean (95% CI)	-5·88 (-6·74, -5·01)	-5·95 (-6·83, -5·08)	-4·03 (-4·96, -3·10)
LSmean difference vs placebo (95% CI)	*-1·85 (-3·04, -0·65)*	*-1·92 (-3·15, -0·70)*	
Unadjusted p value	*0·002*	*0·002*	
Enthesitis LEI			
DISCOVER-1 resolution, 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	*0·013*	*0·094*	
DISCOVER-1 change from baseline, LSmean (95% CI)	-1·75 (-2·13, -1·38)	-1·35 (-1·72, -0·98)	-1·01 (-1·37, -0·66)
LSmean difference vs placebo (95% CI)	*-0·74 (-1·24, -0·24)*	*-0·33 (-0·83, 0·16)*	
Unadjusted p value	*0·004*	*0·185*	
DISCOVER-2 resolution, n/N (%)	74/170 (43·5%)	85/158 (53·8%)	54/178 (30·3%)
% difference vs placebo (95% CI)	*12·3 (2·6, 22·1)*	*23·3 (13·1, 33·5)*	
Unadjusted p value	*0.017*	*<0.001*	

Table 3. Summary of Dactylitis and Enthesitis Results at Week 24 (FAS[a])

	Guselkumab 100 mg		Placebo
	q4w	q8w	
DISCOVER-2 change from baseline, LSmean (95% CI)	1·52 (1·75, 1·29)	1·60 (1·84, 1·37)	1·03 (1·25, 0·81)
LSmean difference vs placebo (95% CI)	*0·49 (0·80, 0·19)*	*0·57 (0·89, 0·26)*	
Unadjusted p value	*0·002*	*<0·001*	

See Table 2 for further details of statistical testing.

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

[b] Per the preplanned statistical analysis plan, resolution of dactylitis and enthesitis data were combined across DISCOVER-1 and DISCOVER-2 as major secondary endpoints in the US testing procedure (See Figure S1A).

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

CI – confidence interval, FAS – full analysis set, LEI – Leeds Enthesitis Index, LS – least squares, q4/8w – every 4/8 weeks, US – United States

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

	Guselkumab 100 mg			Placebo
	q4w	**q8w**	**Combined**	
Number of patients	245	248	493	246
Mean length of follow up (weeks)	23·8	23·9	23.9	24·0
Mean number of administrations	5·9	5·9	5.9	5·9
Patients with 1 or more AE, n (%)	113 (46·1%)	114 (46·0%)	227 (46·0%)	100 (40·71%)
AEs occurring in ≥3% of patients in any group (in alphabetical order)				
Alanine aminotransferase increased	25 (10·2%)	15 (6·0%)	40 (8·1%)	11 (4·5%)
Aspartate aminotransferase increased	11 (4·5%)	14 (5·6%)	25 (5·1%)	6 (2·4%)
Bronchitis	10 (4·1%)	1 (0·4≤1%)	11 (2·2%)	3 (1·2%)
Nasopharyngitis	12 (4·95%)	10 (4·0%)	22 (4·5%)	9 (3·74%)
Upper respiratory tract infection	12 (4·95%)	6 (2·4%)	18 (3·74%)	8 (3·3%)
Patients with 1 or more SAE, n (%)	8 (3·3%)[a]	3 (1·2%)[b]	11 (2·2%)	7 (2·83%)[c]
Patients with AE resulting in study drug d/c, n (%)	6 (2·4%)[d]	2 (0·81%)[e]	8 (1·62%)	4 (1·62%)[f]
MACE, n (%)	1 (<10·4%)	0	1 (0·2<1%)	0
Malignancy, n (%)	0	1 (0·4≤1%)	1 (0·2≤1%)	1 (0·4≤1%)
Patients with infections[g], n (%)	49 (20·0%)	40 (16·1%)	89 (18·1%)	45 (18·3%)
Serious infections	3 (1·2%)	1 (<10·4%)	4 (0·81%)	1 (0·4≤1%)
Patients with injection-site reactions, n (%)	3 (1·2%)	3 (1·2%)	6 (1·2%)	1 (0·4≤1%)
Patients with suicidal ideation, n (%)	1 (0·4≤1%)	0	1 (0·2≤1%)	1 (0·4≤1%)

[a] 1 patient each with acute hepatitis B, blue toe syndrome, femur fracture, influenza pneumonia, ischaemic stroke, lower limb fracture/metal poisoning, oophoritis, osteoarthritis.

[b] 1 patient each with ankle fracture, coronary artery disease, pyrexia.

[c] 1 patient each with clear cell renal cell carcinoma, isoniazid-induced liver injury, inflammatory bowel disease (suspected), obesity, post-procedural fistula, tubulointerstitial nephritis, unstable angina.

[d] 1 patient each with acute hepatitis B (*de novo*), allergic dermatitis, isoniazid-induced liver injury, ischaemic stroke, rhinovirus infection, and injection-site erythema/swelling/warmth.

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

	Guselkumab 100 mg			Placebo
	q4w	q8w	Combined	

[e] 1 patient each with rash, malignant melanoma in situ.

[f] 1 patient each with clear cell renal cell carcinoma, isoniazid-induced liver injury, inflammatory bowel disease, tubulointerstitial nephritis

[g] AEs identified by investigators as infections

AE – adverse event, d/c – discontinuation, MACE – major adverse cardiovascular event, q4/8w – every 4/8 weeks, SAE – serious adverse event, SAS – safety analysis set (treated patients)

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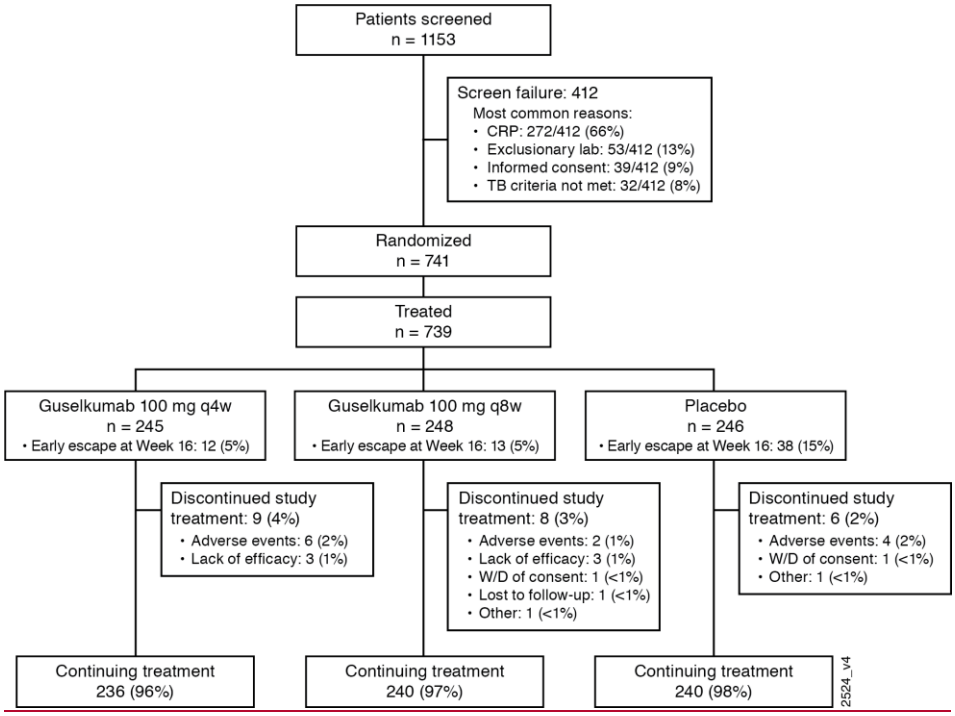
Figure 1. ~~**Patient disposition through Week 24.** Two patients (1 guselkumab q4w, 1 placebo were randomized in error and never treated). *CRP = C-reactive protein, q4/8w = every 4/8 weeks, TB = tuberculosis, W/D = withdrawal*~~



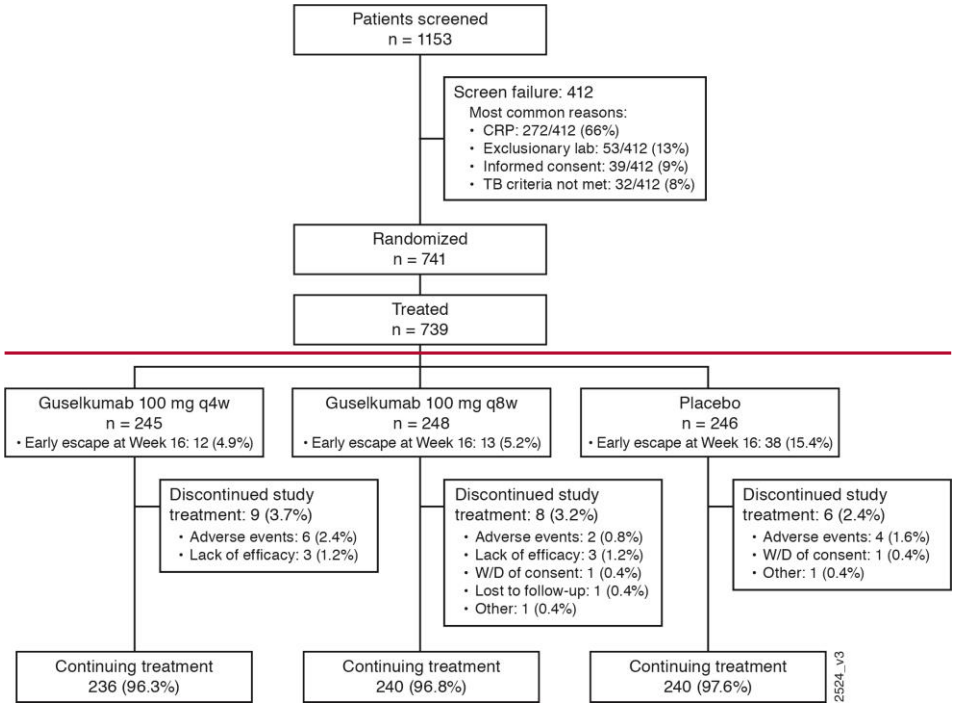
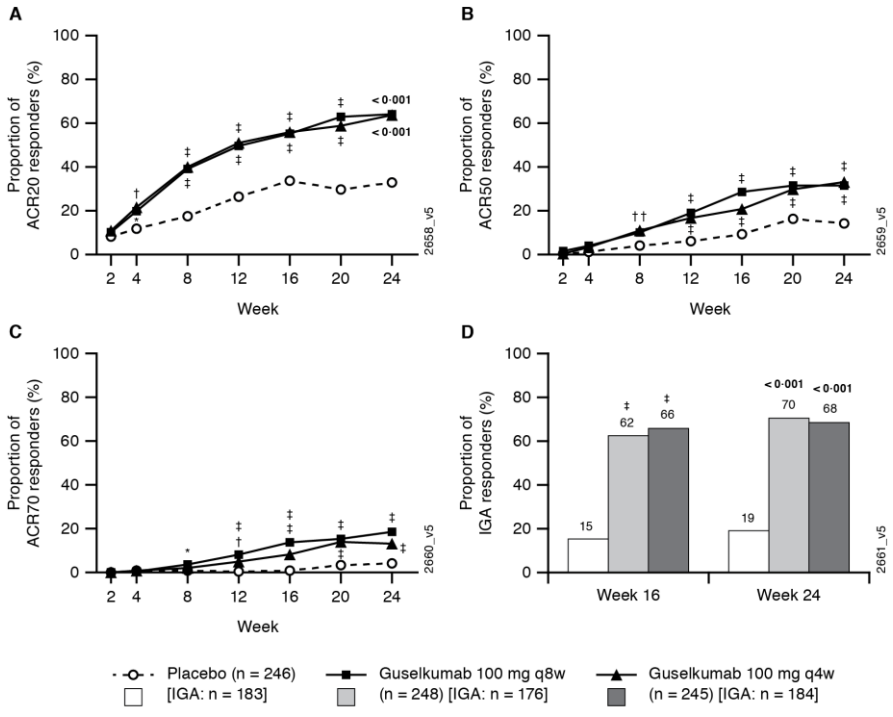
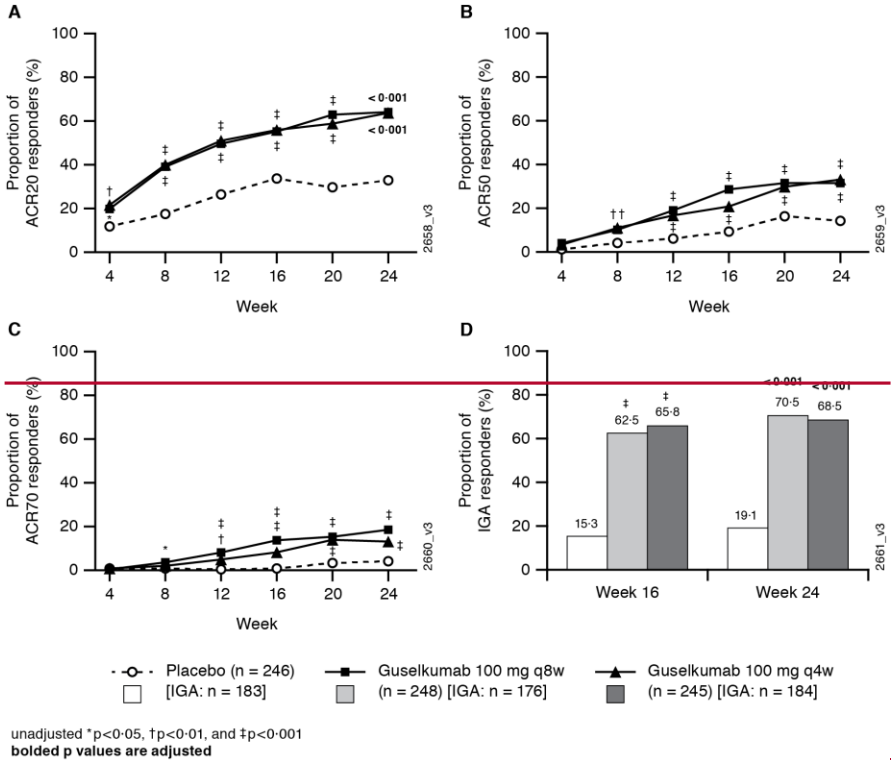

Patients screened
n = 1153
Screen failure: 412
Most common reasons:
• CRP: 272/412 (66%)
• Exclusionary lab: 53/412 (13%)
• Informed consent: 39/412 (9%)
• TB criteria not met: 32/412 (8%)
Randomized
n = 741
Treated
n = 739
Guselkumab 100 mg q4w
n = 245
• Early escape at Week 16: 12 (4.9%)
Guselkumab 100 mg q8w
n = 248
• Early escape at Week 16: 13 (5.2%)
Placebo
n = 246
• Early escape at Week 16: 38 (15.4%)
Discontinued study treatment: 9 (3.7%)
• Adverse events: 6 (2.4%)
• Lack of efficacy: 3 (1.2%)
Discontinued study treatment: 8 (3.2%)
• Adverse events: 2 (0.8%)
• Lack of efficacy: 3 (1.2%)
• W/D of consent: 1 (0.4%)
• Lost to follow-up: 1 (0.4%)
• Other: 1 (0.4%)
Discontinued study treatment: 6 (2.4%)
• Adverse events: 4 (1.6%)
• W/D of consent: 1 (0.4%)
• Other: 1 (0.4%)
Continuing treatment
236 (96.3%)
Continuing treatment
240 (96.8%)
Continuing treatment
240 (97.6%)
2524_v3

Figure 2.



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



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

Guselkumab, an Interleukin-23-Inhibitor That Specifically Binds the IL-23p19-Subunit:

Week 24 Clinical and Radiographic Results of a Phase 3, Randomized, Double-blind, Placebo-controlled Study

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Words: 4499/4500

Summary (282/300 words)

Background: The interleukin-23/Th17 pathway is implicated in psoriatic arthritis pathogenesis. Guselkumab, an interleukin-23-inhibitor that specifically binds the IL23p19-subunit, significantly and safely improved psoriatic arthritis in a Phase-2 study.

Methods: This Phase-3, double-blind, placebo-controlled study (118 sites in 13 countries) enrolled biologic-naïve patients with active psoriatic arthritis (≥5 swollen, ≥5 tender joints, C-reactive-protein ≥0·6 mg/dL) despite standard therapies. Patients were randomised (1:1:1; computer-generated permuted blocks; stratified by baseline disease-modifying antirheumatic drug use and C-reactive-protein) to subcutaneous guselkumab 100 mg every-4-weeks (q4w); guselkumab 100 mg at Weeks 0, 4, every-8-weeks (q8w); or placebo. The primary endpoint was ACR20 response at Week24 among randomized and treated patients. Clinicaltrials.gov identifier-NCT03158285 (active-not recruiting).

Findings: From 07/13/2017–03/06/2019, 739 randomised patients received guselkumab q4w (N=245), q8w (N=248), or placebo (N=246); 716 patients continued treatment through Week24. Significantly greater proportions of guselkumab q4w- (156 [64%] of 245; 95% confidence interval: 57%, 70%) and q8w- (159 [64%] of 248; 95% confidence interval: 58%, 70%) than placebo- (81 [33%] of 246; 95% confidence interval: 27%, 39%) treated patients achieved Week24 ACR20 response (% differences [95% confidence intervals]: 31 (22, 39) and 31 (23, 40), respectively; both p<0·0001). Through Week24, serious adverse events, and specifically serious infections, occurred in eight (3%) and three (1%) of 245 patients receiving guselkumab q4w, three (1%) and one (<1%) of 248 receiving guselkumab q8w, and seven (3%) and one (<1%) of 246 receiving placebo, respectively. No deaths occurred.

Interpretation: Guselkumab, a human monoclonal antibody that specifically inhibits interleukin-23 by binding the cytokine's p19-subunit, was efficacious and well tolerated in patients with active psoriatic arthritis who were biologic naive. These data support the further development of guselkumab for treating psoriatic arthritis.

Funding: Janssen Research & Development, LLC

Panel - Research in context

Evidence before this study – Current literature indicates that interleukin-23 is instrumental in driving the chronic inflammation associated with several immune-mediated diseases, including psoriasis and psoriatic arthritis. Guselkumab is a high-affinity, anti-interleukin-23 human monoclonal antibody that specifically bind's the cytokine's p19-subunit and is approved to treat moderate-to-severe psoriasis. In a Phase-2 study, selective blockade of interleukin-23 by guselkumab significantly improved signs and symptoms of active psoriatic arthritis and was well tolerated during 1 year of exposure.

Added value of this study – Results of this pivotal study, the larger of two comprising the first Phase-3 program investigating a novel mechanism of action to treat psoriatic arthritis, confirm that targeting the p19-subunit of interleukin-23 effectively treats the diverse domain manifestations of psoriatic arthritis. Specifically, in patients with active disease despite non-biologic disease-modifying antirheumatic, apremilast, and/or nonsteroidal anti-inflammatory drug treatment, but no prior exposure to biologics, subcutaneous guselkumab 100 mg significantly improved joint symptoms, dactylitis, enthesitis, psoriasis, physical function, and quality of life when administered every 4 or 8 weeks. Progression of structural damage through Week24 was significantly lower with guselkumab q4w, and numerically lower with q8w, dosing vs. placebo, providing initial evidence of inhibition of radiographic progression by an interleukin-23 inhibitor that target its p19-subunit. The guselkumab safety profile in psoriatic arthritis patients was comparable to profiles observed in placebo-treated psoriatic arthritis patients and guselkumab-treated patients with psoriasis.

Implications of all the available evidence – Consistent with previous findings of a proof-of-concept study confirming that interleukin-23 plays a critical role in the pathogenesis of psoriatic arthritis, these Phase-3 trial data provide pivotal evidence that guselkumab offers a novel mechanism of action to treat the diverse clinical manifestations of psoriatic arthritis and inhibit structural damage progression.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with peripheral joint inflammation, enthesitis, dactylitis, axial disease, and cutaneous and nail involvement, all of which can significantly limit physical function and impair quality of life. While the introduction of biologic (e.g., tumor necrosis factor-α inhibitors [TNFi], ustekinumab, interleukin [IL]-17A inhibitors, abatacept) and oral (e.g., apremilast, tofacitinib) agents has increased the extent and duration of achievable clinical responses, new therapies are needed to treat the diverse manifestations of PsA while maintaining a favorable risk-benefit profile.[1]

The origins of the varying clinical manifestations of PsA remain under study. The IL-23/T-helper cell 17 (Th17) pathway – via downstream IL-17 expression - appears critical to skin manifestations. IL-23 can also induce IL-22, a cytokine implicated in enthesitis and bone formation,[2] and, in part via IL-17A and TNF induction, elicit the joint symptoms and damage that are hallmarks of PsA. IL-23 is a heterodimer formed by pairing p19- and p40-subunits, the latter of which is shared with IL-12. Although IL-12 and IL-23 share the p40-subunit, they also encompass unique p35- (for IL-12) and p19- (for IL-23) subunits.[3,4] Whereas IL-23 has been determined to be a predominant promoter of autoimmune-mediated articular inflammation, IL-12 more likely facilitates protection from autoimmune inflammation and T-cell exhaustion.[4-7] The divergent roles of these closely related cytokines are highlighted by differential skin effects, whereby abnormal differentiation of keratinocytes is triggered by IL-23, but not IL-12,[6] and differing roles in the body's response to bacterial and viral infections, as well as tumour control via their regulation of T-cell function.[5] Targeting the p19-subunit of IL-23, and thus sparing IL-12, has demonstrated robust efficacy in psoriasis,[7-10] suggesting a prominent upstream position in

101 the inflammatory hierarchy across the psoriatic disease spectrum, which thereby merits
102 evaluation of selective IL-23 inhibition via IL23-p19 binding in PsA.

103 Guselkumab (Janssen Biotech, Inc., Horsham, PA, USA), a high-affinity, human monoclonal
104 antibody that binds specifically to the p19-subunit of IL-23, is approved to treat patients with
105 moderate-to-severe psoriasis who are candidates for systemic and/or phototherapy. In a
106 randomised, placebo-controlled, Phase-2 study evaluating subcutaneous guselkumab 100 mg at
107 Weeks 0, 4 and every 8 weeks (q8w) in 149 patients with active PsA, including ≥3% body
108 surface area (BSA) of psoriasis, guselkumab demonstrated efficacy across all endpoints related
109 to joint signs and symptoms, physical function, skin disease, enthesitis, dactylitis, and health-
110 related quality of life.[11]

111 Herein, we report 24-week results from one of two Phase-3 trials, i.e., DISCOVER-2, conducted
112 to evaluate guselkumab in biologic-naïve patients with active PsA. DISCOVER-2 evaluations
113 included joint and skin manifestations, as well as structural damage. Results from the other
114 registrational trial of guselkumab in PsA (DISCOVER-1), which aimed to enroll patients with a
115 broader range of baseline levels of disease activity, some of whom were previously treated with
116 one or two TNFi, are reported elsewhere (Lancet.org doi.xxxx).

117

METHODS

Study design

This Phase-3, randomised, double-blind, placebo-controlled, multicenter, 3-arm study of guselkumab in patients with active PsA, who were biologic-naïve and demonstrated inadequate response to standard therapies (non-biologic disease-modifying antirheumatic drugs [DMARDs], apremilast, and/or nonsteroidal anti-inflammatory drugs [NSAIDs]), was conducted at 118 sites worldwide (see Online Supplement). Screening began 07/13/2017; the final Week-24 visit occurred on 02/25/2019. The trial design includes a 6-week screening period; a 100-week treatment phase, with a placebo-controlled period from Week0–Week24 and an active treatment period from Week24–Week100; and 12-weeks of safety follow-up after the last administration of study agent. 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 ≤3g/day, hydroxychloroquine ≤400 mg/day, or leflunomide ≤20 mg/day). Study results through Week24 are reported. This trial (NCT03158285) is being conducted per Declaration of Helsinki and Good Clinical Practice guidelines. The protocol (available at Lancet.org) was approved by each site's governing ethical body.

Participants

Approximately 684 eligible patients were planned for this study. Adults with PsA for ≥6 months, fulfilling the Classification Criteria for Psoriatic Arthritis[12] and with ≥5 tender and ≥5 swollen joints; C-reactive protein (CRP) ≥0·6 mg/dL; current or documented history of psoriasis; and either inadequate response to, or intolerance of, standard non-biologic treatment were eligible. Standard treatment included ≥3 months of non-biologic DMARDs, ≥4 months of apremilast at the approved dose (if discontinued >4 weeks before receiving study agent), or ≥4 weeks of NSAIDs for PsA. Previous exposure to biologic agents or Janus kinase inhibitors precluded participation. Patients were permitted, but not required, to continue stable use of selected non-biologic DMARDs (limited to those allowed for early escape), and NSAIDs/other analgesics. Only one DMARD was permitted through Week52. Patients also had to meet screening criteria for laboratory evaluations and tuberculosis (TB) history/testing/treatment (for latent TB). Full inclusion and exclusion criteria, and further details of permitted and prohibited therapies, are included in the protocol (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 the most recent high-sensitivity serum CRP value prior to randomization [<2·0/≥2·0 mg/dL]) in a 1:1:1 ratio to receive guselkumab 100 mg every 4 weeks (q4w); guselkumab 100 mg at Week0, Week4, and every 8 weeks (q8w); or placebo. Blinding was accomplished as reported for DISCOVER-1 (Lancet.org doi.xxxx).

Procedures

Guselkumab was administered as a 100-mg subcutaneous injection at Week0, Week4, and then q4w or q8w. Dose selection for DISCOVER-2 was as described for DISCOVER-1 (Lancet.org doi.xxxx). Clinical efficacy and safety assessments were performed at screening, baseline, Week2, Week4, and q4w through Week24. An independent joint assessor evaluated 66 joints for swelling, 68 joints for tenderness, and determined the presence/severity of enthesitis (Leeds Enthesitis Index [LEI]) and dactylitis. Dactylitis severity for each digit was scored as 0–no dactylitis, 1–mild dactylitis, 2–moderate dactylitis, or 3–severe dactylitis (total score 0–60). Serum pharmacokinetic and immunogenicity assessments are as reported for DISCOVER-1 (Lancet.org doi.xxxx). As well, details of joint (American College of Rheumatology [ACR] response, 28-joint Disease Activity Score incorporating CRP [DAS28-CRP]), skin (Investigator's Global Assessment of psoriasis [IGA], Psoriasis Area and Severity Index [PASI]), physical function (Health Assessment Questionnaire-Disability Index [HAQ-DI]), health-related quality of life (36-item Short-Form [SF-36] Health Survey), and safety (adverse events [AEs], routine haematology and chemistry assessment, electronic Columbia-Suicide Severity Rating Scale [eC-SSRS] questionnaires) assessments are as reported for DISCOVER-1 (Lancet.org doi.xxxx).

In DISCOVER-2, single radiographs of the hands (posteroanterior) and feet (anteroposterior) were obtained at screening and Week24. Radiographs were evaluated independently by two central readers (blinded to order of radiographs and clinical data), with the van der Heijde-Sharp (vdH-S) score modified for PsA (distal interphalangeal joints of hands added).[13] Adjudication was employed as mandated by primary reader disagreement. The total PsA-modified vdH-S score (0–528) sums the joint erosion score (0–320; 0–no erosions, 5–extensive loss of bone from

>50% of the articulating bone) and the joint space narrowing (JSN) score (0–208; 0–no JSN, 4–complete loss of joint space, bony ankylosis, or complete luxation). The average score of the two readers was employed in analyses.

Outcomes

The primary endpoint was the ACR20 response rate at Week24. Major secondary endpoints included ACR50 and ACR70 responses, changes from baseline in DAS28-CRP scores, 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, changes from baseline in HAQ-DI and PsA-modified vdH-S scores, changes from baseline in, and resolution of, enthesitis and dactylitis pooled across DISCOVER-1&2 (*Statistical analyses*), changes in the SF-36 physical/mental component summary (PCS/MCS) scores, all at Week24, and ACR20/ACR50 responses at Week16. Other selected key secondary outcomes included clinically meaningful improvement (≥0.35) in HAQ-DI scores in patients with baseline HAQ-DI scores ≥0·35, ≥75/90/100% improvement in the PASI (PASI75/PASI90/PASI100) in patients with mild-to-severe psoriasis at baseline, and minimal disease activity (MDA; see Lancet.org doi.xxxx), all at Week24. Safety outcomes were as reported for DISCOVER-1 (Lancet.org doi.xxxx).

Statistical analyses

Assuming Week24 ACR20 response rates of 45% with guselkumab versus 25% with placebo, 684 patients (228/treatment group) were required to provide ~99% statistical power (α=0·05; 2-sided). With 684 patients, the study was estimated to have 90% power to detect a treatment difference in change from baseline in total PsA-modified vdH-S scores, assuming mean changes from baseline at Week24 of 0·9 and 0·3, respectively, in placebo- and across all guselkumab-

203 treated patients and a standard deviation of 2·5 for each treatment. Strategies employed to control
204 the overall Type 1 error rate are described below.

205 Efficacy analyses through Week24 included all randomised patients who received ≥1
206 administration of study treatment and were conducted according to assigned treatment groups
207 (full analysis set). Treatment differences for binary endpoints were assessed via a Cochran-
208 Mantel-Haenszel test; those for continuous endpoints employed an analysis of covariance model.

209 To increase sample size, endpoints related to enthesitis and dactylitis among the smaller number
210 of patients with those conditions at baseline were prespecified to be tested by pooling data from
211 this study with those from DISCOVER-1 (Lancet.org doi.xxxx). Results of these pooled analyses
212 are presented herein.

213 Owing to differences in health authority requirements for multiplicity control between the United
214 States (US) and other countries, two graphical testing procedures were prespecified to control
215 overall Type I error at α=0·05 (2-sided). For both approaches, the primary endpoint (ACR20
216 response at Week24) was first tested for the q4w group and then for the q8w group (each at 0·05
217 level). The first graphical procedure (Figure S1A) controlled the overall Type 1 error rate across
218 both dosing regimens at the 0·05 level for the primary and the following major secondary
219 endpoints at Week24: IGA skin response among patients with mild-to-severe psoriasis; changes
220 in HAQ-DI, PsA-modified vdH-S, and SF-36 PCS scores; resolution of dactylitis and enthesitis
221 among patients with the respective condition at baseline pooled across both DISCOVER trials,
222 and changes in SF-36 MCS scores. Results of this testing procedure are presented in the main
223 manuscript text and those from the second graphical procedure (Figure S1B), which controlled
224 the overall Type 1 error rate for each dosing regimen at the 0·05 level for all major secondary

endpoints, except changes from baseline in enthesitis and dactylitis scores at Week24, with two parallel procedures, are provided online (Table S1). For endpoints not controlled for multiplicity, unadjusted (nominal) p values provided should be interpreted only as supportive.

Data handling rules were applied to all clinical efficacy analyses. Patients who met treatment-failure criteria (discontinued study agent, terminated study participation, initiated or increased DMARD or oral corticosteroid doses, initiated protocol-prohibited PsA treatment) 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 and using multiple imputation for continuous endpoints. For radiographic endpoints, treatment failure rules were not applied, and missing data (five in guselkumab q4w group, one in guselkumab q8w group, one in placebo group) were imputed using multiple imputation.

An independent data monitoring committee examined data on an ongoing basis through the Week24 database lock to ensure the safety of the study participants. 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 (NCT03158285).

Role of the funding source

Janssen Research and Development, LLC funded this trial. All authors, including employees of Janssen (APK, ECH, XLX, SS, PA, BZ, YZ), were involved in data collection, analysis, and/or interpretation; trial design; manuscript preparation; and the decision to submit the paper for publication. Janssen provided funding to a professional medical writer who assisted with manuscript preparation and submission. The corresponding author (PJM) had full access to all study data and final responsibility to submit for publication.

RESULTS

From 1,153 screened patients, 741 were randomised. Patients failed screening most often for serum CRP levels <0·6 mg/dL. Overall, 739 randomised patients were treated with guselkumab q4w (N=245), guselkumab q8w (N=248), or placebo (N=246) and included in the full analysis set. At Week16, 12 (5%) of 245 guselkumab q4w-, 13 (5%) of 248 guselkumab q8w-, and 38 (15%) of 246 placebo-treated patients had <5% improvement in both tender and swollen joint counts and qualified for early escape, of which seven (3%) of 245 guselkumab q4w-, six (2%) of 248 guselkumab q8w-, and 14 (6%) of 246 placebo-treated patients initiated or increased the dose of NSAIDs, oral corticosteroids, and/or permitted non-biologic DMARDs. Overall, 23 (3%) of 739 treated patients discontinued study agent, most commonly due to AEs, resulting in robust patient retention through Week24 (Figure 1).

Baseline characteristics were generally well balanced across randomised groups. Modest numerical differences were observed between the guselkumab and placebo groups for the proportions of males, severity of psoriasis assessed by the PASI score, and presence of dactylitis and enthesitis at study outset. Background medication use was consistent across randomised treatment groups; among the 739 treated patients, 512 (69%) were receiving non-biologic DMARDs, including 443 (60%) receiving MTX, 145 (20%) were receiving oral corticosteroids for PsA, and 504 (68%) reported NSAID use at baseline (Table 1).

Major protocol deviations were evenly distributed between guselkumab- (35 [7%] of 493) and placebo- (23 [9%] of 246) treated patients. Overall, 11 patients (five guselkumab, six placebo) entered the study without satisfying all criteria, six (four guselkumab, two placebo) received the incorrect treatment/dose), six (three guselkumab, three placebo) received a disallowed

medication, and one (guselkumab) met a withdrawal criterion but was not withdrawn. No deviation was considered to impact overall results.

For the study's primary endpoint, significantly greater proportions of patients in the guselkumab q4w (156 [64%] of 245; 95% confidence interval [CI]: 57%, 70%) and q8w (159 [64%] of 248; 95% CI: 58%, 70%) groups than in the placebo group (81 [33%] of 246; 95% CI: 27%, 39%) groups achieved an ACR20 response at Week24 (% differences [95% confidence interval (CIs): 31 [22, 39] and 31 [23, 40], respectively; both $p<0{\cdot}0001$; Table 2). Results of all prespecified sensitivity analyses were consistent with the primary analysis (data on file).

A consistent treatment benefit was observed for the primary efficacy endpoint for both guselkumab dosing regimens across patient subgroups defined by demography, baseline disease characteristics, and prior and baseline medication use. In particular, ACR20 response at Week24 was consistent in the subgroup of patients with MTX use at baseline (q4w: 92 [63%] of 146 and q8w: 85 [60%] of 141),

With both guselkumab dosing regimens, more patients achieved ACR20 response vs. placebo by Week4 (following one injection of guselkumab); response rates continued to increase through Week24 (Figure 2A). ACR50 and ACR70 response rates were also consistently higher with both guselkumab dosing regimens vs. placebo (Figures 2B, 2C). Higher rates of ACR20 response at Week16, ACR50 response at Week16 and Week24, and ACR70 response at Week24 were observed among guselkumab q4w- and q8w-treated than placebo-treated patients. Further, greater improvements in DAS28-CRP scores at Week24 were observed with guselkumab q4w (LS mean change: -1·62) and q8w (-1·59) vs. placebo (-0·97; Table 2).

Among DISCOVER-1 (Lancet.org doi.xxxx) and DISCOVER-2 patients with the respective manifestations at baseline, dactylitis resolved at Week24 in significantly higher proportions of guselkumab q4w- (101 [64%] of 159) and q8w- (95 [59%] of 160) than placebo- (65 [42%] of 154) treated patients (p=0·0110 and p=0·0301, respectively). Resolution of enthesitis was also observed in significantly higher proportions of guselkumab q4w- (109 [45%] of 243) and q8w- (114 [50%] of 230) than placebo- (75 [29%] of 255) treated patients (both p=0·0301) when combined across both trials. Improvements from baseline in the enthesitis LEI and dactylitis scores at Week24 were also numerically greater with both guselkumab dosing regimens than placebo when pooled across DISCOVER-1 and DISCOVER-2 (Table 3), and consistent trends were observed in the individual trials (Table S2).

Patients treated with guselkumab q4w demonstrated significantly less progression of structural damage, as reflected by smaller changes from baseline in the PsA-modified vdH-S score at Week24, than placebo-treated patients (LS mean [95% CI]: 0·29 [-0·05, 0·63] vs. 0·95 [0·61, 1·29], respectively; p=0·0110). Guselkumab administered q8w resulted in numerically less radiographic progression (LS mean [95% CI]: 0·52 [0·18, 0·86]) than placebo, but the treatment difference did not achieve statistical significance (p=0·07; Table 2). A probability plot of changes in modified vdH-S scores from baseline at Week24 is provided in Figure S2.

In patients with mild-to-severe psoriasis at baseline, guselkumab q4w and q8w significantly improved skin disease, as assessed by IGA response rates, at Week24 vs. placebo (126 [68%] of 184 and 124 [70%] of 176, respectively vs. 35 [19%] of 183; both p<0·0001; Table 2, Figure 2D). PASI75, PASI90, and PASI100 response rates were also higher among guselkumab- than placebo-treated patients (Table 2).

Guselkumab q4w and q8w significantly improved HAQ-DI scores from baseline at Week24 vs. placebo (LSmean [95% CI] changes: -0·40 [-0·46, -0·34] and -0·37 [-0·43, -0·31], respectively, vs. -0·13 [-0·19, -0·07]; both p<0·0001). The proportions of patients with improvement in the HAQ-DI score ≥0·35 at Week24, among those with baseline HAQ-DI ≥0·35, also indicated that guselkumab q4w (128 [56%] of 228) and q8w (114 [50%] of 228) improved physical function to a greater extent than placebo (74 [31%] of 236; Table 2).

Patients started the study with impaired health-related quality-of-life as assessed by mean SF-36 PCS (32·4–33·3) and MCS (47·2–48·4) scores (US general population norm=50.0). Significant improvements in SF-36 PCS scores from baseline at Week24 were demonstrated by guselkumab q4w and q8w, respectively, vs. placebo (LSmean changes: 7·04 and 7·39 vs. 3·42; both p=0·0110). Numerical improvements in SF-36 MCS scores (4·22 and 4·17 vs. 2·14; both p=0·07) were also observed for both guselkumab dosing regimens vs. placebo; although the lower bounds of the 95% CIs of the differences from placebo exceeded 0, differences were not significant after multiplicity adjustment (Table 2). At Week24, MDA was achieved by 46 (19%) of 245 and 62 (25%) of 248 patients receiving guselkumab q4w and q8w, respectively, vs. 15 (6%) of 246 placebo-treated patients (Table 2).

An overview of guselkumab pharmacokinetic and immunogenicity findings can be found in the Online Supplement.

Guselkumab was generally well-tolerated. Through Week24, AEs were reported by 113 (46%) of 245, 114 (46%) of 248, and 100 (41%) of 246 patients receiving guselkumab q4w, guselkumab q8w, and placebo, respectively. Serious AEs (SAEs) were reported by eight (3%) of 245, three (1%) of 248, and seven (3%) of 246 patients, and AEs led to discontinuation of study agent for

six (2%) of 245, two (1%) of 248, and four (2%) of 246 patients receiving guselkumab q4w, guselkumab q8w, and placebo, respectively (Table 4).

The AEs reported by ≥3% of patients in any treatment group were infections (upper respiratory tract infection, nasopharyngitis, bronchitis) and laboratory investigations (alanine aminotransferase [ALT] increased, aspartate aminotransferase [AST] increased; Table 4). Serious infections occurred in three (1%) of 245 patients receiving guselkumab q4w (acute hepatitis B [*de novo*], influenza pneumonia, oophoritis), one (<1%) of 248 patients receiving guselkumab q8w (pyrexia [likely of urinary origin]), and one (<1%) of 246 placebo-treated patients (post-procedural fistula). No *Candida* or opportunistic infections, or cases of active TB, occurred through Week24. No AEs of inflammatory bowel disease were reported in guselkumab-treated patients, whereas there was one suspected case in the placebo group through Week24.

No deaths were reported through Week24. One patient in each of the guselkumab q4w (at Week2 only) and placebo (pre-existing and at Week12) groups experienced suicidal ideation (Level 1 – wish to be dead); no patient reported suicidal or self-injurious behavior without suicidal intent through Week24. Two patients were diagnosed with a malignancy through Week24 (guselkumab q8w: melanoma *in situ* at Week4; placebo: clear-cell renal cell carcinoma at Week12). One patient had a major acute cardiovascular event: a 58-year-old female with a history of hypertension, hyperlipidemia, and diabetes and who was receiving guselkumab 100 mg q4w had an ischaemic stroke at Week20. The patient recovered, and study drug was discontinued.

Two patients demonstrated maximum National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) Grade-3 or 4 neutropenia, one in the placebo group (Grade-3 [<1·0–0·5 x 10^9/L] at Week 8 only) and one in the guselkumab q4w group (did not recur upon retest the

following week, not associated with infections or study drug interruptions). No other NCI-CTCAE Grade-3 or higher hematology abnormalities were observed in guselkumab-treated patients, except a case of anemia in one guselkumab q8w-treated patient (Grade-3 hemoglobin [<80·0 g/L] of 69 g/L at Week16 only).

The proportions of patients with increased ALT or AST levels reported as AEs appeared slightly higher in the guselkumab than placebo groups (Table 4). The overall incidences of maximum NCI-CTCAE Grade-2 (>3.0–5.0 x upper limit of normal [ULN]) ALT and AST increases were low and slightly more common in guselkumab- (nine [2%] and 11 [2%] of 490 patients, respectively) than placebo- (four [2%] and none of 246 patients, respectively) treated patients. Maximum NCI-CTCAE Grade-3 (>5·0–20·0 x ULN) or Grade-4 (>20·0 x ULN) ALT values were observed in four (2%) of 243 patients receiving guselkumab q4w (all Grade-3), three (1%) of 247 patients receiving guselkumab q8w (all Grade-3), and two (1%) of 246 placebo-treated patients (one patient each with Grade-3 and Grade-4 values). For AST, maximum NCI-CTCAE Grade-3 (>5·0–20·0 x ULN) or Grade-4 (>20·0 x ULN) values were observed in five (2%) of 243 patients receiving guselkumab q4w (all Grade-3), one (<1%) of 247 patients receiving guselkumab q8w (Grade-3), and two (1%) of 246 placebo-treated patients (all Grade-3). These laboratory abnormalities resulted in study drug discontinuation in one placebo-treated patient (Week8 ALT/AST of 1053/665 U/L related to serious isoniazid-induced hepatitis that resolved by Week12) and two patients receiving guselkumab q4w (one with Week4 ALT/AST of 479/484 U/L related to non-serious AE of isoniazid-induced hepatitis that resolved by Week16 and one with Week20 ALT/AST of 373/238 U/L related to an SAE of acute hepatitis B with no clinically significant increase in bilirubin; AEs were resolving at the last contact).

DISCUSSION

Results of the Phase-3, multicenter, randomised, double-blind, placebo-controlled, DISCOVER-2 study through Week24 indicate that guselkumab, a selective IL-23 inhibitor that binds the cytokine's p19-subunit, effected robust improvements in signs and symptoms of joint disease in patients with PsA. The study met its primary endpoint for both guselkumab 100 mg q4w and q8w, with 64% and 64% of these patients, respectively, achieving an ACR20 response at Week24, compared with 33% of placebo-treated patients. Similarly, ACR50 and ACR70 response rates demonstrated that treatment with guselkumab results in clinically meaningful reductions in the joint signs and symptoms of PsA. Improvement occurred at early timepoints and increased over time through Week24.

Guselkumab, whether administered q4w or q8w, also elicited significant improvements in skin psoriasis, physical function, and health-related quality of life, all of which significantly impact mental health, work productivity, and the economic burden of PsA.[14,15] Of particular note, >60% of guselkumab-treated patients achieved PASI90 and 45% achieved PASI100 responses at Week24. These findings are consistent with the established efficacy of guselkumab in treating moderate-to-severe plaque psoriasis.[7,9,10] Guselkumab q4w inhibited progression of structural damage vs. placebo at Week24, based on changes in the PsA-modified vdH-S score. Guselkumab q8w dosing also reduced structural damage progression, but the difference from placebo was not statistically significant. This observation could derive from differences in total guselkumab exposure between q4w and q8w dosing from Weeks0-24. Radiographic data being collected through 1 year will provide additional data with which to evaluate the ability of the q8w dosing regimen to limit progression of structural damage.

Inflammation of periarticular tissues such as dactylitis and enthesitis, is a hallmark of PsA that can present a treatment challenge.[16] IL-23 is essential for both activating Th17 cells, which produce IL-17A, and maintaining IL-17A production thereafter.[2] IL-23 also regulates innate cells (e.g., γδ T, natural killer T, and innate lymphoid cell subsets), which are predominantly located in non-lymphoid tissue and, upon stimulation by IL-23, produce pro-inflammatory cytokines (IL-17, IL-22, and interferon-γ), thereby inducing local tissue inflammation.[17-20] Given that guselkumab 100 mg q8w has been shown to decrease serum IL-17A concentrations of PsA patients to levels observed in healthy controls by Week16,[21] it is not unexpected that both guselkumab regimens afforded significantly higher proportions of patients with clinically resolved dactylitis and enthesitis at Week24 when data were pooled across DISCOVER-1 and DISCOVER-2.

As a downstream effector cytokine of IL-23, IL-17A has been implicated mechanistically in both inflammation and bone remodeling in a murine rheumatoid arthritis model by stimulating osteoclastogenesis; promoting bone resorption in fetal mouse long bones; and inducing expression of the receptor activator of nuclear factor kappa-B-ligand, an osteoclast differentiation factor, in osteoclast-supporting cells.[22] IL-23 can also induce IL-22, a cytokine implicated in bone formation.[2] Because IL-23 regulates several effector cytokines that are thought to contribute to PsA disease pathology, inhibition of multiple effector cytokines through IL-23 targeting may provide more effective modulation of these processes than single cytokine inhibition.

Guselkumab 100 mg was generally well tolerated in this PsA population, with no clinically meaningful differences between q4w and q8w dosing through Week24. No *Candida* or opportunistic infections or cases of active TB occurred. One suspected case of inflammatory

bowel disease was reported in a placebo-treated patient. There was no apparent association between the development of antibodies to guselkumab and the occurrence of injection-site reactions (see Online Supplement). The overall safety profile was generally consistent with that reported for patients with psoriasis.[7,9,23] Specifically, guselkumab 100 mg q8w demonstrated a stable safety profile through 100 weeks of treatment, with no safety signals with regard to serious infection, malignancy, MACE, or suicidality, in an analysis of data from more than 1,800 patients enrolled in two Phase-3 psoriasis studies.[23] Further, in >800 patients with psoriasis who participated in the VOYAGE-1 study, no new safety signals were observed through up to 4 years of guselkumab 100 mg when given q8w.[24]

The biologic-naïve DISCOVER-2 patients presented with an average of 12–13 swollen and 20–22 tender joints, along with substantial systemic inflammation (median serum CRP: 1·2–1·3 mg/dL), possibly limiting the applicability of findings to patients with less active disease. The relatively high placebo response rates observed for joint (ACR20-33%) and skin (IGA-19%) outcomes may also affect data interpretation. However, these response rates are consistent with other recently reported findings in biologic-naïve PsA populations,[25,26] and likely reflect higher expectations for efficacy as more potent therapies have become available for PsA. It will be important to evaluate whether the favourable responses and safety profile through Week24 are maintained; such data are being collected throughout this 2-year study.

Thus, guselkumab was well tolerated and demonstrated robust efficacy in DISCOVER-2 across clinical domains crucial to achieving PsA remission (e.g., synovitis, enthesitis, dactylitis, psoriasis), including reducing structural damage progression.[27] By binding to IL-23's p19-subunit, but not the p40-subunit it shares with IL-12, guselkumab targets the key upstream regulatory cytokine responsible for the Th17 pathway implicated in PsA, thereby providing a

446 targeted yet comprehensive means of controlling the downstream inflammatory cascade and thus
447 safely and effectively treating PsA's diverse manifestations.

CONTRIBUTORS

Authors

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FIGURE LEGENDS

Figure 1. Patient disposition through Week 24. Two patients (1-guselkumab q4w, 1-placebo were randomized in error and never treated). *CRP – C-reactive protein, q4/8w – every 4/8 weeks, TB – tuberculosis, W/D – withdrawal*

Figure 2. Proportions of patients achieving ACR20 (A), ACR50 (B), ACR70 (C), and Psoriasis IGA (D) responses over time (FAS). *ACR20/50/70 – American College of Rheumatology 20/50/70% improvement, FAS – full analyses set, IGA – Investigator's Global Assessment, q4/8w – every 4/8 weeks*

573 # TABLES

Table 1. Summary of baseline patient characteristics (FAS)

	Guselkumab 100 mg		Placebo
	q4w	q8w	
Number of patients	245	248	246
Age (years)	45·9 (11·5)	44·9 (11·9)	46·3 (11·7)
Male, n (%)	142 (58%)	129 (52%)	117 (48%)
White, n (%)	242 (99%)	240 (97%)	242 (98%)
Body weight (kg)	85·8 (19·5)	83·0 (19·31)	84·0 (19·7)
PsA duration (years)	5·53 (5·9)	5·11 (5·5)	5·75 (5·6)
Number of swollen joints (0-66)	12·9 (7·8)	11·7 (6·8)	12·3 (6·9)
Number of tender joints (0-68)	22·4 (13·5)	19·8 (11·9)	21·6 (13·06)
Patient's assessment of pain (0-10 cm VAS)	6·2 (2·0)	6·3 (2·0)	6·3 (1·8)
Patient's global assessment (arthritis, 0-10 cm VAS)	6·4 (1·9)	6·5 (1·9)	6·5 (1·8)
Physician's global assessment (0-10 cm VAS)	6·6 (1·5)	6·6 (1·6)	6·6 (1·5)
HAQ-DI score (0-3)	1·2 (0·6)	1.3 (0.6)	1·3 (0·6)
CRP (mg/dL), median (IQR)	1·2 (0·6–2·3)	1·3 (0·7–2·5)	1·2 (0·5–2·6)
Psoriatic BSA, %	18·2 (20%)	17·0 (21%)	17·1 (20%)
IGA score=3/4, n (%)	117 (48%)	108 (44%)	115 (47%)
PASI score (0-72)	10·8 (11·7)	9·7 (11·7)	9·3 (9·8)
PsA-modified vdH-S score (0-528)	27·2 (42·2)	23·0 (37·8)	23·8 (37·8)
Patients with enthesitis, n (%)	170 (69%)	158 (64%)	178 (72%)
Enthesitis (LEI) score (1-6)[a]	3·0 (1·7)	2·6 (1·5)	2·8 (1·6)
Patients with dactylitis, n (%)	121 (49%)	111 (45%)	99 (40%)
Dactylitis score (1-60)[b]	8·6 (9·6)	8·0 (9·6)	8·4 (9·3)
SF-36			
PCS score	33·3 (7·1)	32·6 (7·9)	32·4 (7·0)

Table 1. Summary of baseline patient characteristics (FAS)

	Guselkumab 100 mg		Placebo
	q4w	q8w	
MCS score	48·4 (11·0)	47·4 (10·8)	47·2 (12·0)
Patients with prior apremilast use, n (%)	5 (2%)	4 (2%)	4 (2%)
Patients receiving at baseline, n (%)			
DMARDs	170 (69%)	170 (68%)	172 (70%)
Methotrexate	146 (60%)	141 (60%)	156 (63%)
Dose (mg/week)	15·6 (5·0)	15·3 (5·2)	15·2 (4·6)
Oral corticosteroids for PsA	46 (19%)	50 (20%)	49 (20%)
Dose equivalent to prednisone (mg/day)	7·0 (2·4)	6·8 (2·5)	7·8 (2·5)
NSAIDs for PsA	171 (70%)	165 (66%)	168 (68%)

Data presented are mean (SD) unless noted otherwise.

[a] Among patients with LEI enthesitis score at baseline (q4w, n=166; q8w, n=157; placebo, n=175)

[b] Among patients with dactylitis score at baseline (q4w, n=121; q8w, n=111; placebo, n=99)

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, TNF – tumor necrosis factor, VAS – visual analog scale, vdH-S - van der Heijde-Sharp

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Table 2. Summary of efficacy findings through Week24 (FAS[a])

	Guselkumab 100 mg		Placebo
	q4w	**q8w**	
Number of patients	245	248	246
Primary endpoint			
ACR20 response at Week24, n (%)	156 (64%)	159 (64%)	81 (33%)
% difference vs placebo (95% CI)	*31 (22, 39)*	*31 (23, 40)*	
US procedure[b]-adjusted p value	*<0·0001*	*<0·0001*	
Major secondary endpoints controlled by US procedure			
Psoriasis IGA response at Week24[c], n/N (%)	126/184 (68%)	124/176 (70%)	35/183 (19%)
% difference vs placebo (95% CI)	*50 (41, 58)*	*51 (42, 60)*	
US procedure[b]-adjusted p value	*<0·0001*	*<0·0001*	
HAQ-DI, LSmean (95% CI) change at Week24	-0·40 (-0·46, -0·34)	-0·37 (-0·43, -0·31)	-0·13 (-0·19, -0·07)
LSmean difference vs placebo (95% CI)	-0·27 (-0·35, -0·19)	*-0·24 (-0·32, -0·15)*	
US procedure[b]-adjusted p value	*<0·0001*	*<0·0001*	
PsA-modified vdH-S, Median (IQR) change at Week24	0·00 (-0·50–0·50)	0.00 (-0.50–1.00)	0·00 (0·00–1·00)
LSmean (95% CI) change at Week24	0·29 (-0·05, 0·63)	0·52 (0·18, 0·86)	0·95 (0·61, 1·29)
LSmean difference vs placebo (95% CI)	*-0.66 (-1.13, -0.19)*	*-0·43 (-0·90, 0·03)*	
US procedure[b]-adjusted p value	*0·0110*	*0·07*	
SF-36 PCS, LSmean (95% CI) change at Week24	7·04 (6·14, 7·94)	7·39 (6·50, 8·29)	3·42 (2·53, 4·32)
LSmean difference vs placebo (95% CI)	*3·62 (2·39, 4·85)*	*3·97 (2·75, 5·20)*	
US procedure[b]-adjusted p value	*0·0110*	*0·0110*	
SF-36 MCS, LSmean (95% CI) change at Week24	4·22 (3·14, 5·29)	4·17 (3·10, 5·23)	2·14 (1·07, 3·22)
LSmean difference vs placebo (95% CI)	*2·07 (0·60, 3·54)*	*2·02 (0·56, 3·49)*	
US procedure[b]-adjusted p value	*0·07*	*0·07*	
Major secondary endpoints not controlled by US procedure			

ACR20 response at Week16, n (%)	137 (56%)	137 (55%)	83 (34%)
% difference vs placebo (95% CI)	*22 (14, 31)*	*22 (13, 30)*	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	
ACR50 response at Week24, n (%)	81 (33%)	78 (32%)	35 (14%)
% difference vs placebo (95% CI)	*19 (12, 26)*	*17 (10, 24)*	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	
ACR50 response at Week16, n (%)	51 (21%)	71 (29%)	23 (9%)
% difference vs placebo (95% CI)	*12 (5, 18)*	*19 (13, 26)*	
Unadjusted p value[d]	*0·0004*	*<0·0001*	
ACR70 response at Week24, n (%)	32 (13%)	46 (18%)	10 (4%)
% difference vs placebo (95% CI)	*9 (4, 14)*	*14 (9, 20)*	
Unadjusted p value[d]	*0·0004*	*<0·0001*	
DAS28-CRP, LSmean (95% CI) change at Week24	-1·62 (-1·76, -1·49)	-1·59 (-1·72, -1·45)	-0·97 (-1·11, -0·84)
LSmean difference vs placebo (95% CI)	*-0·65 (-0·83, -0·47)*	*-0·61 (-0·80, -0·43)*	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	
Additional secondary endpoints not controlled by US procedure			
HAQ-DI improvement ≥0.35[e] **at Week24**, n/N (%)	128/228 (56%)	114/228 (50%)	74/236 (31%)
% difference vs placebo (95% CI)	24 (16, 33)	19 (10, 27)	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	
PASI75 response at Week24[c], n/N (%)	144/184 (78%)	139/176 (79%)	42/183 (23%)
% difference vs placebo (95% CI)	*55 (47, 64)*	*56 (47, 64)*	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	
PASI90 response at Week24[c]**,** n/N (%)	112/184 (61%)	121/176 (69%)	18/183 (10%)
% difference vs placebo (95% CI)	*51 (43, 59)*	*59 (51, 67)*	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	
PASI100 response at Week24[c], n/N (%)	82/184 (45%)	80/176 (46%)	5/183 (3%)
% difference vs placebo (95% CI)	*42 (35, 50)*	*42 (35, 50)*	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	

MDA response at Week24, n (%)	46 (19%)	62 (25%)	15 (6%)
% difference vs placebo (95% CI)	13 (7, 18)	19 (13, 25)	
Unadjusted p value[d]	*<0·0001*	*<0·0001*	

Patients meeting treatment-failure criteria (13 [5%] q4w, 12 [5%] q8w, and 17 [7%] placebo patients) were considered nonresponders for binary clinical endpoints and as having no improvement from baseline for continuous clinical endpoints. After application of treatment failure rules, there were limited instances of patients with missing data (ACR20: 2 q8w, 1 placebo; DAS28-CRP: 2 q8w, 3 placebo; IGA: 1 per group; HAQ-DI: 2 q8w, 2 placebo; vdH-S: 5 q4w, 1 q8w, 1 placebo; PCS/MCS: 2 q8w, 2 placebo; PASI: 1 per group; enthesitis/dactylitis resolution: 1 q8w, 1 placebo). Missing data were imputed as nonresponders for binary clinical endpoints; multiple imputation was used to impute missing data for continuous clinical endpoints assuming missing at random and using the predicted value from the Full Conditional Specification regression method (requiring 200 successful imputations) for any missing pattern. Each variable eligible for imputation was to be restricted to only impute within its possible range of values. 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), most current CRP value prior to randomization (<2·0/≥2·0 mg/dL), and baseline value as explanatory factors. Continuous radiographic endpoints were compared using an analysis of covariance test; missing data were assumed to be missing at random and were imputed using multiple imputation. The 95% CIs surrounding the % differences vs. placebo were determined based on the Wald statistic.

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

[b] See Figure S1A.

[c] Assessed in patients with ≥3% BSA 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 Week0.

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, 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, PASI/75/90/100 – Psoriasis Area and Severity Index 50/75/90/100% improvement, PCS – physical component summary, q4/8w – every 4/8 weeks, SF-36 – 36-item Short Form, PsA – psoriatic arthritis, US – United States, vdH-S – van der Heijde-Sharp

Table 3. Summary of Dactylitis and Enthesitis Results at Week 24 (FAS[a])

	Guselkumab 100 mg		Placebo
	q4w	q8w	
Major secondary endpoints controlled by US procedure[b]			
DISCOVER-1 + DISCOVER-2 Pooled			
Resolution of dactylitis, n/N (%)	101/159 (64%)	95/160 (59%)	65/154 (42%)
% difference vs placebo (95% CI)	*21 (10, 32)*	*18 (7, 29)*	
US procedure-adjusted p value	*0·0110*	*0·0301*	
Resolution of enthesitis, n/N (%)	109/243 (45%)	114/230 (50%)	75/255 (29%)
% difference vs placebo (95% CI)	*15 (6, 23)*	*20 (12, 28)*	
US procedure-adjusted p value	*0·0301*	*0·0301*	
Major secondary endpoints not controlled by US procedure[c]			
DISCOVER-1 + DISCOVER-2 Pooled			
Dactylitis score, LSmean (95% CI) change	-5·97 (-6·84, -5·11)	-6·10 (-6·92, -5·27)	-4·21 (-5·05, -3·36)
LSmean difference vs placebo (95% CI)	*-1·77 (-2·87, -0·66)*	*-1·89 (-2·99, -0·79)*	
Unadjusted p value	*0·0025*	*0·0020*	
Enthesitis LEI score, LSmean (95% CI) change	-1·59 (-1·79, -1·38)	-1·52 (-1·73, -1·31)	-1·02 (-1·22, -0·82)
LSmean difference vs placebo (95% CI)	*-0·57 (-0·83, -0·31)*	*-0·50 (-0·77, -0·23)*	
Unadjusted p value	*0·0017*	*0·0003*	

See Table 2 for further details of statistical testing.

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

[b] Per the preplanned statistical analysis plan, resolution of dactylitis and enthesitis data were combined across DISCOVER-1 and DISCOVER-2 as major secondary endpoints in the US testing procedure (See Figure S1A).

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

CI – confidence interval, FAS – full analysis set, LEI – Leeds Enthesitis Index, LS – least squares, q4/8w – every 4/8 weeks, US – United States

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

	Guselkumab 100 mg			Placebo
	q4w	**q8w**	**Combined**	
Number of patients	245	248	493	246
Mean length of follow up (weeks)	23·8	23·9	23.9	24·0
Mean number of administrations	5·9	5·9	5.9	5·9
Patients with 1 or more AE, n (%)	113 (46%)	114 (46%)	227 (46%)	100 (41%)
AEs occurring in ≥3% of patients in any group (in alphabetical order)				
Alanine aminotransferase increased	25 (10%)	15 (6%)	40 (8%)	11 (4%)
Aspartate aminotransferase increased	11 (4%)	14 (6%)	25 (5%)	6 (2%)
Bronchitis	10 (4%)	1 (<1%)	11 (2%)	3 (1%)
Nasopharyngitis	12 (5%)	10 (4%)	22 (4%)	9 (4%)
Upper respiratory tract infection	12 (5%)	6 (2%)	18 (4%)	8 (3%)
Patients with 1 or more SAE, n (%)	8 (3%)[a]	3 (1%)[b]	11 (2%)	7 (3%)[c]
Patients with AE resulting in study drug d/c, n (%)	6 (2%)[d]	2 (1%)[e]	8 (2%)	4 (2%)[f]
MACE, n (%)	1 (<1%)	0	1 (<1%)	0
Malignancy, n (%)	0	1 (<1%)	1 (<1%)	1 (<1%)
Patients with infections[g], n (%)	49 (20%)	40 (16%)	89 (18%)	45 (18%)
Serious infections	3 (1%)	1 (<1%)	4 (1%)	1 (<1%)
Patients with injection-site reactions, n (%)	3 (1%)	3 (1%)	6 (1%)	1 (<1%)
Patients with suicidal ideation, n (%)	1 (<1%)	0	1 (<1%)	1 (<1%)

[a] 1 patient each with acute hepatitis B, blue toe syndrome, femur fracture, influenza pneumonia, ischaemic stroke, lower limb fracture/metal poisoning, oophoritis, osteoarthritis.

[b] 1 patient each with ankle fracture, coronary artery disease, pyrexia.

[c] 1 patient each with clear cell renal cell carcinoma, isoniazid-induced liver injury, inflammatory bowel disease (suspected), obesity, post-procedural fistula, tubulointerstitial nephritis, unstable angina.

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

	Guselkumab 100 mg			Placebo
	q4w	q8w	Combined	

[d] 1 patient each with acute hepatitis B (*de novo*), allergic dermatitis, isoniazid-induced liver injury, ischaemic stroke, rhinovirus infection, and injection-site erythema/swelling/warmth.

[e] 1 patient each with rash, malignant melanoma in situ.

[f] 1 patient each with clear cell renal cell carcinoma, isoniazid-induced liver injury, inflammatory bowel disease, tubulointerstitial nephritis

[g] AEs identified by investigators as infections

AE – adverse event, d/c – discontinuation, MACE – major adverse cardiovascular event, q4/8w – every 4/8 weeks, SAE – serious adverse event, SAS – safety analysis set (treated patients)

577

Figure 1.

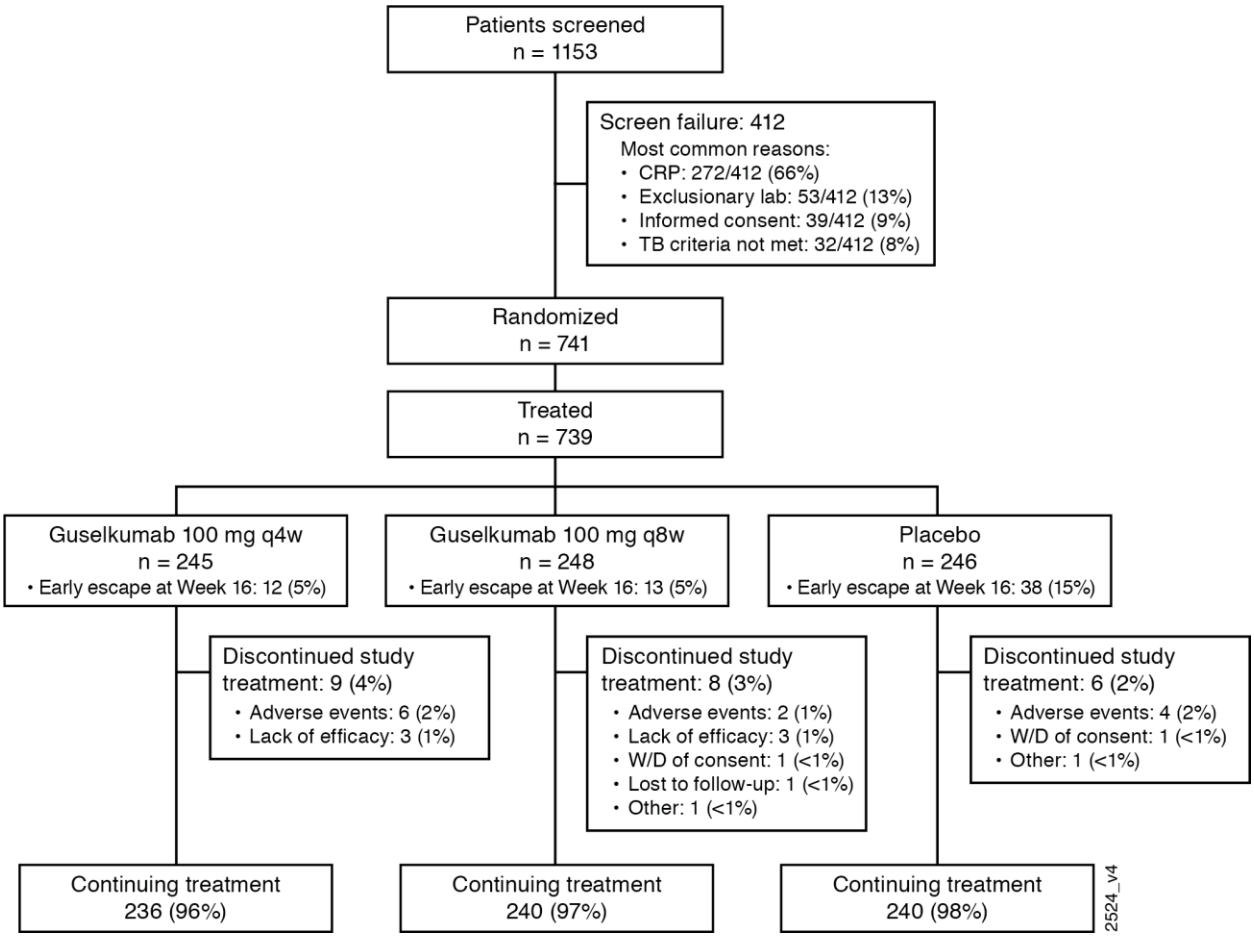
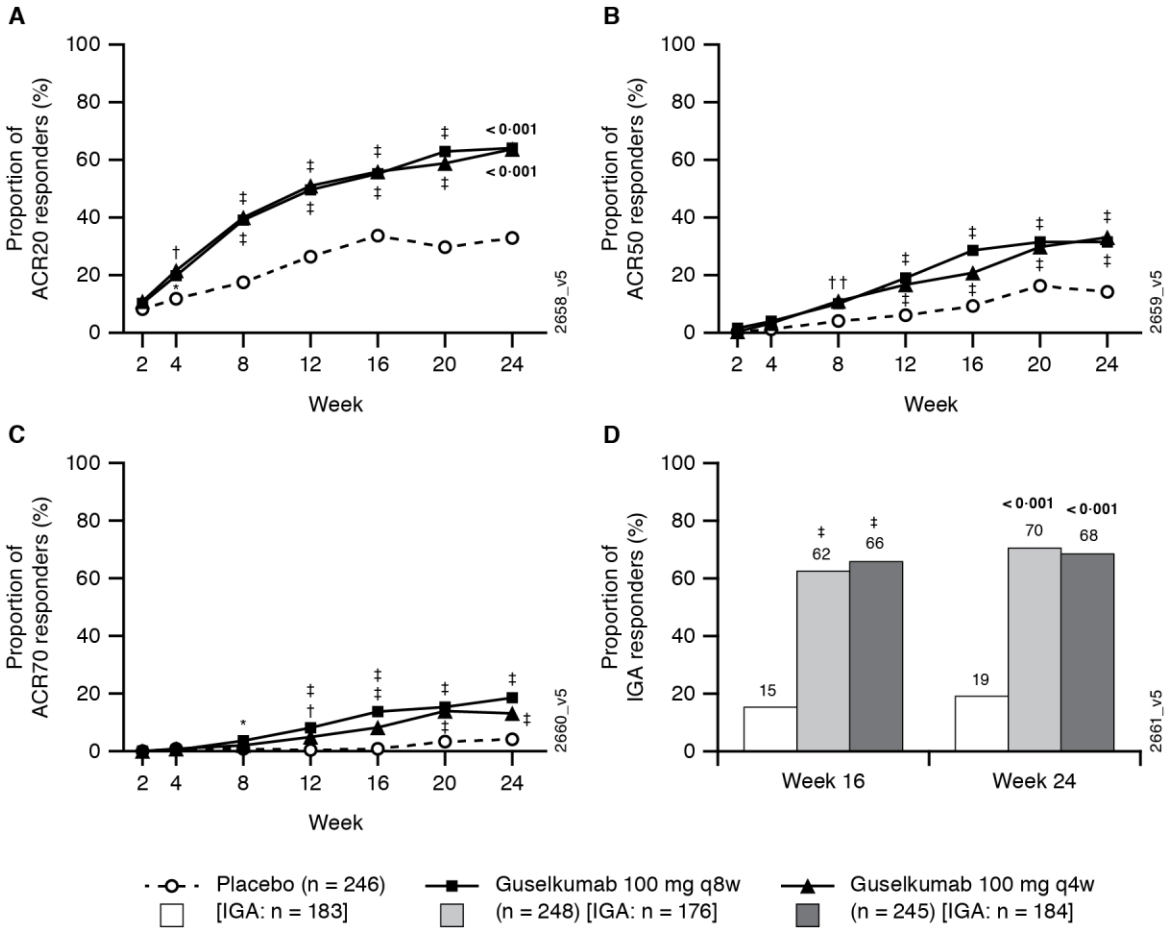

Patients screened
n = 1153
Screen failure: 412
Most common reasons:
• CRP: 272/412 (66%)
• Exclusionary lab: 53/412 (13%)
• Informed consent: 39/412 (9%)
• TB criteria not met: 32/412 (8%)
Randomized
n = 741
Treated
n = 739
Guselkumab 100 mg q4w
n = 245
• Early escape at Week 16: 12 (5%)
Guselkumab 100 mg q8w
n = 248
• Early escape at Week 16: 13 (5%)
Placebo
n = 246
• Early escape at Week 16: 38 (15%)
Discontinued study treatment: 9 (4%)
• Adverse events: 6 (2%)
• Lack of efficacy: 3 (1%)
Discontinued study treatment: 8 (3%)
• Adverse events: 2 (1%)
• Lack of efficacy: 3 (1%)
• W/D of consent: 1 (<1%)
• Lost to follow-up: 1 (<1%)
• Other: 1 (<1%)
Discontinued study treatment: 6 (2%)
• Adverse events: 4 (2%)
• W/D of consent: 1 (<1%)
• Other: 1 (<1%)
Continuing treatment
236 (96%)
Continuing treatment
240 (97%)
Continuing treatment
240 (98%)
2524_v4

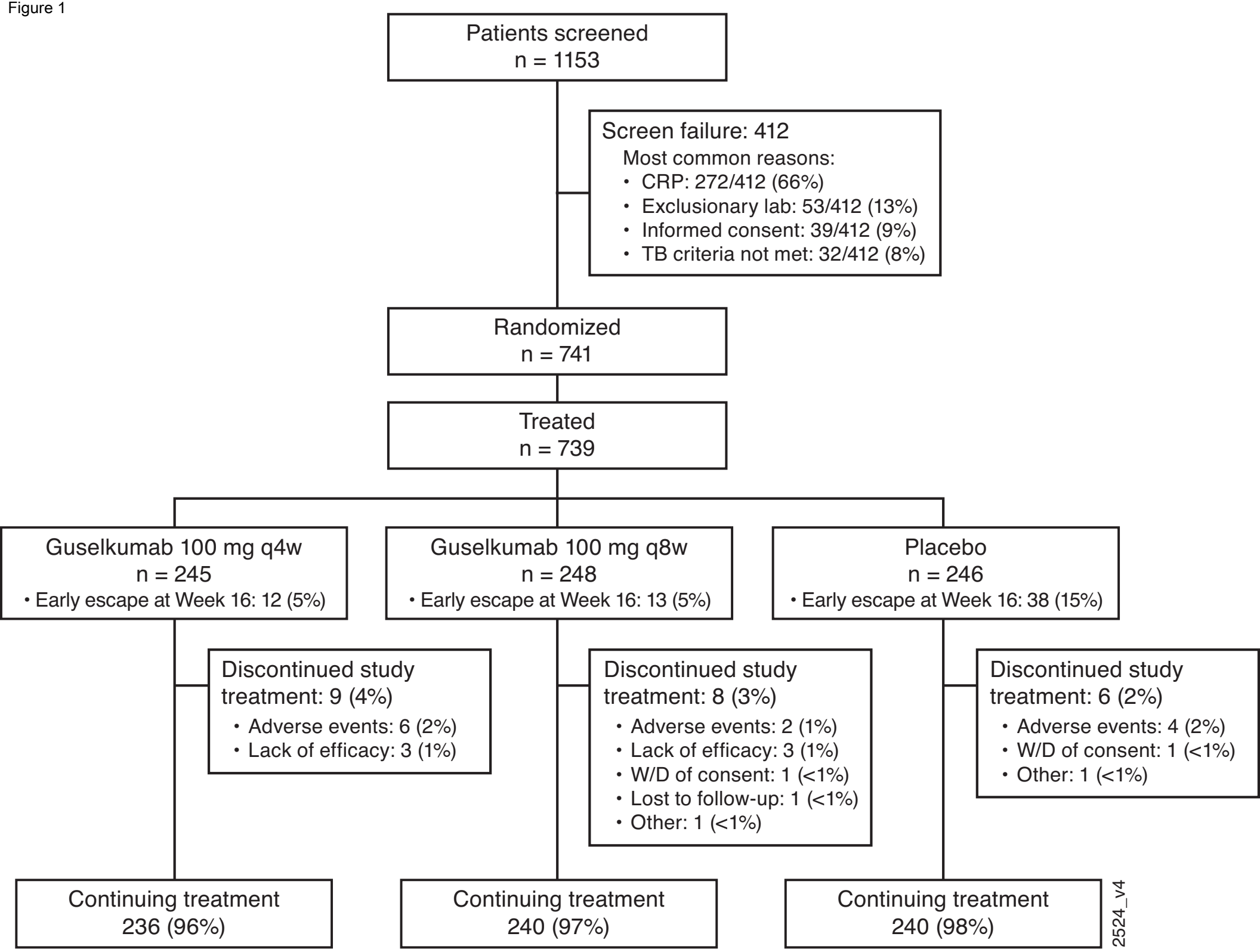
Figure 2.



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

Supplementary Material with revisions highlighted

Figure 1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• Adverse events: 4 (2%)
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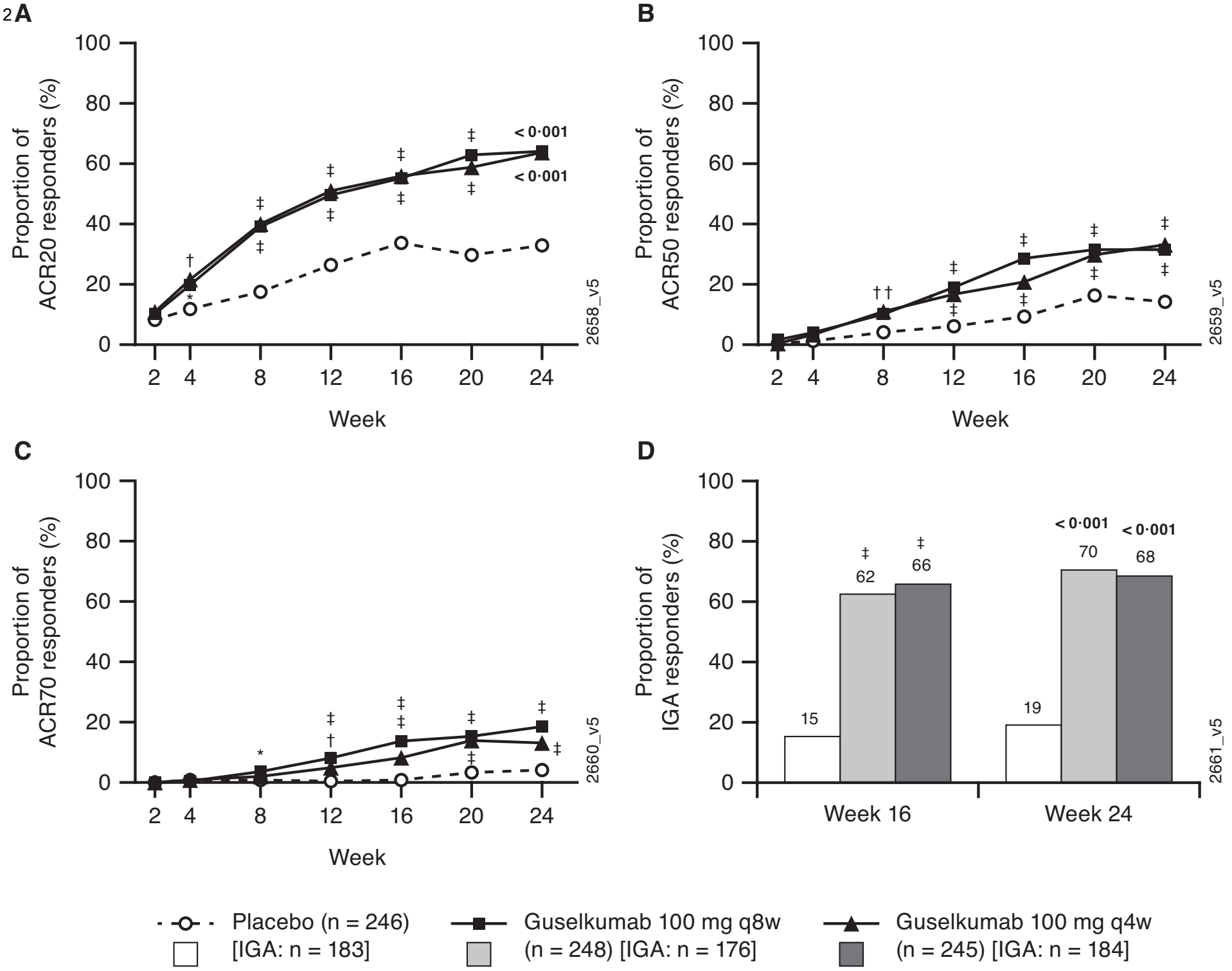
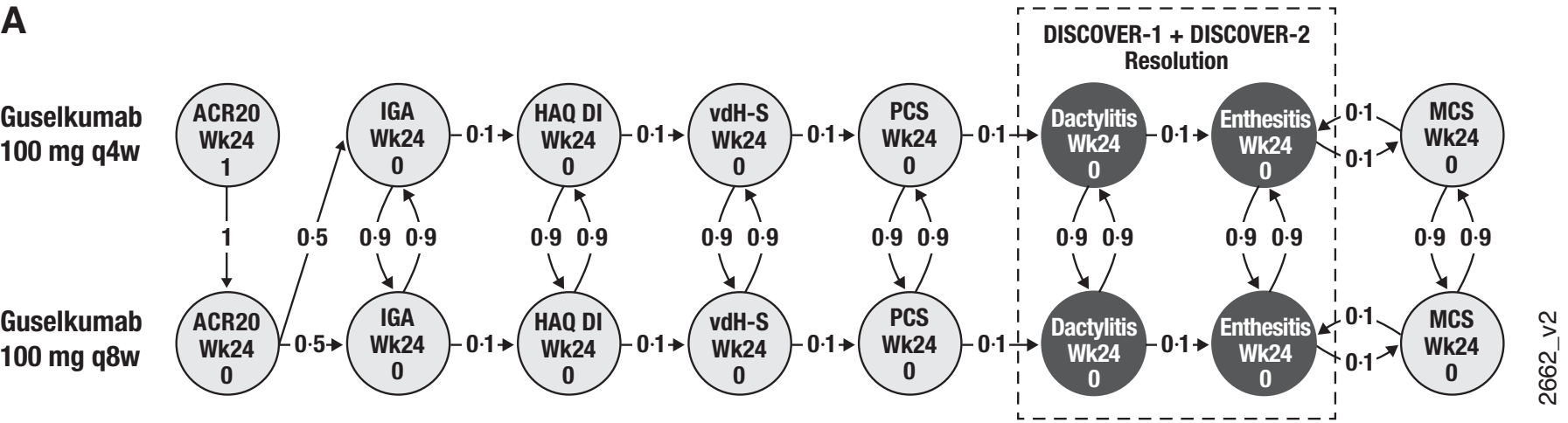
• Other: 1 (<1%)
Continuing treatment
236 (96%)
Continuing treatment
240 (97%)
Continuing treatment
240 (98%)
2524_v4

Figure 2



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

Figure S1


A
DISCOVER-1 + DISCOVER-2
Resolution
Guselkumab
100 mg q4w
Guselkumab
100 mg q8w
ACR20 Wk24 1
ACR20 Wk24 0
IGA Wk24 0
HAQ DI Wk24 0
vdH-S Wk24 0
PCS Wk24 0
Dactylitis Wk24 0
Enthesitis Wk24 0
MCS Wk24 0
0·1
0·5
0·9
1
2662_v2

B

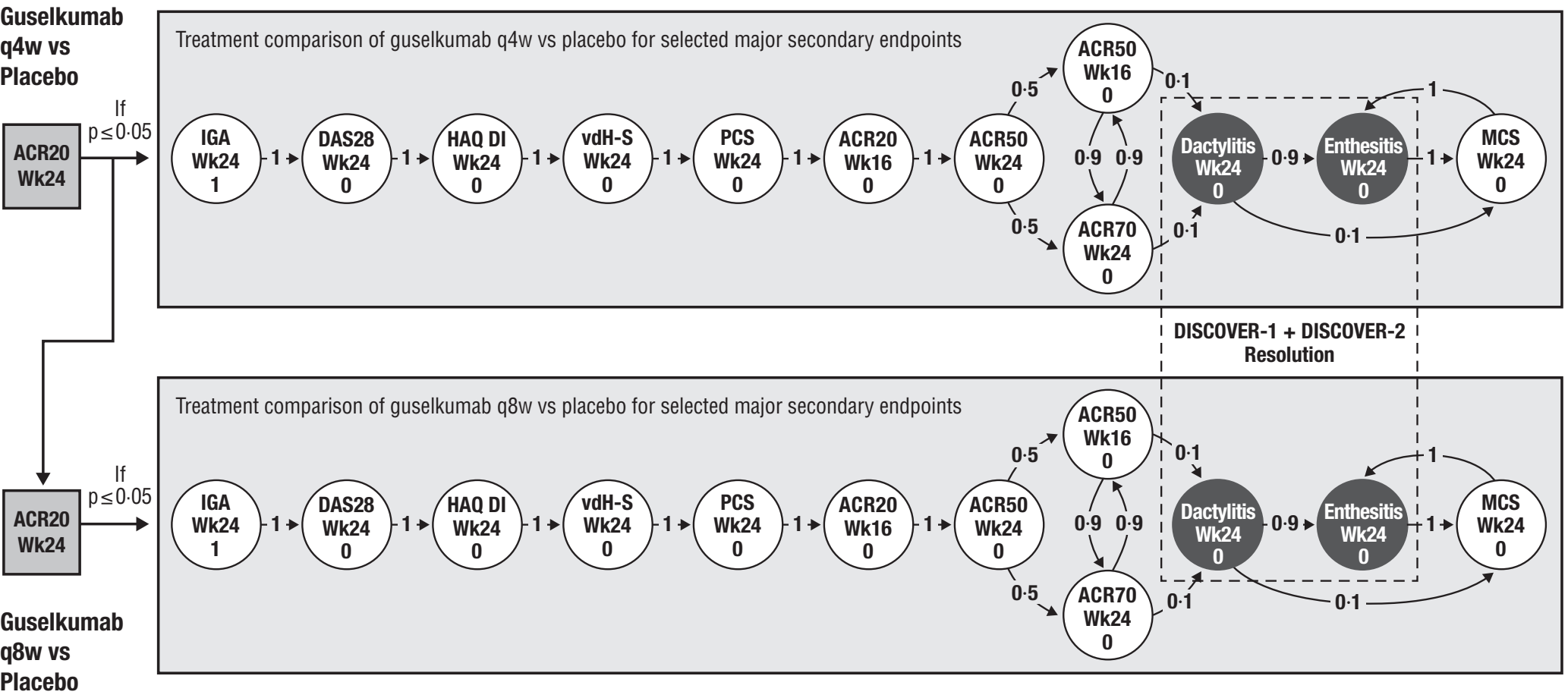
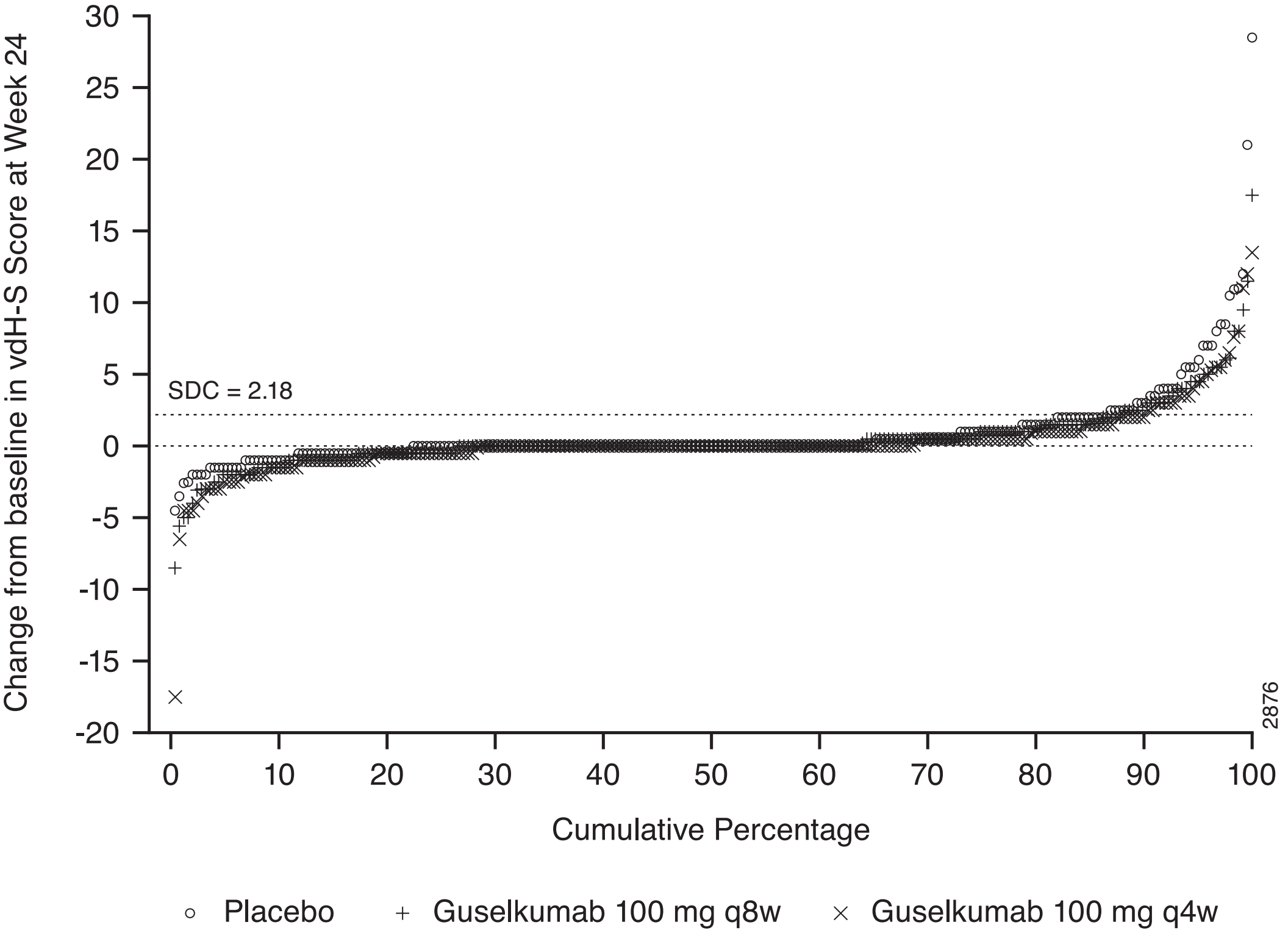

Guselkumab
q4w vs
Placebo
Guselkumab
q8w vs
Placebo
ACR20 Wk24
If
p≤0·05
Treatment comparison of guselkumab q4w vs placebo for selected major secondary endpoints
Treatment comparison of guselkumab q8w vs placebo for selected major secondary endpoints
IGA Wk24 1
DAS28 Wk24 0
HAQ DI Wk24 0
vdH-S Wk24 0
PCS Wk24 0
ACR20 Wk16 0
ACR50 Wk24 0
ACR50 Wk16 0
ACR70 Wk24 0
Dactylitis Wk24 0
Enthesitis Wk24 0
MCS Wk24 0
DISCOVER-1 + DISCOVER-2
Resolution
0·5
0·9
0·1
1
2663_v2

Figure S2


Change from baseline in vdH-S Score at Week 24
30
25
20
15
10
5
0
-5
-10
-15
-20
SDC = 2.18
2876
0
10
20
30
40
50
60
70
80
90
100
Cumulative Percentage
Placebo
Guselkumab 100 mg q8w
Guselkumab 100 mg q4w