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Efficacy of Guselkumab, a Monoclonal Antibody that Specifically Binds the p19 Subunit of IL-23, on Axial Involvement in Patients with Active PsA with Sacroiliitis: Post-hoc Analyses Through Week 52 from the Phase 3, Randomized, Double-blind, Placebo-controlled DISCOVER Studies

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Research in context.

Evidence before this study: We searched PubMed from October 24 - November 1, 2019 using terms related to axial psoriatic arthritis (PsA) pathogenesis and treatment, including "axial psoriatic arthritis," "guidelines," "assessment tools," "treatment," and "biologic." Interleukin (IL)-23 has been implicated in the pathogenesis of PsA. Guselkumab is a human monoclonal antibody specifically targeting the p19 subunit of IL-23. The efficacy and safety of guselkumab in patients with PsA were evaluated in two Phase 3, randomized, placebo-controlled studies, DISCOVER-1 and DISCOVER-2. Guselkumab-treated patients had greater improvements in the signs and symptoms of PsA compared with placebo, and the adverse events were consistent with the known safety profile of guselkumab in patients with plaque psoriasis.

Added value of this study: These post hoc analyses focused on the effect of guselkumab in DISCOVER-1 and DISCOVER-2 patients who were identified by the investigator as having axial symptoms and confirmation of sacroiliitis either prior to enrollment or at screening. In this pooled analysis, guselkumab-treated patients had greater improvements in assessments related to axial disease, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS), through week 24 compared with patients in the placebo group. Exploratory analyses suggest that inhibition of the IL-23 p19 subunit by guselkumab may be an effective therapy for both *HLA-B*27+* and *HLA-B*27-* patients with axial PsA.

Implications of all the available evidence: Because PsA is a heterogeneous disease that manifests in a variety of symptoms, treatment choice should consider all relevant domains of disease for each individual patient. This post hoc analysis suggests that therapies inhibiting the IL-23 p19 subunit may be effective in addressing axial symptoms in patients with PsA. A prospective study

with additional imaging evaluations and assessment tools specific to axial PsA is needed to fully explore this hypothesis.

Abstract

Background: Guselkumab was efficacious in reducing signs and symptoms of psoriatic arthritis (PsA) in DISCOVER-1 and DISCOVER-2. We evaluated the efficacy of guselkumab in post hoc analyses of PsA patients with imaging-confirmed sacroiliitis consistent with axial involvement.

Methods: In DISCOVER-1, 381 patients with active PsA (≥3 swollen joints, ≥3 tender joints; CRP ≥ 0·3mg/dL) and in DISCOVER-2, 739 patients with active PsA (≥5 swollen joints, ≥5 tender joints, CRP ≥ 0·6mg/dL) were randomized to guselkumab 100mg Q4W, guselkumab 100mg Q8W (Wk0, Wk4, then Q8W), or placebo. These pooled, post hoc analyses included patients judged to have axial disease by documented prior imaging or pelvic radiograph at screening consistent with sacroiliitis (confirmed by investigator). Efficacy assessments included BASDAI score, BASDAI50, modified BASDAI (mBASDAI; excluding peripheral joint pain), spinal pain, ASDAS-CRP score, and ASDAS responses of inactive disease, major improvement, and clinically important improvement.

Findings: Of the 1120 patients in the two studies, 312 (28%) (placebo, n=126; Q4W, n=128; Q8W, n=127) were included here. *HLA-B*27* status was assessed in 190 patients; 57 (30%) were *HLA-B*27*+, and 133 (70%) were *HLA-B*27*-. At week24, LS mean reductions from baseline in BASDAI were 2·7 in both guselkumab groups vs 1·3 in the placebo group; similar results were observed for mBASDAI and spinal pain. LS mean changes in ASDAS scores at week 24 were -1·4 in both guselkumab groups and -0·7 for placebo. At week24, 38% of Q4W and 40% of Q8W patients achieved BASDAI50 vs 19% of placebo patients; greater proportions of guselkumab-treated patients achieved ASDAS responses vs placebo. Treatment effect was observed at week24 independent of *HLA-B*27* status. These improvements were maintained through week52 in the guselkumab groups.

Interpretation: Guselkumab Q4W and Q8W provided sustained improvements in BASDAI and ASDAS (as early as Wk8) through week52 in patients with active PsA with imaging-confirmed sacroiliitis.

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INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, immune-mediated disease characterized by psoriatic skin lesions and peripheral arthritis,[1] and other musculoskeletal manifestations, including enthesitis, dactylitis, and axial involvement.[2] Axial involvement (i.e., inflammation of sacroiliac joints and/or spine),[3] has been estimated to occur in 5%-28% of patients with early disease[4] and over 40% of those with established disease.[5] In patients with PsA, approximately 20% have the major histocompatibility complex (MHC) class one surface antigen human leukocyte antigen (*HLA)-B*27*.[6] *HLA-B*27* in patients with PsA has previously been thought to be associated with axial involvement and more severe disease.[7]

Interleukin (IL)-23 is a critical upstream regulatory cytokine in the pathogenesis of PsA, and elevated levels of the p19 subunit of IL-23 have been found in synovial fluid from patients with PsA.[8] The IL-23/Th17 pathway is thought to be a critical element in the pathogenesis of PsA; in contrast, the role of IL-23 in axial spondyloarthritis (SpA) appears to be more nuanced, with data demonstrating that IL-12/23 and IL-23 inhibition are ineffective in treating ankylosing spondylitis (AS), the prototypical form of axial SpA.[9,10]

Guselkumab is a human monoclonal antibody that specifically targets the p19 subunit of IL-23. In the Phase 3 DISCOVER-1[11] and DISCOVER-2[12] studies, guselkumab was efficacious in reducing the signs and symptoms of active PsA in adult patients. In this post hoc analysis, we examined in depth the efficacy of guselkumab in endpoints related to axial involvement in patients who had imaging-confirmed sacroiliitis from the DISCOVER-1 and DISCOVER-2 studies.

METHODS

Patients and study designs

The DISCOVER-1[11] and DISCOVER-2[12]studies were randomized, placebo-controlled, Phase 3 trials of guselkumab in adult patients with active PsA. Patient eligibility criteria for both studies have been previously described in detail. In DISCOVER-1, patients were eligible if they had active PsA, defined as ≥3 swollen joints, ≥3 tender joints, and C-reactive protein (CRP) ≥0·3 mg/dL, despite standard therapies (ie, disease-modifying anti-rheumatic drugs [DMARDs], non-steroidal anti-inflammatory drugs [NSAIDs], or apremilast). Patients in DISCOVER-1 also had to have current (plaque ≥2 cm) or documented history of psoriasis, and up to 30% of patients could have received previous anti-tumor necrosis factor (TNF) therapy. In DISCOVER-2, patients had to have ≥5 swollen joints, ≥5 tender joints, and CRP ≥0·6 mg/dL; current (plaque ≥2 cm) or documented history of psoriasis; and either intolerance or inadequate response to non-biologic standard therapies as in DISCOVER-1. Prior anti-TNF therapy was not permitted in DISCOVER-2.

Patients in both studies were randomized (1:1:1) to receive subcutaneous injections of guselkumab 100 mg every 4 weeks, guselkumab 100 mg at weeks 0 and 4 and every 8 weeks thereafter, or placebo every 4 weeks with crossover to guselkumab 100 mg every 4 weeks at week 24. At week 16, patients in any treatment group with <5% improvement in both the tender and swollen joint counts were allowed to initiate or increase the dose of NSAIDs, oral corticosteroids, or non-biologic DMARDs (consistent with doses allowed in the inclusion criteria).

These studies were conducted in accordance with the Declaration of Helsinki. The protocols were approved by the Institutional Review Board or Ethics Committee at each site. All patients gave written informed consent, with an additional consent provided for voluntary genetic testing.

Patients were included in this post-hoc analysis if they were identified by the investigator as having PsA with axial involvement (yes/no) and evidence of sacroiliitis on either prior radiograph or magnetic resonance imaging (MRI) of sacroiliac joints (DISCOVER-1 and DISCOVER-2) or pelvic radiograph at screening (DISCOVER-2 only). Sacroiliitis was assessed by the investigators, and all radiographs were reviewed locally.

Assessments

Symptoms related to axial involvement were assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[13] and the Ankylosing Spondylitis Disease Activity Score using CRP (ASDAS). The BASDAI is a self-assessment of the degree of the following symptoms on a visual analog scale (VAS; 0-10 cm): Question 1) fatigue, Q2) spinal pain, Q3) joint pain, Q4) pain at entheseal sites, Q5) severity of morning stiffness, and Q6) duration of morning stiffness. Question 2, related to spine and hip pain, was also analyzed independently. A modified BASDAI (mBASDAI)[14] excluding the question on peripheral joint pain (Q3) was also utilized to reduce the effect of peripheral joint disease on the total score. The mBASDAI was developed to focus more on axial-related disease activity without influence from peripheral symptoms and has been shown to correlate with physician and patient global disease activity scores.[14] The ASDAS is a composite score, originally developed for patients with AS, that includes measures of back pain, duration of morning stiffness, patient global assessment, peripheral pain and swelling, and CRP.[15] The proportions of patients achieving ≥50% improvement in BASDAI score (BASDAI 50), ASDAS [16] clinically important improvement

(change ≥1·1),[16] ASDAS major improvement (change ≥2·0),[16] ASDAS inactive disease (score <1·3),[16] and ASDAS score <2·1 (low disease activity)[17] were also determined. General PsA disease activity was assessed using the Disease Activity Index for Psoriatic Arthritis (DAPSA).[18]

Blood samples for genetic testing were obtained from patients who provided additional consent. Samples from these patients were analyzed for the presence of *HLA-B*27* using RNA sequencing methods previously described by Buchkovich, et al.[19] Patients were classified as *HLA-B*27* positive if they had ≥ 1 *HLA-B*27* allele.[20]

Statistical methods

Results were summarized by randomized treatment group in patients who received ≥1 study agent administration. Least square (LS) mean changes from baseline (Mixed-Effect Repeated Measures model) in BASDAI (prespecified analysis through week 24), mBASDAI, BASDAI components (including Question 2 on spinal pain), and ASDAS scores and corresponding 95% confidence intervals were analyzed at weeks 8, 16, 24, and 52. The model for LS mean changes through week 24 included all available data from week 0-24; the model for LS mean changes at week 52 included data from week 0 and week 52. Additionally, in patients who were *HLA-B*27* positive and *HLA-B*27* negative, the model for LS mean change in BASDAI and ASDAS scores were adjusted for baseline PsA disease duration, CRP level, and respective baseline score (BASDAI or ASDAS).

The proportions of patients achieving ≥50% improvement in BASDAI score (BASDAI 50; in patients with baseline score >0) and ASDAS responses were also determined by treatment group and by *HLA-B*27* status. For response variables through week 24, patients who met the treatment failure criteria[11,12] were classified as nonresponders from that point onward, and

patients with missing data were also classified as nonresponders; after week 24, patients with missing data were classified as nonresponders. For continuous endpoints through week 24, patients who met the treatment failure criteria were assigned a change of 0 from baseline for subsequent timepoints. After week 24, patients who discontinued the study agent early (prior to week 48 for DISCOVER-1; prior to week 52 for DISCOVER-2) for any reason were assigned a change of 0 for subsequent timepoints; all other missing data were not imputed from week 0 to week 52. Through week 24, p values were calculated using the Cochran–Mantel–Haenszel test or Fisher's exact test for dichotomous endpoints; p values were not adjusted for multiplicity. Therefore, the p-values displayed are nominal, and statistical significance has not been established. No treatment group comparisons were performed after week 24 (placebo crossover). The change in BASDAI score and proportion of patients with a BASDAI 50 response as well as the imputation rules for missing data were prespecified in each study; the pooled analyses here were post hoc. The mBASDAI and ASDAS endpoints were calculated post hoc.

Role of the funding source

Authors who were employees of the study sponsor participated in the study design and collection, analysis, and interpretation of the data. A medical writer employed by the study sponsor provided writing and editorial support. All authors reviewed and approved the manuscript for submission. All authors had full access to the full data in the study and accept responsibility to submit for publication.

RESULTS

Patients

A total of 1,120 patients were randomized and received study agent in DISCOVER-1[11] (n=381) and DISCOVER-2[12] (n=739) (appendix p 10). Of these, 312 patients were identified by the investigator as having PsA with axial involvement and either documented imaging confirmation of sacroiliitis in the past (n= 211) or pelvic radiographic confirmation of sacroiliitis at screening (n = 101) and were included in this analysis (placebo, n = 118; guselkumab 100 mg every 4 weeks, n = 103; guselkumab 100 mg every 8 weeks, n = 91). Baseline demographic and disease characteristics of all randomized patients were generally similar among the treatment groups within each study,[11,12] and characteristics for the patients in this analysis (appendix p 1) were generally consistent with those for the total study populations in DISCOVER-1 and DISCOVER-2. Among patients included in this analysis, 61% were male, the mean PsA disease duration was 5·7 years, and the mean BASDAI, mBASDAI, and ASDAS scores at baseline were 6·5, 6·5, and 3·9, respectively. Baseline characteristics were generally similar for patients who did (n=214) and did not receive concomitant methotrexate (MTX) (n = 98) (appendix pp 2-3).

Of the 312 patients included in this analysis, 190 had available data for determining *HLA-B*27* status; of these, 57 (30%) were *HLA-B*27* positive and 133 (70%) were *HLA-B*27* negative (appendix pp 4-5). Patients who were *HLA-B*27*+ tended to have longer PsA disease duration, higher baseline CRP values, and more severe disease as assessed by BASDAI and ASDAS scores compared with *HLA-B*27*- patients.

Assessments of axial symptoms

At week 24, patients in the every-4-weeks and every-8-weeks guselkumab groups had greater improvements in LS mean changes in BASDAI (-2·7 and -2·7, respectively) compared with placebo (-1·3) (difference [95% CI] = -1·3 [-1·9, -0·7] and -1·3 [-1·9, -0·7], respectively) (Figure 1). Guselkumab-treated patients also had greater LS mean changes in mBASDAI scores, all six BASDAI components, including spinal pain (BASDAI question 2), and ASDAS scores at week 24 compared with placebo (Figure 1, Table 1). A treatment effect was observed in both guselkumab groups as early as week 8 (the earliest post-baseline assessment available) and at week 16. These improvements in the guselkumab groups were maintained at week 52 (Figure 3 and appendix p 6). At week 52, following crossover from placebo to guselkumab 100 mg every 4 weeks at week 24, LS mean changes in BASDAI, mBASDAI, spinal pain, and ASDAS scores were similar to those in the guselkumab-randomized groups (Figure 3 and appendix p 6).

Greater proportions of patients in the guselkumab every-4-weeks group and the guselkumab every-8-weeks group achieved a BASDAI 50 response at week 24 compared with placebo (38% and 40% vs 19%;p = 0·0044 and p = 0·0054, respectively; difference [95% CI] = 19% [7, 31] and 21% [9, 34]), with a treatment effect observed as early as week 8 (Figure 2). At week 52, BASDAI 50 response rates were maintained in the guselkumab groups, with a similar response rate in the placebo crossover patients (Figure 3). Similar results were also observed for the proportions of patient achieving ASDAS clinically important improvement, major improvement, and inactive disease (Figure 2, Figure 3). Greater proportions of patients in the guselkumab every-4-week group (35%, p<0·0014) and every-8-week group (40%, p<0·0006) had an ASDAS score <2·1 compared with placebo (16%) at week 24. Similar trends in improvements in BASDAI and ASDAS endpoints were observed in patients who did and did not receive

concomitant MTX; however, these data should be interpreted with caution due to the low number of patients receiving concomitant MTX (appendix pp 7, 8).

*HLA-B*27* status was available for 190 patients (*HLA-B*27+*, n = 57 [30%]; *HLA-B*27-*, n = 133 [70%]). Among these patients, LS mean changes in BASDAI, spinal pain, mBASDAI, and ASDAS scores at week 24 were greater for guselkumab-treated patients compared with placebo in both *HLA-B*27+* and *HLA-B*27-* patients (Figure 4). Similar results were observed for LS mean changes in the individual BASDAI questions in both *HLA-B*27+* and *HLA-B*27-* patients (appendix p 9). Likewise, response rates for BASDAI 50, ASDAS clinically important improvement, ASDAS major improvement, and ASDAS inactive disease were greater in the guselkumab groups compared with placebo in both *HLA-B*27+* and *HLA-B*27-* patients (Figure 4). At week 52, trends in BASDAI and ASDAS endpoints were similar for *HLA-B*27+* and *HLA-B*27-* patients and consistent with the overall study population (appendix p 11).

DISCUSSION

In the Phase 3 DISCOVER-1[11] and DISCOVER-2[12] studies, guselkumab-treated patients had greater improvements in the overall signs and symptoms of PsA at week 24 compared with placebo. This post hoc analysis of pooled data from these two studies suggests that guselkumab improved axial symptoms in patients with PsA who had evidence of sacroiliitis. Across both studies, patients in the guselkumab groups had greater improvements in disease indices used to assess axial disease, BASDAI (including the individual component on spinal pain), mBASDAI (excluding peripheral joint pain), and ASDAS at week 24 compared with placebo. Among patients randomized to guselkumab at baseline, efficacy was sustained through 1 year. Among placebo-crossover patients, efficacy measures at week 52 were similar to those in the

guselkumab-randomized groups. Improvements in the mBASDAI and individual components of the BASDAI, as well as the ASDAS, suggest that guselkumab may be efficacious in reducing axial symptoms in this cohort. Similar trends were observed for patients who did (n=214) and did not (n=98) receive concomitant MTX, which is consistent with the clinical efficacy results reported for the overall study populations.[11,12] However, it is difficult to make comparisons between these two subgroups of patients due to the relatively small number of patients.

PsA is a heterogeneous disease that can present with a variety of symptoms involving both the musculoskeletal system (i.e., peripheral arthritis, inflammatory back pain, enthesitis, dactylitis) as well as skin and nail disease.[21] The Group for Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and the Assessment of SpondyloArthritis international Society (ASAS) are collaborating to develop a consensus definition of axial PsA in a prospective study.[22] Current treatment recommendations from GRAPPA,[23] the American College of Rheumatology/National Psoriasis Foundation,[24] and the European League Against Rheumatism[25] are centered on choosing the optimal treatment to address individual patient's constellation of symptoms across the multiple domains of PsA, including axial disease.

*HLA-B*27* has been associated with axial inflammation and more severe disease in patients with PsA.[7] Exploratory analyses of efficacy in *HLA-B*27+* and *HLA-B*27-* patients suggested that guselkumab-treated patients had greater improvements in axial symptoms at week 24 vs placebo regardless of *HLA-B*27* status. While the *HLA-B*27* allele is associated with axial PsA, the prevalence is much lower in these patients than in patients with AS,[4] and other *HLA-B* alleles have been identified as genetic risk factors for axial PsA.[4] Only 61% of patients in this analysis had available samples for assessing *HLA-B*27* status, thus these results should be interpreted with caution.

The signs and symptoms of axial PsA and AS also have distinct features. PsA patients are generally older and more often female compared with AS patients. AS is characterized by the presence of inflammatory back pain, while patients with axial PsA may often be asymptomatic despite having radiographic evidence of axial disease.[4] Additionally, in patients with axial PsA, peripheral involvement is more common,[26] and sacroiliitis tends be less severe and more asymmetrical compared with AS.[4] Syndesmophytes are common to both axial PsA and AS; however, radiographic differences in morphology have been observed, with syndesmophytes in axial PsA being nonmarginal[4] and having a larger volume[3] in comparison with AS. The IL-23/Th17 pathway has been an area of research in many chronic, inflammatory diseases, including PsA and AS. A Phase 3 study demonstrated that secukinumab (anti-IL-17) was efficacious in axial PsA patients as assessed by ASAS20 response.[27] Despite observations indicating that this pathway was critical to the pathogenesis of AS, clinical trials of ustekinumab[10] and risankizumab,[9] which target this pathway, did not demonstrate efficacy in AS. Phenotypic diversity in axial PsA suggest distinct disease processes in comparison to AS and therefore, there may be differences in the response to therapy. It has been previously suggested that the pathogenesis of AS may involve a pathway for IL-17 production independent of IL-23 stimulation of Th17 cells.[28]

These results are limited by the post-hoc nature of the analysis. All patients had to have evidence of peripheral arthritis to be eligible for inclusion in either DISCOVER-1 or DISCOVER-2. However, assessments of axial disease were limited to those patients identified by the investigator as having axial symptoms. Thus, the studies were not powered for this subgroup of patients, and randomization was not stratified by symptoms of axial disease; thus, there could be differences in the disease characteristics due to chance. Additionally, assessment of response

among patients who had previously received anti-TNF therapy was precluded by the limited number of patients (n=23).

In DISCOVER-1 and DISCOVER-2, radiographic sacroiliitis was assessed locally by the investigators, without a central reader, as only present or absent on prior imaging (either by radiograph or MRI) or with pelvic radiograph at screening, without grading for severity or the details of how the images were interpreted. Imaging confirmation was limited to evaluation of the sacroiliac joint; thus, changes in other regions of the spine were not captured. It should be noted that radiographs are the first-line imaging tool for detecting sacroiliitis that is attributable to the structural damage, while MRI is the imaging tool for detection of both active inflammatory and structural changes.[29] However, interpretation of both radiographs and MRI is subjective, with diagnosis of spondylitis complicated by evidence of sacroiliitis in healthy subjects and a substantial discordance between local and central readers assessing the presence of sacroiliitis by MRI observed in another study.[30] The clinical importance of this discordance on classification and diagnosis remains unclear.[30]

Although the BASDAI and ASDAS were initially developed for axial spondyloarthritis, they are often used to evaluate axial symptoms in PsA patients due to the lack of assessment tools specific for axial PsA. Improvements in BASDAI and ASDAS scores could have been influenced by extra-axial symptoms, including peripheral arthritis and enthesitis.[14] The interpretation of the current analyses is limited by the lack of post-baseline imaging to assess changes during treatment. Assessment of SpondyloArthritis International Society (ASAS) responses could not be assessed in these patients, as the required component of BASFI was not collected in either study. In addition, the number of patients with available samples for assessing *HLA-B*27* status was relatively small, which limits the generalizability of the results.

In conclusion, these results suggest that guselkumab may be an effective therapy for patients with PsA who have axial symptoms, and that response to guselkumab therapy can be achieved for both *HLA-B*27+* and *HLA-B*27-* patients. A prospective, randomized, controlled trial of guselkumab in patients with PsA with axial involvement is required to test this hypothesis further.

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Contributors

PJM, DP, XB, SDC, APK, ECH, XLX, SS, PA, BZ, MS, CSK, AD contributed to the concept and study design. ECH, XLX, SS, KS collected the data. PSH, SDC, APK, ECH, SS, PA, KS, DvdH analyzed the data. PJM, PSH, DDG, DP, XB, SDC, APK, ECH, XLX, SS, PA, BZ, KS, MS, CSK, AD, DvdH interpreted the data, revised the manuscript, and approved the final version for submission. PJM and SDC have accessed and verified the underlying data.

Declaration of Interests

PJM has received grants and personal fees from AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, Pfizer, SUN, and UCB, and personal fees from Boehringer Ingelheim and GlaxoSmithKline.

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APK, ECH, XLX, SS, PA, BZ and KS are employees of Janssen Research & Development, LLC (a subsidiary of Johnson & Johnson) and own Johnson & Johnson stock or stock options.

SDC is an employee of Janssen Scientific Affairs, LLC (a subsidiary of Johnson & Johnson) and owns Johnson & Johnson stock or stock options.

MS and CSK are employees of Janssen Global Services, LLC (a subsidiary of Johnson & Johnson) and own Johnson & Johnson stock or stock options.

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

Figure Legends

Figure 1. Least squares (LS) mean changes in BASDAI (A), mBASDAI (B), spinal pain (C), and ASDAS (D) through week 24. ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath ankylosing spondylitis disease activity index; mBASDAI, modified BASDAI excluding question 3. LS mean changes for BASDAI endpoints were calculated using Mixed-Effect Repeated Measures where the number of patients included in the model = 95 for guselkumab every 4 weeks, 83 for guselkumab every 8 weeks, and 110 for placebo. LS mean changes for ASDAS scores were calculated using Mixed-Effect Repeated Measures where the number of patients included in the model = 95 for guselkumab every 4 weeks, 82 for guselkumab every 8 weeks, and 110 for placebo.

Figure 2. Proportion of patients achieving a BASDAI 50 response (A), clinically important improvement in ASDAS (B), major improvement in ASDAS (C), and ASDAS inactive disease (D) at weeks 8, 16, and 24. ASDAS = ankylosing spondylitis disease activity score. BASDAI 50 = ≥50% improvement in Bath ankylosing spondylitis disease activity index. For BASDAI 50: guselkumab 100 mg every 4 weeks, n = 95; guselkumab 100 mg every 8 weeks, n = 84; placebo, n = 110. For ASDAS responses: guselkumab 100 mg every 4 weeks, n = 103; guselkumab 100 mg every 8 weeks, n = 91; placebo, n = 118.

Figure 3. Least squares (LS) mean changes in BASDAI, mBASDAI, spinal pain, and ASDAS (A) and the proportion of patients achieving a BASDAI 50 response, clinically important improvement in ASDAS, major improvement in ASDAS, and ASDAS inactive disease (B) at week 52. ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath ankylosing spondylitis disease activity index; BASDAI 50 = ≥50% improvement in Bath ankylosing spondylitis disease activity index; mBASDAI, modified BASDAI excluding question 3. LS

mean changes for BASDAI and ASDAS endpoints were calculated using Mixed-Effect Repeated Measures where the number of patients included in the model = 95 for guselkumab every 4 weeks, 82 for guselkumab every 8 weeks, and 110 for placebo. For BASDAI 50: guselkumab 100 mg every 4 weeks, n = 95; guselkumab 100 mg every 8 weeks, n = 84; placebo, n = 110. For ASDAS responses: guselkumab 100 mg every 4 weeks, n = 103; guselkumab 100 mg every 8 weeks, n = 91; placebo, n = 118.

Figure 4. Least squares (LS) mean change in BASDAI (A), mBASDAI (B), and ASDAS (C) and proportions of patients achieving a BASDAI 50 response (D), clinically important improvement in ASDAS (E), major improvement in ASDAS (F), and ASDAS inactive disease (G) at week 24 by *HLA-B*27* status at baseline. ASDAS = ankylosing spondylitis disease activity score. BASDAI = Bath ankylosing spondylitis disease activity index. BASDAI 50 = ≥50% improvement in Bath ankylosing spondylitis disease activity index. HLA = human leukocyte antigen. mBASDAI = modified BASDAI excluding question 3 (peripheral joint pain). *HLA-B*27+*: LS mean changes for BASDAI and ASDAS endpoints were calculated using Mixed-Effect Repeated Measures where the number of patients included in the model = 20 for guselkumab every 4 weeks, 16 for guselkumab every 8 weeks, and 17 for placebo. For BASDAI 50: guselkumab every 4 weeks, n = 20, guselkumab every 8 weeks, n = 16, placebo, n = 17; for ASDAS response: guselkumab every 4 weeks, n = 22, guselkumab every 8 weeks, n = 17, placebo, n = 18.

*HLA-B*27-*: LS mean changes for BASDAI and ASDAS endpoints were calculated using Mixed-Effect Repeated Measures where the number of patients included in the model = 36 for guselkumab every 4 weeks, 33 for guselkumab every 8 weeks, and 48 for placebo. For BASDAI 50: guselkumab every 4 weeks, n = 36, guselkumab every 8 weeks, n = 34, placebo, n = 48; for

ASDAS responses: guselkumab every 4 weeks, n = 41, guselkumab every 8 weeks, n = 39, placebo, n = 53.