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ORIGINAL RESEARCH

Guselkumab provides durable improvement across psoriatic arthritis disease domains: post hoc analysis of a phase 3, randomised, double-blind, placebo-controlled study

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ABSTRACT

Objective Evaluate long-term guselkumab effectiveness across Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)-recognised domains/related conditions of psoriatic arthritis (PsA).

Methods Post hoc analyses used data from DISCOVER-2 (NCT03158285) biologic/Janus-kinase inhibitor-naïve participants with active PsA (≥5 swollen/≥5 tender joints, C-reactive protein ≥0.6 mg/dL), randomised (1:1:1) to guselkumab every 4 or 8 weeks (Q4W/Q8W) or placebo with crossover to guselkumab. Outcomes aligned with key GRAPPA-recognised domains of overall disease activity, peripheral arthritis, axial disease, enthesitis/dactylitis and skin psoriasis (nail psoriasis was not evaluated). PsA-related conditions (inflammatory bowel disease (IBD)/uveitis) were assessed via adverse events through W112. Least squares mean changes from baseline through W100 in continuous outcomes employed repeated measures mixed-effects models adjusting for baseline scores. Binary measure response rates were determined with non-responder imputation for missing data.

Results 442/493 (90%) of guselkumab-randomised patients completed treatment through W100. Following early reductions in disease activity with guselkumab, durable improvements were observed across key PsA domains (swollen/tender joints, psoriasis, spinal pain, enthesitis/dactylitis) through W100. Response rates of therapeutically relevant targets generally increased through W100 with guselkumab Q4W/Q8W: Disease Activity Index for PsA low disease activity (LDA) 62%/59%, enthesitis resolution 61%/70%, dactylitis resolution 72%/83%, 100% improvement in Psoriasis Area and Severity Index 59%/53%, Psoriatic Arthritis Disease Activity Score LDA 51%/49% and minimal disease activity

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Guidelines from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommend that psoriatic arthritis (PsA) therapy achieves lowest possible levels of disease activity across six domains and consider the related conditions of inflammatory bowel disease and uveitis.

⇒ Guselkumab, a fully human monoclonal interleukin-23p19-subunit inhibitor, has previously been shown to significantly improve signs and symptoms of PsA by Week 24, with improvements sustained or further increased through Week 52.

WHAT THIS STUDY ADDS

⇒ Treatment with guselkumab every 4 or 8 weeks provided early and durable improvements in all assessed GRAPPA-recognised PsA domains through 2 years of treatment, resulting in considerable proportions of patients achieving low levels of joint disease activity, enthesitis/dactylitis resolution, complete skin clearance and low/minimal levels of overall disease activity.

⇒ Through Week 100 among guselkumab-randomised patients, no exacerbation or new onset of inflammatory bowel disease occurred, and a single occurrence of uveitis (iridocyclitis) was reported.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given the multidomain nature of PsA, as well as the comprehensive and durable effectiveness and favourable safety profile of guselkumab shown in the current analysis, guselkumab represents an important treatment option to address key GRAPPA-recognised therapeutic goals for patients with PsA.

38%/40%. Through W112, no cases of IBD developed among guselkumab-randomised patients and one case of uveitis was reported.

Conclusion In biologic-naïve patients with active PsA, guselkumab provided early and durable improvements in key GRAPPA-recognised domains through 2 years, with substantial proportions achieving important treatment targets.

INTRODUCTION

Psoriatic arthritis (PsA) is a clinically heterogeneous, progressive, chronic inflammatory disease involving the skin and musculoskeletal systems with potential to irreversibly damage joints and impair health-related quality of life (HRQoL).[1–3] PsA affects approximately 30% of individuals with psoriasis[4] and has an estimated worldwide prevalence between 0.3% and 1%.[5]

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recognises six disease domains (peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis and psoriatic nail disease), two related conditions (inflammatory bowel disease (IBD) and uveitis)[6] and several comorbidities (eg, obesity, metabolic syndrome, diabetes mellitus) of PsA, all of which impact patients' HRQoL.[7] Current international guidelines for PsA put forward optimising functional status, improving HRQoL, preventing structural damage and minimising complications both from untreated active disease and from treatment as key therapeutic goals.[6 8 9] Furthermore, the GRAPPA guidelines specifically highlight achieving the lowest possible level of disease activity across all disease domains affected in an individual patient.[6]

Guselkumab, a fully human monoclonal antibody that is an interleukin (IL)-23p19-subunit inhibitor, is approved to treat adults with moderate-to-severe plaque psoriasis, as well as those with active PsA. In two separate Phase 3 randomised trials in PsA (DISCOVER-1 and DISCOVER-2), participants treated with guselkumab, either every 4 (Q4W) or 8 weeks (Q8W), were reported to have significantly higher rates of response or greater mean improvements in joint signs and symptoms, enthesitis and dactylitis, skin disease, physical function and HRQoL at Week 24 compared with the placebo group.[10 11] In pooled analyses of these studies, guselkumab provided robust and sustained benefits through 1 year of treatment as measured by composite disease activity indices (including Disease Activity Index for Psoriatic Arthritis (DAPSA), Psoriatic Arthritis Disease Activity Score (PASDAS) and minimal disease activity (MDA)), of which the latter two incorporate multiple domains recognised by GRAPPA.[12] In the DISCOVER-2 study of biologic-naïve patients with highly active PsA, improvements with guselkumab treatment were found to be durable through 2 years of follow-up across multiple disease domains.[13]

Informed by the GRAPPA treatment goal of achieving the lowest possible level of disease activity in all affected disease domains, in the context of minimal side effects and knowledge that residual disease burdens patients and impairs function,[14] the objective of the present post hoc analysis was to evaluate the long-term (Week 100) effectiveness of guselkumab across GRAPPA-identified PsA domains and related conditions assessed in DISCOVER-2. These included peripheral arthritis, axial symptoms, enthesitis, dactylitis and skin disease, as well as the incidence of new onset or exacerbation of IBD and uveitis.

METHODS

Full details of the study design and eligibility criteria for DISCOVER-2 (NCT03158285) have been reported.[11] Briefly, this was a Phase 3, randomised, double-blind, placebo-controlled trial of guselkumab in adults with active PsA, conducted between July 2017 and November 2020. The trial was carried out at 118 sites across 13 countries in Europe, Asia and the USA. The DISCOVER-2 study conformed with the Declaration of Helsinki and Good Clinical Practice guidelines and obtained all necessary ethics approvals.

Eligible patients had active PsA (swollen joint count (SJC) ≥5, tender joint count (TJC) ≥5 and serum C-reactive protein (CRP) level ≥0.6 mg/dL) and an inadequate response to, or intolerance of, standard non-biological treatment. Patients could not have previously received biologics or Janus-kinase inhibitors. Study participants were randomised (1:1:1) to receive subcutaneous injections of guselkumab 100 mg Q4W; guselkumab 100 mg at Week 0, Week 4, then Q8W; or placebo with crossover to guselkumab 100 mg Q4W at Week 24 through Week 100.

Outcome measures

Efficacy assessments selected for the current post hoc analysis aligned with GRAPPA-identified domains, that is, peripheral arthritis (66-joint SJC, 68-joint TJC), axial symptoms (patient-reported spinal pain; Bath Ankylosing Spondylitis Disease Activity Index Question 2[15]), enthesitis (Leeds Enthesitis Index (LEI)[16]), dactylitis (Dactylitis Severity Score (DSS)[17]) and skin psoriasis (Psoriasis Area and Severity Index (PASI),[18] Investigator's Global Assessment of psoriasis (IGA),[19] Patient's Assessment of Skin Disease on a Visual Analogue Scale (Skin VAS)). As longitudinal nail disease assessments were not performed in DISCOVER-2, nail psoriasis was not considered in the present analysis.

Composite scores were also assessed as measures of joint and overall disease activity. Peripheral joint disease activity was assessed with DAPSA,[20] calculated via the addition of SJC, TJC, patient assessment of arthritis disease activity on a VAS, patient assessment of joint pain on a VAS and CRP level, as well as clinical DAPSA (cDAPSA),[21] a simplified version of DAPSA that omits CRP. PASDAS[22] is a multidomain measure of overall disease activity that combines SJC, TJC, tender dactylitis count, LEI, serum CRP concentration, physician global assessment of disease activity, patient global assessment

of disease activity and Short Form (SF)-36 physical component summary (PCS) score. MDA[23] is defined as meeting ≥5 of the following seven criteria: TJC ≤1, SJC ≤1, PASI ≤1, patient pain VAS ≤15, patient global assessment of disease activity VAS ≤20 mm, Health Assessment Questionnaire-Disability Index (HAQ-DI) score ≤0.5 and ≤1 tender entheseal points.

Continuous outcomes evaluated were changes from baseline through Week 100 in SJC, TJC, spinal pain (in patients with axial symptoms and imaging-confirmed sacroiliitis[24 25]), LEI (in patients with baseline enthesitis), DSS (in patients with baseline dactylitis), Skin VAS and PASI (in patients with ≥3% psoriatic body surface area (BSA) and IGA score ≥2 at baseline).

Achievement of therapeutic endpoints was assessed with DAPSA low disease activity (LDA; score ≤14) or remission (≤4); cDAPSA LDA (≤13) or remission (≤4); resolution of enthesitis (LEI=0) in patients with enthesitis at baseline; resolution of dactylitis (DSS=0) in patients with dactylitis at baseline; PASDAS LDA (≤3.2) or remission (≤1.9); and MDA. Skin assessments, evaluated among patients with ≥3% BSA and IGA score ≥2 at baseline, included Skin VAS ≤15 mm (among those with baseline Skin VAS >15 mm), PASI improvement ≥90% or 100% (PASI 90/100) and IGA = 0 or 1 with ≥2-grade improvement from baseline. Certain results presented herein, including the proportions of patients achieving MDA at Week 24, and enthesitis and dactylitis resolution, PASI 90, PASI 100 and IGA 0/1 response at Weeks 24, 52 and 100, have been previously reported[11 13] and are shown here to provide context surrounding the patterns of group-level effectiveness through Week 100.

Adverse events (AEs) were assessed through Week 112 of DISCOVER-2. The occurrence of IBD (defined by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class preferred terms (PTs) of Crohn's disease, ulcerative colitis or IBD) and uveitis (defined by MedDRA PTs of uveitis, iridocyclitis or iritis), or their exacerbation in patients with IBD or uveitis at baseline, was determined following blinded review of the reported AEs.

Statistical methods

Analyses were limited to patients randomised to guselkumab. Least squares mean (LSM) changes from baseline to available visits between Week 8 and Week 100 in SJC, TJC, spinal pain, LEI, DSS and Skin VAS were analysed by repeated measures generalised linear mixed-effects models adjusting for respective baseline score, time, guselkumab dosing regimen and the interaction of time with guselkumab regimen. Although SJC and TJC were first assessed at Week 4, Week 8 was used as the first time point of assessment to standardise time frames across outcome measures, except for PASI, which was first evaluated at Week 16. Radar plots, reported logarithmically due to scale differences in the outcomes assessed, were used to describe changes in SJC, TJC, spinal pain, LEI, DSS and Skin VAS at each time point for each guselkumab regimen. Achievement of therapeutic endpoints was summarised by descriptive statistics using non-responder imputation (NRI) for missing data applied at rates approximating study discontinuations (<10%). Composite scores with missing component data were imputed as non-response. The incidence and exacerbation of IBD and uveitis were summarised descriptively. All analyses were performed using the Statistical Analysis System (SAS) statistical software package, V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient disposition and baseline characteristics

Among the 493 patients who were randomised to guselkumab in DISCOVER-2, 245 and 248 received guselkumab 100 mg Q4W and Q8W, respectively. The additional 246 patients randomised to placebo were not included in these post hoc analyses assessing long-term effectiveness. Baseline demographic and PsA disease characteristics were generally similar across the treatment groups.[11]

Table 1 summarises the baseline characteristics of patients randomised to and treated with guselkumab. Mean PASDAS, DAPSA and cDAPSA scores were consistent with highly active PsA. Approximately one-third of patients were identified by the investigator as having axial symptoms and had imaging-confirmed sacroiliitis, nearly half had dactylitis, two-thirds had enthesitis and three-quarters had BSA ≥3% and IGA ≥2. Approximately 60% and 20% of patients reported concomitant use of methotrexate and corticosteroids, respectively, at baseline (table 1).

Among patients randomised to guselkumab, 93% completed study treatment at Week 52 and 90% did so through Week 100. Patients were analysed by intention-to-treat, and those who discontinued were imputed as non-responders.

Overall patterns of improvement

Substantial LSM improvements were observed as early as Week 8 for each endpoint assessed (with the exception of PASI, first assessed at Week 16) (figure 1). A significant decrease in mean PASI score was observed with both guselkumab regimens at Week 16 ($p<0.0001$), the first time point assessed, which was subsequently maintained through Week 100. In all other PsA domains assessed, specifically SJC, TJC, spinal pain, LEI, DSS and Skin VAS, mean improvements among patients treated with either guselkumab Q4W or Q8W were continuously enhanced through Week 100 (figure 1; online supplemental figure 1).

Similarly, therapeutic endpoint response rates increased over time in all key PsA domains and were generally maintained or continued to increase between Week 52 and Week 100 of guselkumab treatment, regardless of dosing regimen (table 2). Adding to the considerable improvements between baseline and the first analysis time point, notable increases in endpoint response rates

Table 1 Baseline patient and disease characteristics

	Guselkumab 100 mg	
	Q4W (N=245)	Q8W (N=248)
Demographics		
Age, years	45.9 (11.5)	44.9 (11.9)
Male	142 (58)	129 (52)
Body weight, kg	85.8 (19.5)	83.0 (19.3)
PsA characteristics		
PsA disease duration, years	5.5 (5.9)	5.1 (5.5)
CRP, mg/dL	1.2 (0.6–2.3)	1.3 (0.7–2.5)
SJC (0–66)	12.9 (7.8)	11.7 (6.8)
TJC (0–68)	22.4 (13.5)	19.8 (11.9)
Patients with axial symptoms*	82 (33)	68 (27)
Spinal pain (0–10)†	6.5 (2.2)	6.6 (2.2)
Patients with enthesitis	170 (69)	158 (64)
LEI (0–6)‡	3.0 (1.7)	2.6 (1.5)
Patients with dactylitis	121 (49)	111 (45)
DSS (0–60)§	8.6 (9.6)	8.0 (9.6)
BSA, %	18.2 (20.0)	17.0 (21.0)
Skin VAS (0–100 mm)	60.9 (22.6)	59.2 (25.3)
PASI (0–72)	10.8 (11.7)	9.7 (11.7)
Patients with BSA ≥3% and IGA ≥2	184 (75.1)	176 (71.0)
Skin VAS (0–100 mm)¶	64.4 (20.3)	65.3 (21.9)
PASI (0–72)¶	13.8 (12.0)	12.9 (12.5)
DAPSA**	49.7 (21.1)	46.3 (19.4)
cDAPSA††	47.9 (20.9)	44.3 (18.8)
PASDAS (0-10)‡‡	6.6 (1.09)	6.6 (1.09)
HAQ-DI (0–3)	1.2 (0.6)	1.3 (0.6)
Concomitant medications		
Methotrexate	146 (60)	141 (57)
Oral corticosteroids	46 (19)	50 (20)

Data are n (%), mean (SD) or median (IQR).
*Patients were identified by the investigator as having axial symptoms and had imaging-confirmed sacroiliitis.
†Among patients with axial symptoms and available spinal pain score at baseline (Q4W group n=79 and Q8W n=62).
‡Among patients with enthesitis and available LEI score at baseline (Q4W group n=166 and Q8W n=157).
§Among patients with dactylitis and available DSS at baseline (Q4W group n=121 and Q8W n=111).
¶Among patients with BSA ≥3% and IGA score ≥2 at baseline (Q4W group n=184 and Q8W n=176).
**DAPSA disease activity states include remission (≤4), low disease activity (>4 and ≤14), moderate disease activity (>14 and ≤28) and high disease activity (>28). [21]
††cDAPSA disease activity states include remission (≤4), low disease activity (>4 and ≤13), moderate disease activity (>13 and ≤27) and high disease activity (>27).[21]
‡‡PASDAS disease activity states include very low (≤1.9), low (>1.9 to ≤3.2) moderate (score >3.2 to <5.4) and high disease activity (≥5.4).[17 22]
BSA, body surface area; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; CRP, C-reactive protein; DAPSA, Disease Activity Index for Psoriatic Arthritis; DSS, dactylitis severity score; HAQ-DI, Health Assessment Questionnaire-Disability Index; IGA, Investigator's Global Assessment of psoriasis; LEI, Leeds Enthesitis Index; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; SJC, swollen joint count; TJC, tender joint count; VAS, Visual Analogue Scale.

between consecutive visits were also observed later in the follow-up period. For most endpoints assessed, in one or both guselkumab regimens, the between-time point increase in response rate was highest or second highest for the period between Week 24 and Week 52 (table 2).

Arthritis improvement

For both guselkumab regimens, significant reductions in SJC and TJC were observed by Week 8 (all p<0.0001), the first analysis time point, and improvements at the group level continued through Week 100 (figure 1; online supplemental figure 1). In patients receiving guselkumab Q4W, the LSM changes from baseline to Week 24 and Week 100, respectively, were −8.4 and −10.4 for SJC and −11.2 and −15.5 for TJC. The same pattern was seen in Q8W-randomised patients at Week 24 and Week 100, with LSM changes of −8.4 and −10.3 for SJC and −10.9 and −15.5 for TJC, respectively (figure 1). These improvements represent 69%–88% reductions in the mean joint counts by Week 100.

Skin psoriasis improvement

For both skin assessments (Skin VAS and PASI), a significant improvement was seen in patients with ≥3% BSA and IGA score ≥2 at baseline at the first time point of assessment (Weeks 8 and 16, respectively; both p<0.0001; figure 1). With both guselkumab regimens, LSM improvements in Skin VAS continued through Week 100, and the significant LSM decreases in PASI scores recorded as of the first assessment time point were maintained through Week 100 (figure 1; online supplemental figure 1).

Among Q4W-randomised patients, the respective LSM changes from baseline to Week 24 and Week 100 were −39.0 and −46.1 for Skin VAS and −12.1 and −12.7 for PASI. Similarly, in Q8W-randomised patients, changes averaged −39.8 and −47.2 for Skin VAS and −12.0 and −12.4 for PASI at these time points (figure 1). Overall, these results indicate a 72%–96% improvement in symptoms of skin psoriasis by Week 100. Achievement of PASI 90 response by patients receiving guselkumab Q4W and Q8W (54% and 55% at Week 16, 77% and 74% at Week 52, respectively) and IGA score of 0 or 1 and a ≥2 grade improvement (66% and 62% at Week 16, 80% and 74% at Week 52, respectively) showed consistent durability of response across guselkumab dosing regimens and was maintained through Week 100 (table 2). Between Week 16 and Week 100, the proportions of patients achieving skin clearance (PASI 100) increased by 25% and 26% with guselkumab Q4W and Q8W, respectively (table 2).

Among patients with Skin VAS >15 mm, BSA ≥3% and IGA ≥2 at baseline, achievement of Skin VAS ≤15 mm was seen in 14% and 22% of patients receiving Q4W and Q8W, respectively, by Week 8; by Week 100, 53% and 56%, respectively, achieved minimal skin involvement (table 2).

Spinal pain improvement

Among patients with axial symptoms in the guselkumab Q4W (33%) and Q8W (27%) groups, significant improvement in spinal pain was recorded as of Week 8 (first time point assessed; both p<0.0001). Between subsequent follow-up visits through Week 100, LSM improvements were either maintained or further enhanced (figure 1, online supplemental figure 1). The respective LSM

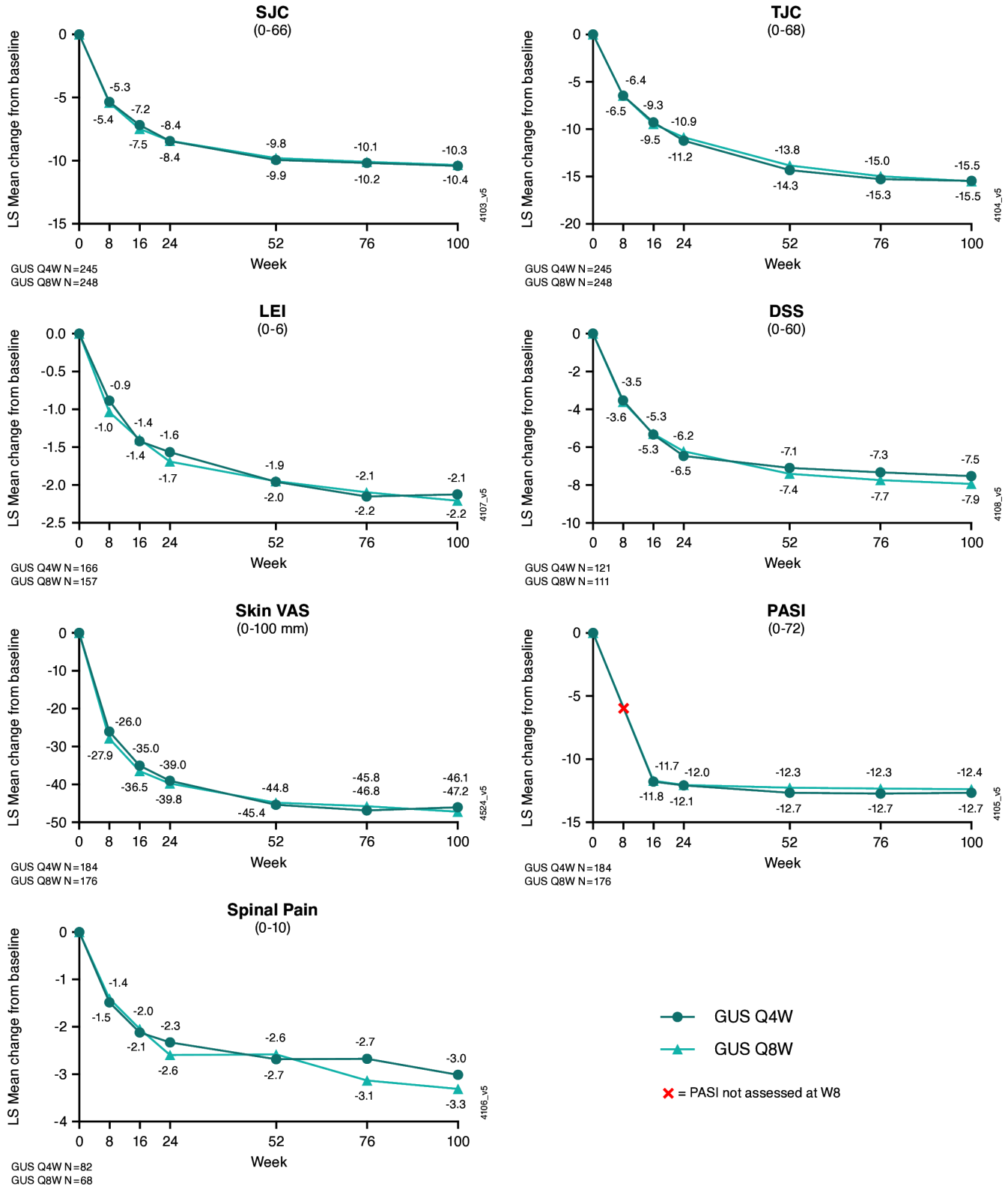

Figure 1 Least squares mean changes from baseline over time in continuous outcomes assessing key PsA domains among guselkumab-randomised patients. All changes from baseline were significant at the 0.05 level. x=PASI not assessed at Week 8. N represents patients with an available score at baseline. LEI was analysed among patients with enthesitis and available LEI score at baseline. DSS was analysed among patients with dactylitis and available DSS at baseline. Skin VAS and PASI were analysed among patients with body surface area ≥3% and Investigator's Global Assessment of psoriasis score ≥2 at baseline. Spinal pain was analysed among patients with axial symptoms and imaging-confirmed sacroiliitis. DSS, Dactylitis Severity Score; GUS, guselkumab; LEI, Leeds Enthesitis Index; LS, least squares; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; SJC, swollen joint count; TJC, tender joint count; VAS, Visual Analogue Scale.

Table 2 Achievement of therapeutic targets among guselkumab-randomised patients over time (NRI)

	Guselkumab 100 mg Q4W					Guselkumab 100 mg Q8W				
Week	8	16	24	52	100	8	16	24	52	100
DAPSA										
LDA (≤14)	43 (18)	61 (25)	88 (36)	125 (51)	151 (62)	43 (17)	79 (32)	97 (39)	130 (52)	147 (59)
Remission (≤4)	5 (2)	12 (5)	21 (9)	39 (16)	52 (21)	3 (1)	15 (6)	23 (9)	46 (19)	60 (24)
cDAPSA										
LDA (≤13)*	41 (17)	58 (24)	89 (36)	125 (51)	150 (61)	44 (18)	75 (30)	95 (38)	131 (53)	147 (60)
Remission (≤4)	5 (2)	13 (5)	29 (12)	44 (18)	59 (24)	4 (2)	19 (8)	25 (10)	53 (21)	65 (26)
Enthesitis resolution†	45 (27)	66 (40)	71 (43)	93 (56)	102 (61)	50 (32)	75 (48)	87 (55)	97 (62)	110 (70)
Dactylitis resolution†	39 (32)	64 (53)	80 (66)	90 (74)	87 (72)	34 (31)	51 (46)	66 (59)	86 (77)	92 (83)
Skin response										
PASI 90‡§	–	100 (54)	114 (62)	142 (77)	136 (74)	–	97 (55)	121 (69)	131 (74)	123 (70)
PASI 100‡§	–	62 (34)	83 (45)	106 (58)	109 (59)	–	48 (27)	80 (45)	93 (53)	94 (53)
IGA 0/1 response‡§¶	–	122 (66)	127 (69)	147 (80)	140 (76)	–	110 (62)	124 (70)	131 (74)	126 (72)
Skin VAS ≤15 mm§**	26 (14)	58 (32)	68 (37)	93 (51)	96 (53)	38 (22)	61 (36)	71 (42)	88 (52)	95 (56)
PASDAS										
LDA (≤3.2)	25 (10)	44 (18)	58 (24)	105 (43)	126 (51)	28 (11)	56 (23)	76 (31)	106 (43)	122 (49)
Remission (≤1.9)	4 (2)	11 (4)	22 (9)	36 (15)	51 (21)	2 (1)	16 (6)	23 (9)	52 (21)	58 (23)
MDA*	8 (3)	33 (14)	47 (19)	83 (34)	93 (38)	9 (4)	42 (17)	63 (25)	77 (31)	100 (40)
	Absolute change in response rate from previous visit									
	±1 to <5		+5 to <10		+10 to <15		+15 to <20		≥20	

Number (%) of guselkumab-randomised patients (N=493) achieving therapeutic endpoints over time (NRI) are shown.
*Excludes patients who achieved endpoint at baseline.
†Among patients with domain at baseline.
‡PASI and IGA not assessed at Week 8.
§Among patients with baseline BSA ≥3% and IGA ≥2 .
¶IGA skin response=score of 0 or 1 and ≥2 grade improvement from baseline.
**Patients with Skin VAS >15mm at baseline.
BSA, body surface area; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; DAPSA, Disease Activity Index for Psoriatic Arthritis; IGA, Investigator's Global Assessment of psoriasis; LDA, low disease activity; MDA, minimal disease activity; NRI, non-responder imputation; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI 90/100, ≥90% improvement/100% improvement in Psoriasis Area and Severity Index; Q4W, every 4 weeks; Q8W, every 8 weeks; VAS, Visual Analogue Scale.

changes in spinal pain from baseline to Week 24 and Week 100 were −2.3 and −3.0 among patients treated with guselkumab Q4W and −2.6 and −3.3 for those receiving the Q8W regimen, representing 46%–50% improvement by Week 100 (figure 1).

Enthesitis and dactylitis improvement

Among patients with baseline enthesitis (Q4W: 69%; Q8W: 64%) and those with baseline dactylitis (Q4W: 49%; Q8W: 45%), significant improvements in both enthesitis and dactylitis were recorded as of the first follow-up assessment at Week 8 (both p<0.0001), regardless of guselkumab regimen. Mean improvements were either maintained or further increased between subsequent follow-up visits through Week 100 (figure 1; online supplemental figure 1).

In affected patients randomised to the Q4W regimen, the respective LSM changes from baseline to Week 24 and Week 100 were −1.6 and −2.1 for LEI and −6.5 and −7.5 for DSS. Consistent improvements were seen in Q8W-randomised patients, with respective LSM changes from baseline to Week 24 and Week 100 of −1.7 and −2.2 for LEI and −6.2 and −7.9 for DSS (figure 1).

Among patients with enthesitis at baseline, the proportions achieving enthesitis resolution (LEI=0) increased continuously through Week 100 in both guselkumab groups, whereby response rates were 27% and 32% at Week 8, 56% and 62% at Week 52, and 61% and 70% at Week 100 for guselkumab Q4W and Q8W, respectively (table 2).

Proportions of patients achieving dactylitis resolution (DSS=0), among those with baseline dactylitis, increased through Week 52 and were then maintained or continued to improve through Week 100 (32%, 74% and 72% at Weeks 8, 52 and 100 with guselkumab Q4W and 31%, 77% and 83% with guselkumab Q8W; table 2).

Composite responses

Despite mean composite scores indicative of high disease activity at baseline, NRI response rates for DAPSA LDA/

remission, cDAPSA LDA/remission, PASDAS LDA/remission and MDA increased continuously through Week 100, regardless of guselkumab regimen (table 2). More precisely, among patients in the Q4W group, respective response rates at Weeks 8, 24, 52 and 100 for DAPSA LDA/remission were 18%/2%, 36%/9%, 51%/16% and 62%/21%; for PASDAS LDA/remission were 10%/2%, 24%/9%, 43%/15% and 51%/21%; and MDA were 3%, 19%, 34% and 38%. A similar pattern of achievement was seen with the Q8W dosing regimen, with response rates at Weeks 8, 24, 52 and 100 of 17%/1%, 39%/9%, 52%/19% and 59%/24% for DAPSA LDA/remission; 11%/1%, 31%/9%, 43%/21% and 49%/23% for PASDAS LDA/remission; and 4%, 25%, 31% and 40% for MDA, respectively. Results for cDAPSA were comparable to those obtained for DAPSA for both guselkumab regimens (table 2).

PsA-related conditions

Among guselkumab-randomised patients, one patient had a history of IBD and four had a history of uveitis; none of these patients experienced an AE of exacerbation of these conditions through Week 112. Furthermore, through Week 112, no guselkumab-randomised patient developed IBD. One case of uveitis was reported (Q8W group; Week 70) that resolved following treatment with steroidal and non-steroidal anti-inflammatory drugs, and the patient continued guselkumab with no dosing changes.

DISCUSSION

Previous analyses of the Phase 3 DISCOVER-1 and DISCOVER-2 studies have demonstrated that, compared with placebo, treatment with guselkumab was associated with significantly greater improvements in signs and symptoms of PsA by Week 24[10 11] and that these improvements were sustained through Week 52[26 27] and, in DISCOVER-2, Week 100.[13] In the current post hoc analysis of DISCOVER-2 data, each guselkumab regimen provided both early significant improvements and continuously increasing response rates through Week 100 in key GRAPPA-recognised domains. The robust improvements in skin disease seen in these patients with PsA were highly durable over time. Importantly, early significant improvements in peripheral arthritis, dactylitis, enthesitis and axial symptoms were also enhanced and durable over time. Following the considerable improvements between baseline and the first analysis time point (Week 8, except for PASI (Week 16)), both joint and skin response rates were further increased at 1 year. Furthermore, the substantial increases in overall disease response rates (PASDAS LDA and MDA) as well as achievement of remission targets (cDAPSA/DAPSA and PASDAS) generally found at 1 year were sustained through 2 years.

Regardless of guselkumab dosing regimen, considerable proportions of patients achieved disease control across domains at Week 100. Specifically, approximately 60% of guselkumab-randomised patients reached low levels of joint disease activity as defined by either DAPSA or cDAPSA; 61%–83% achieved enthesitis or dactylitis resolution; 53%–76% achieved almost clear or clear skin as indicated by PASI 90, PASI 100, or IGA scores of 0 or 1 and a ≥2 grade improvement from baseline; approximately 50% achieved PASDAS LDA; and 38%–40% achieved MDA. In patients with axial symptoms and imaging-confirmed sacroiliitis, spinal pain was diminished by nearly 50% on average. Overall, findings were in agreement with previous guselkumab trials in patients with psoriasis demonstrating substantial and durable improvement in skin disease[28] and with a network meta-analysis of data from randomised controlled trials[29] of patients with PsA that found guselkumab provides comparable joint disease efficacy and superior skin disease efficacy relative to other advanced PsA treatments.

Although nail disease, an important GRAPPA-identified domain, was not assessed in DISCOVER-2, a post hoc analysis of pooled data from the VOYAGE-1 and VOYAGE-2 studies of patients with moderate-to-severe psoriasis found that, among patients with fingernail psoriasis, guselkumab-treated patients achieved clearance of or minimal fingernail disease in significantly higher proportions by Week 16 than those receiving placebo.[30] Furthermore, a subgroup analysis of VOYAGE-1 and VOYAGE-2 patients with self-reported PsA also found that, compared with placebo, a significantly greater proportion of guselkumab-treated patients saw improvements in nail, scalp and palmoplantar psoriasis by Week 16.[31]

In addition to achieving the lowest possible level of disease activity in all disease domains affected, the GRAPPA, American College of Rheumatology/National Psoriasis Foundation and European Alliance of Associations for Rheumatology treatment guidelines promote optimising functional status, improving HRQoL, preventing structural damage and minimising complications both from untreated active disease and from therapy.[6 8 9 32] Analyses of the DISCOVER-1 and DISCOVER-2 studies through Week 24 found that both guselkumab dosing regimens were associated with significant improvements versus placebo in physical function and HRQoL, as measured by the HAQ-DI and SF-36 PCS scores, respectively, as well as numerical improvements in SF-36 mental component summary score.[10 11] Importantly, these improvements achieved by Week 24 were sustained or continued to increase through Week 52[26 27] and, in DISCOVER-2, through Week 100.[13] Furthermore, in DISCOVER-2, which included imaging assessments, patients treated with guselkumab demonstrated less radiographic progression relative to placebo at Week 24, with this effect reaching statistical significance in the Q4W group.[11] Regardless of guselkumab dosing regimen, low rates of radiographic progression were maintained through Week 100 in this same study.[13]

The high retention rate (90%) of guselkumab-randomised patients that was observed in DISCOVER-2 through Week 100 further supports a durable positive risk-benefit profile. Specific to PsA-related conditions, this analysis found no exacerbations or new cases of IBD during the 2-year period of guselkumab treatment and one case of uveitis (iridocyclitis)

through Week 112, with comparable incidence in the placebo group through Week 24.[13] The absence of IBD occurrence and the very low incidence of uveitis are in line with long-term guselkumab safety data previously reported through up to 2 years in the largest cohort of patients with PsA assessed to date,[33] through up to 5 years among patients with moderate-to-severe psoriasis[34 35] and through up to 5 years among a large population of patients with psoriatic disease from 11 Phase 2/3 studies.[36]

The durable effectiveness of guselkumab in such a broad range of PsA domains is likely associated with the central role of IL-23 in the pathophysiology of psoriasis and inhibition of Th17 clonal expansion through IL-23p19-subunit blockade.[37] Biomarker studies in patients with active PsA have shown that guselkumab treatment leads to reductions in circulating protein levels of acute phase and Th17 effector cytokines through Week 24,[38] as well as serum collagen levels (including C1M), through Week 52.[39] These pharmacodynamic effects were sustained, or in some cases, enhanced through Week 100[40] and associated with enduring clinical improvements in PsA disease activity through Week 100.[40 41] Preliminary in vitro studies have demonstrated that guselkumab, as a fully human IgG1 monoclonal antibody with a native Fc region, has high affinity for binding of the IL-23 p19 subunit, high potency for inhibiting IL-23 signalling and dose-dependent Fc-mediated binding to the Fcγ receptor I found on primary human inflammatory monocytes, also known as CD64. CD64-bound guselkumab was further shown to simultaneously capture IL-23 endogenously secreted from the same cells.[42] Although the clinical implications of guselkumab Fcγ receptor binding to CD64 are not yet clear, it is possible that the durable and substantial multidomain effectiveness of guselkumab may be related to its unique molecular attributes. Given that $CD64^+$ IL-23-producing myeloid cells are increased within inflamed tissue of patients with psoriatic disease[43] and joint disease activity positively correlates with frequency of peripheral $CD64^+$ monocytes,[44] these findings may suggest a mechanistic benefit. Thus, the dual-acting capability of guselkumab may neutralise inflammation at its cellular source by potently blocking IL-23 activity and binding CD64 and may contribute to differences in therapeutic profiles across antibodies inhibiting IL-23.[45]

As with all data derived from clinical trials, findings may not be generalisable to all patients seen in routine care and incentives for investigators and patients may have influenced patient retention. Furthermore, the analysis may not have been powered to detect rare safety signals, with additional larger studies required to accurately quantify the incidence of IBD and uveitis during guselkumab treatment. However, a safety analysis involving ~4400 patients with psoriatic disease found the rates of uveitis were similar in guselkumab-treated and placebo-treated patients, with no cases of Crohn's disease or ulcerative colitis reported in guselkumab-treated patients through 5 years.[36] The absence of data collection on nail psoriasis in DISCOVER-2 is an additional limitation of this study assessing key GRAPPA-identified domains. Additionally, identification of patients with axial involvement in this study was limited by the use of locally-read imaging that was restricted to evaluation of sacroiliitis and did not objectively assess spinal inflammation. The present study did not examine the influence of baseline patient characteristics on guselkumab efficacy; however, a previous analysis of a broad population of patients with active PsA in the DISCOVER-1 and -2 studies demonstrated robust and durable guselkumab efficacy across evaluated disease domains irrespective of baseline demographics, disease characteristics and PsA medication use.[46] Specifically, higher response rates were observed with guselkumab than placebo in joint and skin disease, fatigue, functional status and composite measures of PsA disease activity at Week 24 across patient subgroups stratified by patient sex and baseline body mass index, swollen and tender joint counts, CRP levels, PsA duration and use of conventional synthetic disease-modifying antirheumatic drugs or methotrexate. As well, response rates within each baseline subgroup were sustained or increased through 1 year.[46] Direct subgroup comparisons, including males versus females and patients receiving monotherapy versus combination therapy with methotrexate, have not been previously conducted and are an important area of future investigation. Although the current analysis included only biologic-naïve patients with active PsA, the effectiveness of guselkumab has also been shown in tumour necrosis factor inhibitor-experienced patients, including a real-world PsA population characterised by longstanding, treatment-resistant, active disease at baseline.[47–49] Furthermore, the long-term effectiveness of guselkumab in routine care is being examined in the ongoing prospective observational PsABIOnd study conducted in 20 countries worldwide.[50] Strengths of the current analysis include the conservative NRI approach that assigns non-response for all missing data and was employed at low rates (<10%) reflecting those of study discontinuation; the randomised controlled design of DISCOVER-2; and the focus on guselkumab effectiveness across important disease domains, which aligns with GRAPPA recommendations for PsA treatment and is relevant to clinical practice.

CONCLUSION

In the DISCOVER-2 study of biologic-naïve patients with highly active PsA, both guselkumab regimens (Q4W and Q8W) provided early, durable and continuous improvements in key GRAPPA-recognised domains of PsA through up to 2 years of treatment, resulting in considerable proportions of patients achieving low levels of joint disease activity, enthesitis/dactylitis resolution, complete skin clearance and low/minimal levels of overall disease activity. No exacerbations or new onset of IBD were reported, with a single occurrence of uveitis observed through Week 100 in guselkumab-treated patients, aligning with the established safety profile of guselkumab.

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