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Guselkumab, a Selective Interleukin-23 p19 Subunit Inhibitor, Resolves Dactylitis in Patients With Active Psoriatic Arthritis: Pooled Results Through Week 52 From Two Phase 3 Studies

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Objective. Previous analyses of pooled DISCOVER-1 and DISCOVER-2 data through Week 24 showed significantly higher rates of dactylitis resolution in patients treated with guselkumab compared with placebo. Here, we investigate associations between dactylitis resolution and other outcomes through 1 year.

Methods. Patients were randomized 1:1:1 to receive subcutaneous injections of guselkumab 100 mg at Week 0, Week 4, and then every 4 or 8 weeks, or placebo with crossover to guselkumab at Week 24. Independent assessors determined dactylitis severity score (DSS; 0-3/digit; total = 0-60). Dactylitis resolution (DSS = 0) (prespecified) and at least 20%, at least 50%, and at least 70% DSS improvement from baseline (post hoc) were determined through Week 52 (nonresponder imputation for treatment failure through Week 24 and for missing data through Week 52). ACR50, tender/swollen joints, low disease activity (LDA) as assessed by composite indices, and radiographic progression (DISCOVER-2 only) were assessed in patients with dactylitis versus without dactylitis resolution at Week 24 and Week 52.

Results. Patients with dactylitis at baseline (473 of 1118) had more severe joint and skin disease than those without dactylitis (645 of 1118). At Week 52, approximately 75% of guselkumab-randomized patients with dactylitis at baseline had complete resolution; approximately 80% had at least 70% DSS improvement. Through Week 52, new-onset dactylitis (DSS ≥1) was uncommon among patients with a DSS of 0 at baseline. Guselkumab-randomized patients with dactylitis resolution were more likely to achieve ACR50, at least 50% reduction in tender and swollen joints, and LDA at Week 24 and Week 52 than those without resolution. At Week 52, patients with dactylitis resolution had numerically less radiographic progression from baseline (DISCOVER-2).

Conclusion. Through 1 year, approximately 75% of guselkumab-randomized patients had complete resolution of dactylitis; patients exhibiting resolution were more likely to achieve other important clinical outcomes. Given the high burden of dactylitis, resolution may be associated with better long-term patient outcomes.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, immune-mediated inflammatory disease that develops in up to 30% of patients with psoriasis (1). Dactylitis, a characteristic feature of PsA, is one of six clinical domains considered in PsA treatment decisions, along with peripheral arthritis, axial disease, enthesitis, skin disease, and nail disease (2). Dactylitis typically presents as swelling of the whole digit, with inflammation in the joints, soft tissues, and tendon sheaths (3–6). Although dactylitis can occur in patients with

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other diseases, it is a hallmark feature of PsA, developing in up to 50% of patients at some point during their disease course, with toes affected more often than fingers (5–7). Imaging studies in patients with PsA revealed that flexor tenosynovitis with diffuse extra-tendinous inflammation with an epicenter around accessory pulleys is a characteristic feature of dactylitis pathogenesis, helping to differentiate it from rheumatoid and other forms of arthritis (8). Other imaging features of dactylitis that can aid in differential diagnosis of PsA include extracapsular inflammatory changes, enthesitis, diffuse osteitis, and soft-tissue edema (6–8).

PsA treatments that provide high levels of dactylitis improvement and resolution are important because dactylitis is a clinical marker for a more severe disease phenotype in patients with early PsA, characterized by higher swollen joint count (SJC), higher C-reactive protein (CRP) levels, and more synovitis and bone erosions on imaging (5). In patients with chronic PsA, dactylitis is associated with a higher degree of radiographic damage (9). Development of dactylitis is a predictor of future radiographic damage, and patients with PsA with dactylitis and/or enthesitis report higher levels of physical disability, poorer functional status, and greater pain and fatigue than patients without these disease features (10–13). Furthermore, resolution of dactylitis is associated with improvements in physical function, health-related quality of life, and pain (14–16).

Guselkumab, a high-affinity, fully human monoclonal antibody targeting the p19 subunit of interleukin (IL)-23, is approved for the treatment of active PsA and moderate-to-severe plaque psoriasis (17). The pivotal Phase 3 DISCOVER-1 and DISCOVER-2 studies confirmed the safety and efficacy of guselkumab for treating the diverse manifestations of active PsA through 24 (18,19) and 52 (20,21) weeks of treatment, and DISCOVER-2 confirmed low levels of radiographic progression through 2 years of treatment (22). Prespecified analyses of pooled data from DISCOVER-1 and DISCOVER-2 at Week 24 demonstrated significantly higher rates of dactylitis resolution with guselkumab every 4 weeks (Q4W; 64%) and every 8 weeks (Q8W; 59%) than with placebo (42%; both $P < 0.05$) (19). In these same patients, dactylitis response rates were maintained through 1 year (21). Here, we report results from analyses of pooled data from DISCOVER-1 and DISCOVER-2 exploring the specific treatment effects of guselkumab through 1 year in patients with PsA with and without dactylitis, including evaluation of relationships between dactylitis resolution and improvements in other domains of disease.

PATIENTS AND METHODS

Study designs and patients. DISCOVER-1 (NCT03162796) and DISCOVER-2 (NCT03158285) were multicenter, randomized, double-blind, placebo-controlled, Phase 3 studies of guselkumab in patients with active PsA despite treatment with standard therapies (conventional synthetic disease-modifying antirheumatic drugs [csDMARDs], nonsteroidal anti-inflammatory drugs [NSAIDs], and apremilast). Eligible participants in DISCOVER-1 had an SJC of 3 or more, a tender joint count (TJC) of 3 or more, and a CRP level of 0.3 mg/dl or more. Previous exposure to one or two tumor necrosis factor (TNF) inhibitors was permitted in DISCOVER-1 but was limited to approximately 30% of the study population (18). In DISCOVER-2, eligible patients had an SJC of 5 or more, a TJC of 5 or more, and a CRP level of 0.6 mg/dl or more and had not received prior biologics for PsA (19). In both studies, concomitant treatment at stable doses was allowed with NSAIDs or other analgesics up to regionally approved doses; oral corticosteroids (prednisone ≤10 mg/day or equivalent); or one csDMARD (methotrexate ≤25 mg/week, sulfasalazine ≤3 g/day, hydroxychloroquine ≤400 mg/day, or leflunomide ≤20 mg/day) (18,19).

In both studies, patients were randomized 1:1:1 to receive subcutaneous injections of guselkumab 100 mg Q4W, guselkumab 100 mg at Week 0 and Week 4 and then Q8W, or placebo with crossover to guselkumab Q4W at Week 24 (placebo→Q4W). Treatment continued through Week 48 in DISCOVER-1 and through Week 100 in DISCOVER-2. Efficacy data collected through Week 52 are included here.

Ethics. These studies were conducted in accordance with the principles of the Declaration of Helsinki and International Council for Harmonization Guidelines for Good Clinical Practice. Each site's governing ethical body approved study protocols, and all patients provided written informed consent, as previously reported (18,19).

Assessments. Independent joint assessors evaluated each patient for the presence of dactylitis using a dactylitis severity score (DSS) (23) in which each of 20 digits is evaluated on a 0 to 3 scale, where 0 = no dactylitis, 1 = mild dactylitis, 2 = moderate dactylitis, and 3 = severe dactylitis. The total score ranges from 0 to 60 (24), with subscores of 0 to 30 for hands and feet. The same independent joint assessors determined TJC (0-68) and SJC (0-66, excluding hips), and evaluated enthesitis using the Leeds Enthesitis Index (0-6) (25).

Investigators rated global assessment of disease activity on a 0 to 10 cm visual analog scale (VAS) and evaluated skin disease severity using the Psoriasis Area and Severity Index (PASI; score = 0-72) (26) and percentage of body surface area (BSA) affected by psoriasis. Additionally, patients rated their pain and global impression of disease activity (0-100 mm VAS) and

transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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completed the Health Assessment Questionnaire-Disability Index (HAQ-DI; score = 0-3) (27), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue; score = 0-52) (28,29), and 36-item Short-Form (SF-36) questionnaires (30).

In DISCOVER-2, single radiographs of the hands (posteroanterior) and feet (anteroposterior) were obtained at Weeks 0, 24, and 52 (or at discontinuation if between Weeks 24 and 52; Reading Session 2) and scored by blinded central primary readers using the PsA-modified van der Heijde-Sharp (vdH-S) score (range, 0-528 based on joint erosion and joint space narrowing scores) (19,31).

Analyses. Data from DISCOVER-1 and DISCOVER-2 were pooled, and baseline demographic and disease characteristics were summarized for patients with and without dactylitis. As prespecified, dactylitis data (total DSS) were pooled across DISCOVER-1 and DISCOVER-2 to increase the sample size when determining the proportions of patients achieving dactylitis resolution (DSS = 0).

Post hoc analyses of pooled data assessed dactylitis response using the established indices of improvements of at least 20%, 50%, and 70% from baseline in DSS (24); nominal *P* values for comparison of DSS improvement with guselkumab Q4W and Q8W versus placebo were generated using the Cochran-Mantel-Haenszel test. Dactylitis resolution rates at Weeks 24 and 52 were evaluated in patient subgroups defined by baseline characteristics including sex (male/female), age (<45, ≥45 to <65, ≥65 years), body weight (≤90, >90 kg), body mass index (BMI; <25, ≥25 to <30, ≥30 kg/m^2), PsA duration (<1, ≥1 to <3, ≥3 years), TJC (<10, 10 to 15, >15), SJC (<10, 10 to 15, >15), CRP level (<1, ≥1 to <2, ≥2 mg/dl), concomitant baseline csDMARD use (none, any csDMARD use, methotrexate use), PASI score (<12, ≥12 to <20, ≥20), and psoriasis BSA (<3%, ≥3% to <10%, ≥10% to <20%, ≥20%). Through Week 24, patients meeting treatment failure (TF) criteria (ie, discontinued study treatment, terminated study participation, initiated or increased their dose of nonbiologic cDMARDs or oral corticosteroids, or initiated any protocol-prohibited PsA treatments) or with missing data were imputed as nonresponders. After Week 24 and through Week 52, patients with missing data were imputed as nonresponders without application of TF rules. Additionally, the proportion of patients with new-onset dactylitis was determined through Week 52 for those without dactylitis (DSS = 0) at baseline using observed data.

Post hoc analyses of achievement of various clinical efficacy outcomes at Weeks 24 and 52 were conducted in the pooled subgroups of patients with (DSS ≥1) and without (DSS = 0) dactylitis at baseline, including proportions of patients achieving improvements of at least 20%, 50%, and 70% in American College of Rheumatology response criteria (ACR20, ACR50, and ACR70, respectively) and FACIT-Fatigue response (≥4-point improvement) (29), and changes from baseline in HAQ-DI and SF-36 physical and mental component summary (PCS/MCS) scores. Achievement of the following composite measures were also assessed: Disease Activity in Psoriatic Arthritis (DAPSA) and clinical DAPSA (cDAPSA; excluding CRP) low disease activity (LDA; score ≤ 14 and ≤ 13, respectively) and remission (score ≤ 4 for both) (32,33); Psoriatic Arthritis Disease Activity Score (PASDAS) LDA (score ≤ 3.2) and very low disease activity (VLDA; score ≤ 1.9) (34–36); and minimal disease activity (MDA), defined as achievement of five of the following seven criteria: TJC of ≤ 1 or less, SJC of ≤ 1 or less, PASI score of ≤ 1 or less, patient pain VAS of ≤ 15 or less, patient global disease activity VAS of ≤ 20 or less, HAQ-DI of 0.5 or less, and tender entheseal points of ≤ 1 or less (37). For binary endpoints, patients meeting TF criteria and those with missing data were considered nonresponders through Week 24; after Week 24 and through Week 52, patients with missing data were imputed as nonresponders, and no TF rules were applied. For continuous endpoints through Week 24, patients meeting TF criteria were imputed as zero (no change) from baseline, and remaining missing data were assumed to be missing at random and imputed by multiple imputations; after Week 24 and through Week 52, no TF rules were applied, and for patients who discontinued study agent for any reason, the change from baseline, if missing, was set to zero (no change).

Relationships between dactylitis resolution and the following clinical outcomes at Weeks 24 and 52 were assessed using a Chi-squared analysis: ACR50, 50% or more improvement in TJC and SJC, PASDAS LDA, DAPSA LDA, and MDA.

Within treatment group effect size was determined at Weeks 24 and 52 using Cohen's D (38), defined as the difference between mean baseline DSS and mean Week 24 or 52 DSS divided by the pooled standard deviation (SD) of baseline and Week 24 or 52 DSS, respectively, in the same treatment group. Effect size was calculated for all patients with dactylitis at baseline, with and without concomitant methotrexate use at baseline (yes/no). Effect sizes of 0.2 or less are considered small, values of 0.2 to 0.8 are considered moderate, and values of 0.8 or more are considered large (39).

For patients in DISCOVER-2 with and without dactylitis at baseline, mean changes in total vdH-S score were evaluated from Week 0 to 52. For DISCOVER-2 patients with dactylitis at baseline, mean changes in vdH-S score from Week 0 to 52 were also evaluated by dactylitis resolution status at Week 24 and 52.

RESULTS

Patients. As previously reported, baseline demographic and disease characteristics were generally consistent across randomized treatment groups in both studies (18,19). Of 1120 patients in the pooled DISCOVER-1 and DISCOVER-2 full analysis population, dactylitis data were available for 1118 patients. At baseline, 42% (473 of 1118) of patients had dactylitis (DSS ≥1), including 43%

(159 of 373) in the guselkumab Q4W group, 43% (160 of 374) in the Q8W group, and 42% (154 of 371) in the placebo group. Among patients with dactylitis, 24% (114 of 473) had finger dactylitis, 35% (164 of 473) had toe dactylitis, and 41% (195 of 473) had both finger and toe dactylitis. In the 309 patients with hand dactylitis, mean (SD) dactylitis finger count was 3.4 (3.0), and in the 359 patients with foot dactylitis, mean (SD) dactylitis toe count was 3.2 (2.6).

Relative to the subgroup of patients without dactylitis (DSS = 0) at baseline, the subgroup with dactylitis (mean DSS = 8.2) was characterized by numerically higher proportions of patients who were male (58% vs. 48%); who had enthesitis (75% vs. 58%), a PASI score of 20 or more (16% vs. 11%), and a BMI of less than 30 kg/m^2 (64% vs. 57%); and who were receiving csDMARDs (71% vs. 65%) (Table 1). On average, patients with versus without dactylitis at baseline had numerically higher values for indicators of more severe PsA, including SJC (14 vs. 10), TJC (24 vs. 18), PASDAS score (7.2 vs. 6.0), and DAPSA score (53 vs. 42) (Table 1). Patients with dactylitis also had higher mean serum CRP concentration (2.1 vs. 1.5 mg/dl), which is a marker for higher risk of radiographic progression (40). In DISCOVER-2, mean baseline vdH-S scores were numerically higher in patients with dactylitis (26-35 vs. 16-20 units).

Dactylitis resolution and improvement. Prespecified pooled DISCOVER-1 and DISCOVER-2 results showed that among patients with dactylitis at baseline, significantly higher proportions of patients in the Q4W (63.5% [95% confidence interval (CI): 55.7-71.3]) and Q8W (59.4% [51.5-67.3]) groups achieved resolution of dactylitis at Week 24 compared with placebo (42.2% [34.1-50.3]); both $P < 0.05$ (19). Least-squares mean (95% CI) changes in DSS from baseline to Week 24 were – 6.0 (–6.8 to –5.1) in the Q4W group, –6.1 (–6.9 to –5.3) in the Q8W group, and – 4.2 (–5.0 to –3.4) in the placebo group (19).

From Week 24 to 52 (nonresponder imputation), dactylitis resolution rates increased to 74.8% (67.8-81.9) in the Q4W group, 75.6% (68.7-82.6) in the Q8W group, and 70.1% (62.6-77.7) in the placebo→Q4W group. Least-squares mean (95% CI) changes in DSS from baseline to Week 52 were – 6.5 (–7.1 to –5.8) in the Q4W group, –7.1 (–7.8 to –6.5) in the Q8W group, and –6.6 (–7.3 to –5.9) in the placebo→Q4W group.

More than half of all guselkumab-randomized patients achieved 20% or more DSS improvement by Week 4, 50% or more improvement by Week 8, and 70% or more improvement by Week 16 (Figure 1). Owing to relatively high placebo responses at Weeks 4 and 8, separation between guselkumab and placebo first became apparent (nominal $P < 0.05$) at Week 16. By Week 52, approximately 80% of guselkumab-randomized patients achieved 70% or more improvement in DSS (Figure 1).

Dactylitis resolution/improvement by baseline characteristics. At Week 24, higher rates of dactylitis resolution were observed with guselkumab Q4W and Q8W versus placebo across most demographic and disease-specific subgroups with sufficient sample size for evaluation, including subgroups of patients that are more difficult to treat (eg, those with longer PsA duration, more extensive joint and skin involvement, and higher body weight) (Figure 2). At Week 24, guselkumab treatment was associated with numerically greater improvements in both hand and foot DSS subscores compared with placebo, suggesting similar treatment effects regardless of anatomical location. Although dactylitis was more common in males than females (Table 1), there were no notable differences in dactylitis resolution by sex (Figure 2). From Week 24 to 52, dactylitis resolution rates were maintained or increased across all subgroups (Figure 2).

Effect size. At Week 24, effect sizes were 0.84 in the guselkumab Q4W group and 0.77 in the Q8W group, indicating a moderate to large treatment effect, and 0.56 in the placebo group, suggesting a moderate placebo effect (Table 2). Among guselkumab-treated patients, effect sizes at Week 24 were moderate (0.71-0.74) for patients with concomitant methotrexate use and large (0.85-1.03) for patients without concomitant methotrexate use. By Week 52, effect sizes were large in all guselkumab treatment groups (0.99-1.02), including the placebo→guselkumab crossover group, and similar for patients with and without concomitant methotrexate use at baseline (Table 2).

New-onset dactylitis. In patients without dactylitis at baseline, new-onset dactylitis was uncommon. Among patients in each treatment group with a DSS of 0 at baseline, only a small proportion had a DSS of greater than 0 at any assessment time point from Week 4 to 52 (Figure 3).

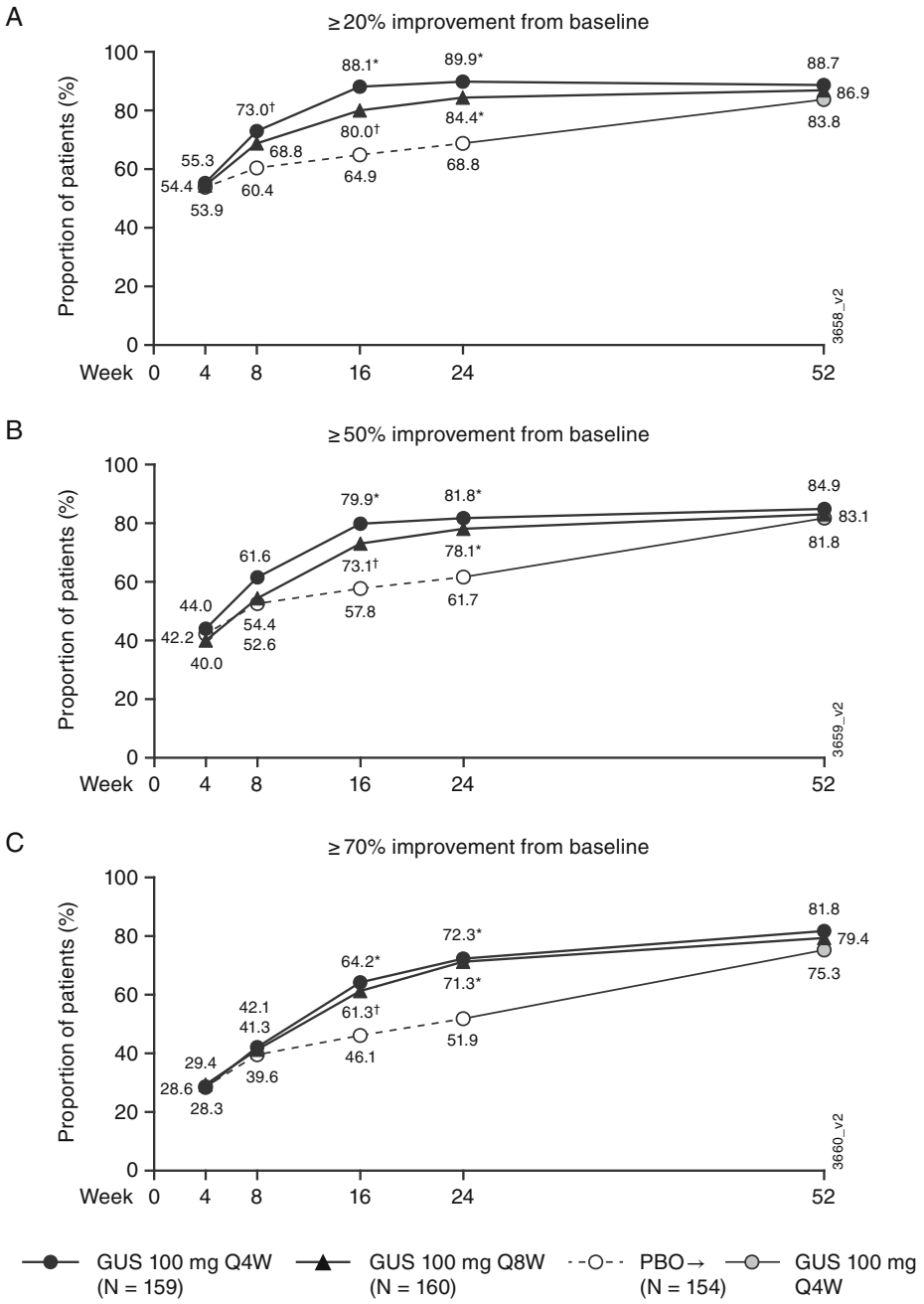
Relationships between dactylitis at baseline and achievement of clinical efficacy endpoints. ACR20 response at Week 24 (primary endpoint) was achieved by similar proportions of guselkumab-treated patients with (58%-62%) and without (61%-63%) dactylitis at baseline; in the placebo group, the ACR20 response rate was the same (29%) for patients with and without dactylitis at baseline (Table 3). Among guselkumab-randomized patients, response rates (nonresponder imputation) were sustained through Week 52, at which time approximately 70% of patients with and without dactylitis at baseline achieved ACR20 response (Table 3).

Patients with dactylitis at baseline were less likely to achieve more rigorous disease activity measures of the magnitude of disease resolution, including ACR50, ACR70, DAPSA and cDAPSA LDA and remission, PASDAS LDA and VLDA, and MDA, at Weeks 24 and 52 (Table 3). These composite indices include assessments of several joint-related components that are more likely to be affected in patients with versus without dactylitis (eg, SJC, pain, elevated CRP levels, enthesitis, and tender dactylitis count). Of note, baseline DAPSA, cDAPSA, and

Table 1. Baseline characteristics in patients with PsA with or without dactylitis at baseline

	All patients	Patients with dactylitis	Patients without dactylitis
Pooled randomized, treated patients, N	1120[a]	473	645
Age (y), mean (SD)	46.6 (11.6)	45.1 (11.2)	47.7 (11.8)
Sex, %			
Male	52.1	57.7	48.1
Female	47.9	42.3	51.9
Weight (kg), mean (SD)	84.9 (19.3)	84.2 (20.0)	85.4 (18.7)
BMI (kg/m^2), mean (SD)	29.2 (6.1)	28.6 (6.1)	29.6 (6.0)
Normal (<25), %	25.5	29.8	22.5
Overweight (≥25 and <30), %	34.5	33.8	34.9
Obesity (≥30), %	40.0	36.4	42.6
PsA disease duration (y), mean (SD)	5.9 (6.1)	5.5 (5.7)	6.2 (6.3)
Joint counts, mean (SD)			
Swollen (0-66)	11.4 (7.4)	13.8 (8.5)	9.7 (6.0)
Tender (0-68)	20.6 (13.3)	24.0 (14.0)	18.1 (12.2)
Enthesitis at baseline, %[b]	65.1	74.6	58.1
Enthesitis (LEI) score (1-6), mean (SD)[b]	2.8 (1.6)	2.9 (1.6)	2.7 (1.5)
Dactylitis at baseline, %	42.3[a]	100	0
Dactylitis (DSS) score (0-60), mean (SD)	8.2 (9.6)	8.2 (9.6)	0
CRP (mg/dl), mean (SD)	1.8 (2.3)	2.1 (2.6)	1.5 (2.0)
HAQ-DI score (0-3), mean (SD)	1.2 (0.6)[c]	1.3 (0.6)	1.2 (0.6)
FACIT-Fatigue score (0-52), mean (SD)	30.0 (10.0)[c]	29.4 (9.7)	30.4 (10.1)
SF-36 MCS score, mean (SD)	47.6 (10.9)[c]	47.5 (10.7)	47.6 (11.1)
SF-36 PCS score, mean (SD)	33.4 (7.7)[c]	32.8 (7.3)	33.8 (7.9)
DAPSA score, mean (SD)	46.3 (20.6)	52.9 (22.3)	41.5 (17.8)
≤14, %	0.5	0.4	0.6
>14 and ≤28, %	14.4	7.2	19.7
>28, %	85.1	92.4	79.7
cDAPSA score, mean (SD)	44.6 (20.2)	50.8 (21.8)	40.0 (17.6)
≤13, %	0.6	0.4	0.8
>13 and ≤27, %	14.8	7.8	20.0
>27, %	84.6	91.8	79.2
PASDAS score, mean (SD)[d]	6.5 (1.1)	7.2 (1.0)	6.0 (0.8)
≤3.2, %	0.1	0	0.2
>3.2 and <5.4, %	15.3	5.1	22.8
≥5.4, %	84.6	94.9	77.0
PASI score (0-72), mean (SD)	9.5 (10.6)[c]	10.4 (11.4)	8.7 (10.0)
<12, %	74.4	72.7	75.7
≥12 and <20, %	12.9	11.6	13.8
≥20, %	12.7	15.6	10.5
Psoriasis BSA, mean (SD)[e]	16.1 (19.5)	17.9 (21.0)	14.7 (18.3)
<3%, %	21.1	18.0	23.3
≥3% and <10%, %	32.4	32.3	32.5
≥10% and <20%, %	19.9	20.5	19.4
≥20%, %	26.6	29.2	24.7
csDMARD use at baseline, %	67.8	71.5	65.1
Methotrexate	58.4	61.7	56.0
Other[f]	9.4	9.7	9.1
NSAID use at baseline, %	64.4	64.5	64.3

Note: Results are pooled across DISCOVER-1 and DISCOVER-2.
Abbreviations: BMI, body mass index; BSA, body surface area; cDAPSA, clinical DAPSA (excludes CRP); CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAPSA, Disease Activity in Psoriatic Arthritis; DSS, dactylitis severity score; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; LEI, Leeds Enthesitis Index; NSAID, nonsteroidal anti-inflammatory drug; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SD, standard deviation; SF-36 PCS/MCS, 36-item Short-Form health survey physical/mental component summary; y, years.
[a]Among 1120 patients, 1118 were included in the dactylitis analysis.
[b]All patients, N = 1118 with baseline LEI score, n = 720 with LEI score >0; patients with dactylitis, n = 349 with LEI score >0; patients without dactylitis, n = 371 with LEI score >0.
[c]N = 1119.
[d]All patients, N = 1108; patients with dactylitis, n = 469; patients without dactylitis, n = 639.
[e]All patients, N = 1116; patients with dactylitis, n = 473; patients without dactylitis, n = 643.
[f]Includes hydroxychloroquine, sulfasalazine, and leflunomide.



*p ≤ 0.001; †p < 0.05

Figure 1. Proportions of patients with ≥20% (A), ≥50% (B), and ≥ 70% (C) improvement in DSS from baseline over time. Data pooled for patients with DSS 1 or higher at baseline across DISCOVER-1 and DISCOVER-2. DSS is a total score of the presence and severity of dactylitis in each digit scored from 0 (no dactylitis) to 3 (severe dactylitis); final score range = 0 to 60. Treatment group comparisons through Week 24 were not adjusted for multiplicity of testing; all reported *P* values are nominal. Through Week 24, patients meeting TF criteria or with missing data were imputed as nonresponders. After Week 24 and through Week 52, patients with missing data were imputed as nonresponders without application of TF rules. DSS, dactylitis severity score; GUS, guselkumab; PBO, placebo; Q4/8W, every 4/8 weeks; TF, treatment failure.

PASDAS scores were substantially higher in those with versus without dactylitis, suggesting more severe disease (Table 1).

Although baseline FACIT-Fatigue and SF-36 MCS scores were similar for patients with and without dactylitis (Table 1), patients with dactylitis at baseline were more likely to achieve FACIT-Fatigue response (≥4-point improvement) and had greater least-squares mean improvements in SF-36 MCS scores. Least-squares mean improvements in HAQ-DI and SF-36 PCS scores at Weeks 24 and 52 were generally similar for patients with and without dactylitis at baseline (Table 3).

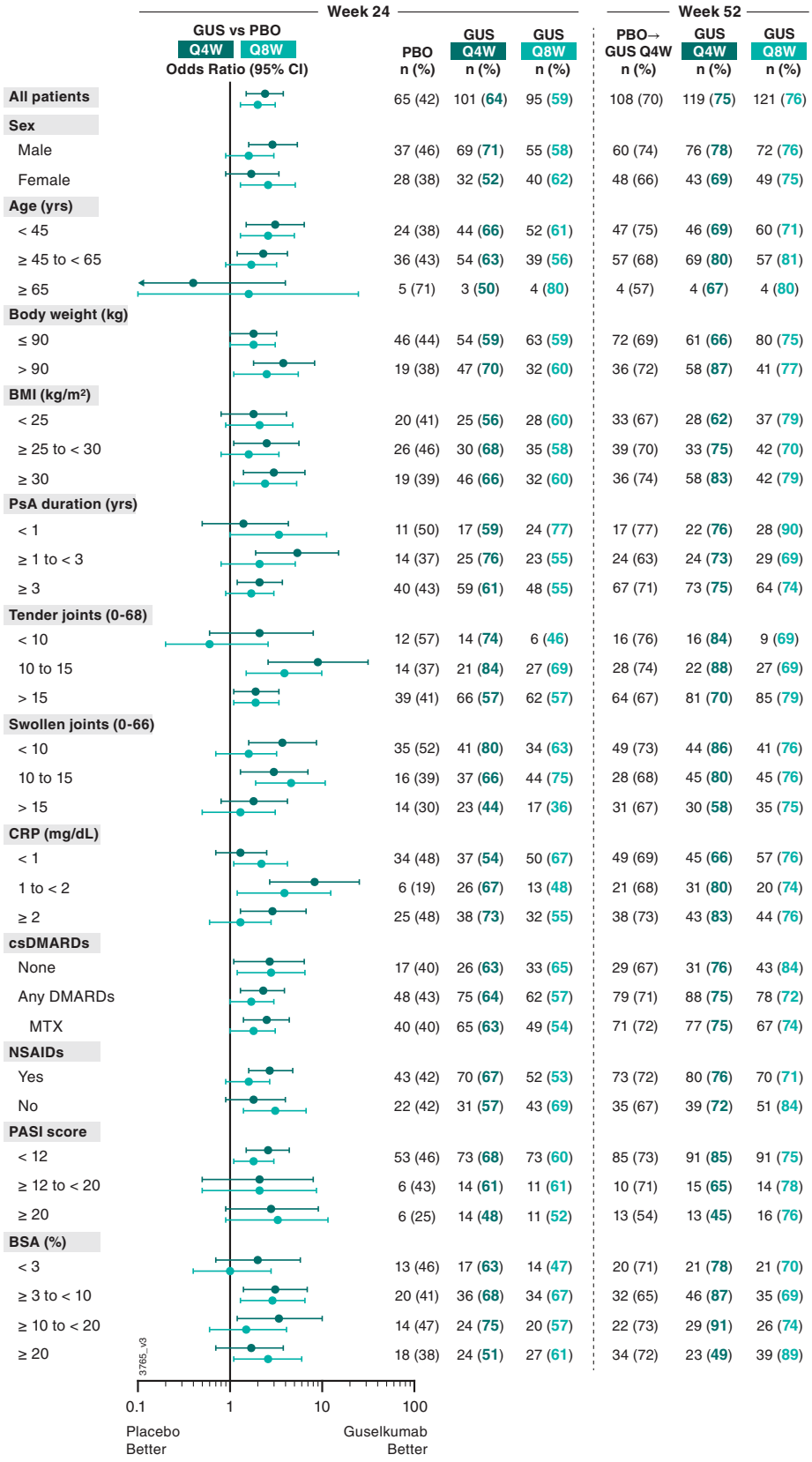


Figure 2. Dactylitis resolution at Week 24 and Week 52 by baseline characteristics in patients with PsA with dactylitis at baseline. Data pooled across DISCOVER-1 and DISCOVER-2. BMI, body mass index; BSA, body surface area of psoriasis; CI, confidence interval; CRP, C-reactive protein; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; GUS, guselkumab; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; PASI, Psoriasis Area and Severity Index; PBO, placebo; PsA, psoriatic arthritis; Q4/8W, every 4/8 weeks.

Table 2. Effect size[a] of mean change from baseline to Week 24 and Week 52 in DSS for all patients with dactylitis at baseline and stratified by concomitant MTX use at baseline

	Guselkumab Q4W	Guselkumab Q8W	Placebo
Patients with dactylitis at baseline, N	159	160	154
Week 24 results			
Patients with DSS data at Week 24, N	159	159	153
Effect size at Week 24	0.84	0.77	0.56
With concomitant MTX use			
Patients with DSS data at Week 24, N	103	89	99
Effect size at Week 24	0.74	0.71	0.65
Without concomitant MTX use			
Patients with DSS data at Week 24, N	56	70	54
Effect size at Week 24	1.03	0.85	0.52
Week 52 results	Guselkumab Q4W	Guselkumab Q8W	Placebo→Guselkumab Q4W
Patients with DSS data at Week 52, N	157	159	153
Effect size at Week 52	0.99	0.99	1.02
With concomitant MTX use			
Patients with DSS data at Week 52, N	102	90	99
Effect size at Week 52	0.92	0.94	1.10
Without concomitant MTX use			
Patients with DSS data at Week 52, N	55	69	54
Effect size at Week 52	1.11	1.09	1.01

Note: Results are pooled across DISCOVER-1 and DISCOVER-2.
Abbreviations: DSS, dactylitis severity score; MTX, methotrexate; Q4/8W, every 4/8 weeks; SD, standard deviation.
[a]Effect size within treatment groups is based on Cohen's D, defined as the difference between the mean baseline DSS and the mean Week 24 or Week 52 DSS divided by the pooled SD of the baseline and Week 24 or 52 DSS, respectively.

Relationships between dactylitis resolution and other clinical responses. Analyses of primary efficacy endpoint results in the subset of guselkumab-randomized patients with dactylitis at baseline showed that at Week 24, 73% (140 of 193) of ACR20 responders and 53% (63 of 119) of ACR20 nonresponders achieved dactylitis resolution. In the placebo group, dactylitis resolution was achieved by 68% (32 of 47) of ACR20 responders and 38% (37 of 97) of ACR20 nonresponders. In guselkumab-randomized patients at Week 52, dactylitis resolution was achieved by 86% (191 of 223) of ACR20 responders and 66% (49 of 74) of ACR20 nonresponders.

Patients who achieved dactylitis resolution at Week 24 were more likely ($P < 0.05$) to achieve other criteria for clinical response, including ACR50, 50% or more improvement in TJC and SJC, PASDAS LDA, and DAPSA LDA (Figure 4). Among guselkumab-randomized patients, these patterns of response were maintained at Week 52. In the guselkumab Q4W and Q8W groups, dactylitis resolution at Week 24 was predictive of 50% or more improvement in TJC and SJC, PASDAS LDA, and DAPSA LDA at Week 52 (Figure 4), suggesting that earlier treatment of dactylitis was associated with long-term improvements in composite measures of disease activity.

In DISCOVER-2, patients with dactylitis resolution at Week 24 showed less radiographic progression at Week 52 than those without dactylitis resolution at Week 24 (mean [SD] changes in vdH-S score from Week 0 to 52: Q4W: 1.0 [3.7] vs. 1.6 [5.0]; Q8W: 0.5 [2.5] vs. 3.1 [6.3]). Similar results were observed for patients with versus without dactylitis resolution at Week 52 (Q4W: 0.9 [3.7] vs. 2.6 [5.7]; Q8W: 1.4 [4.4] vs. 1.9 [5.6]).

DISCUSSION

Results of the current analyses of pooled data from DISCOVER-1 and DISCOVER-2 indicate that guselkumab treatment resolved or reduced the severity of dactylitis by 70% or more in the majority of patients with dactylitis at baseline, and these improvements were sustained through 1 year of treatment. At Week 16, greater mean improvement in dactylitis was achieved with guselkumab compared with placebo. By Week 52, approximately 75% of guselkumab-randomized patients had complete resolution, and approximately 80% had an improvement in DSS of at least 70%. Furthermore, new-onset dactylitis was uncommon in patients with a DSS of 0 at baseline, with 1.4% of these patients having a DSS ≥ 0 at Week 52.

In these studies, patients with baseline dactylitis had more severe disease, on average, than those without dactylitis, including higher prevalence of enthesitis, more severe psoriasis, higher numbers of swollen and tender joints, higher CRP levels, and higher overall disease activity based on PASDAS and DAPSA scores. These findings are consistent with previous observations that dactylitis is a marker of more severe disease manifestations in PsA (5–7,9,11,41). Also consistent with published literature (5,9), in the DISCOVER studies, dactylitis was more common in toes than in fingers. This finding supports the hypothesis that physical trauma or stress is a contributor to dactylitis pathophysiology (ie, the loadbearing function of toes makes them more predisposed to physical-injury-induced dactylitis than fingers) (42).

Dactylitis resolution occurred more frequently in guselkumab-treated patients who achieved ACR20 response

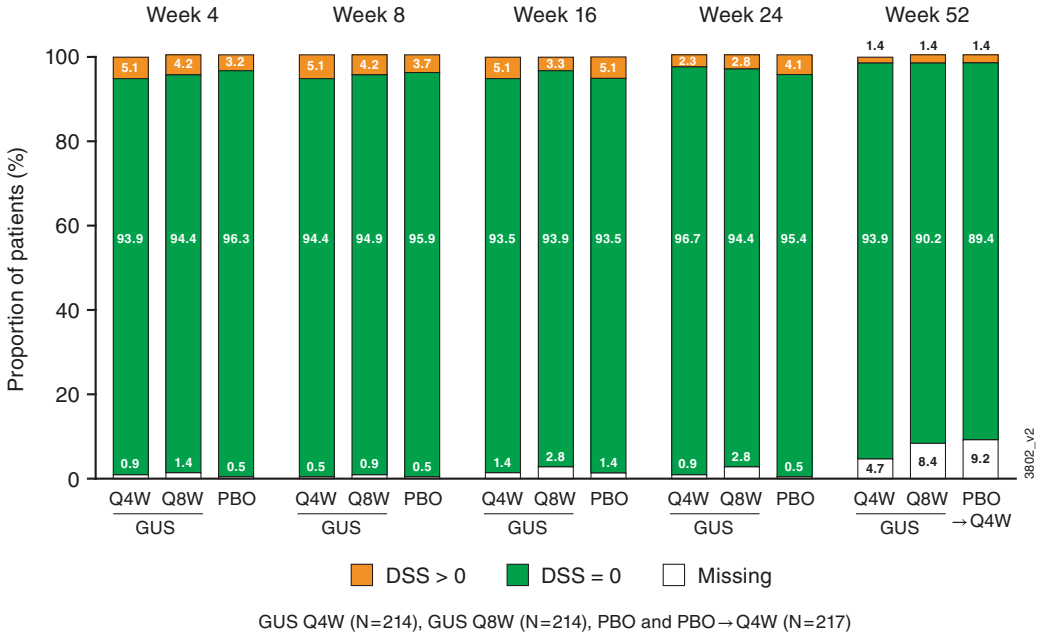


Figure 3. New-onset dactylitis through Week 52 in patients with PsA without dactylitis (DSS = 0) at baseline. Observed data pooled across DISCOVER-1 and DISCOVER-2. DSS, dactylitis severity score; GUS, guselkumab; PBO, placebo; PsA, psoriatic arthritis; Q4/8W, every 4/8 weeks.

at Week 24 (73%) than in ACR20 nonresponders (53%), compared with 68% and 38%, respectively, in the placebo group. However, it is noteworthy that roughly half of guselkumab-treated patients who did not achieve ACR20 did achieve resolution of dactylitis, suggesting that failure to achieve ACR20 does not preclude meaningful improvement in specific PsA core domains. This finding is consistent with a recent study by Mease et al (43) showing that substantial proportions of patients with PsA who failed to achieve ACR20 with apremilast had sustained improvements in several PsA core domains, including dactylitis.

Patients in DISCOVER-2 with dactylitis at baseline had more preexisting structural damage in their hands and feet than those without dactylitis. This finding supports observations of more active disease progression and greater structural damage in patients with PsA with versus without dactylitis (10,11). Results of this analysis further show that, among guselkumab-treated patients, mean changes in vdH-S scores from Week 0 to 52 were smaller, indicating numerically less radiographic progression, in those who achieved dactylitis resolution at Weeks 24 and 52 than in those who did not achieve resolution. As such, findings suggest that attenuating chronic pathophysiologic inflammatory responses with guselkumab may provide resolution of the clinical symptoms of dactylitis and diminish the rate of structural damage progression in the hands and feet of patients with active PsA.

Patients with dactylitis tended to have higher baseline CRP levels (mean 2.1 vs. 1.5 mg/dl), which is an independent indicator of poor radiographic outcomes (40). Subgroup analyses showed high dactylitis resolution rates at Week 52 in guselkumab-randomized patients with baseline CRP level of 1 to less than 2 mg/dl (74%-80%) and 2 mg/dl or more (76%-83%), which were consistent with response rates for all patients with dactylitis at baseline.

Although there has been considerable improvement in understanding the micro-anatomical basis for dactylitis, the underlying immunopathogenesis remains incompletely understood. It is thought that enhanced innate immune responses to biomechanical stress and subsequent T cell migration triggers dactylitis (44). The high levels of dactylitis resolution with guselkumab observed in the current analyses reinforce findings from animal models of experimental dactylitis supporting a key role of the IL-23/IL-17 axis in the pathogenesis of dactylitis and associated enthesitis, osteitis, and nail disease (6,45–47). The central roles of IL-23 and IL-17 in PsA, and specifically in dactylitis, have been confirmed in large-scale clinical development programs that established the robust efficacy of monoclonal antibodies targeting these cytokines (18,19,48–53). The rates of dactylitis resolution observed in DISCOVER-1 and DISCOVER-2 are generally consistent with rates observed in clinical trials of other therapies targeting dactylitis pathogenesis (eg, IL-17A, TNF, IL-23, and Janus kinase inhibition) (53–58).

Dactylitis assessment tools, including the DSS and the Leeds Dactylitis Index (LDI), have been used in PsA clinical trials and in real-world clinical practice to identify and monitor this hallmark feature of PsA. The LDI (58,59) is a validated outcome measure that includes assessment of digit size and tenderness and is sensitive to change. In practice, the LDI can be relatively time-consuming, and intra- and interobserver variability has been reported (59–62). The DSS is a numerical rating scale of dactylitis

Table 3. Clinical response[a] through Week 52 in randomized treated patients with PsA with or without dactylitis at baseline

		Patients with dactylitis			Patients without dactylitis		
		Guselkumab 100 mg		Placebo (W0-24) → Q4W (W24-52)	Guselkumab 100 mg		Placebo (W0-24) → Q4W (W24-52)
	W	Q4W	Q8W		Q4W	Q8W	
N		159	160	154	214	214	217
ACR20, % (95% CI)[b]	24	61.6 (53.8-69.5)	58.1 (50.2-66.1)	29.2 (21.7-36.7)	62.6 (55.9-69.3)	61.2 (54.5-68.0)	29.0 (22.8-35.3)
	52	69.8 (62.4-77.3)	70.0 (62.6-77.4)	55.8 (47.7-64.0)	72.9 (66.7-79.1)	69.2 (62.7-75.6)	65.4 (58.9-72.0)
ACR50, % (95% CI)[b]	24	28.9 (21.6-36.3)	29.4 (22.0-36.7)	10.4 (5.2-15.5)	37.9 (31.1-44.6)	32.2 (25.7-38.7)	13.8 (9.0-18.6)
	52	46.5 (38.5-54.6)	45.6 (37.6-53.7)	33.8 (26.0-41.6)	50.0 (43.1-56.9)	44.9 (38.0-51.8)	39.6 (32.9-46.4)
ACR70, % (95% CI)[b]	24	8.8 (4.1-13.5)	15.6 (9.7-21.6)	7.1 (2.8-11.5)	20.6 (14.9-26.2)	16.8 (11.6-22.1)	2.8 (0.4-5.2)
	52	20.8 (14.1-27.4)	28.1 (20.8-35.4)	20.8 (14.0-27.5)	31.8 (25.3-38.2)	26.6 (20.5-32.8)	14.7 (9.8-19.7)
HAQ-DI, LS mean (95% CI)[b] change from baseline	24	−0.4 (−0.5 to −0.3)	−0.4 (−0.5 to −0.3)	−0.2 (−0.3 to −0.1)	−0.4 (−0.4 to −0.3)	−0.3 (−0.4 to −0.2)	−0.0 (−0.1 to 0.0)
	52	−0.5 (−0.6 to −0.4)	−0.5 (−0.6 to −0.4)	−0.4 (−0.5 to −0.3)	−0.5 (−0.5 to −0.4)	−0.4 (−0.4 to −0.3)	−0.3 (−0.3 to −0.2)
SF-36 PCS, LS mean (95% CI)[b] change from baseline[c]	24	6.6 (5.4-7.8)	7.8 (6.6-9.0)	3.5 (2.3-4.7)	7.0 (6.0-7.9)	6.0 (5.0-7.1)	2.2 (1.2-3.2)
	52	7.9 (6.6-9.3)	8.7 (7.4-10.0)	7.5 (6.2-8.9)	8.7 (7.6-9.8)	7.2 (6.1-8.4)	5.8 (4.6-6.9)
SF-36 MCS, LS mean (95% CI)[b] change from baseline[c]	24	4.9 (3.4-6.3)	4.7 (3.3-6.1)	3.3 (1.9-4.7)	3.3 (2.1-4.4)	3.1 (2.0-4.3)	1.4 (0.2-2.5)
	52	5.2 (3.9-6.6)	5.2 (3.9-6.5)	4.5 (3.2-5.8)	3.8 (2.7-4.9)	3.9 (2.7-5.0)	3.9 (2.7-5.0)
FACIT-Fatigue response,[d] % (95% CI)[b]	24	65.4 (57.7-73.1)	65.6 (58.0-73.3)	44.8 (36.6-53.0)	57.5 (50.6-64.3)	52.8 (45.9-59.7)	40.1 (33.3-46.8)
	52	68.6 (61.0-76.1)	68.1 (60.6-75.7)	61.7 (53.7-69.7)	59.3 (52.5-66.2)	57.9 (51.1-64.8)	59.0 (52.2-65.8)
DAPSA LDA,[e] % (95% CI)[b]	24	32.7 (25.1-40.3)	33.1 (25.5-40.7)	13.0 (7.4-18.6)	45.8 (38.9-52.7)	43.9 (37.0-50.8)	21.2 (15.5-26.9)
	52	46.5 (38.5-54.6)	45.0 (37.0-53.0)	40.9 (32.8-49.0)	59.8 (53.0-66.6)	57.9 (51.1-64.8)	49.8 (42.9-56.7)
DAPSA remission,[e] % (95% CI)[b]	24	3.8 (0.5-7.0)	5.0 (1.3-8.7)	3.2 (0.1-6.4)	15.0 (9.9-20.0)	10.7 (6.4-15.1)	1.4 (0.0-3.2)
	52	10.7 (5.6-15.8)	15.0 (9.2-20.8)	9.7 (4.7-14.7)	23.8 (17.9-29.8)	19.6 (14.1-25.2)	12.0 (7.4-16.5)
cDAPSA LDA,[f] % (95% CI)[b]	24	31.4 (23.9-39.0)	31.9 (24.3-39.4)	12.3 (6.8-17.9)	44.4 (37.5-51.3)	44.4 (37.5-51.3)	21.7 (15.9-27.4)
	52	45.9 (37.9-54.0)	46.3 (38.2-54.3)	39.6 (31.6-47.7)	61.2 (54.5-68.0)	57.9 (51.1-64.8)	49.8 (42.9-56.7)
cDAPSA remission,[f] % (95% CI)[b]	24	3.8 (0.5-7.0)	5.6 (1.7-9.5)	3.9 (0.5-7.3)	19.6 (14.1-25.2)	11.7 (7.1-16.2)	1.8 (0.0-3.9)
	52	11.3 (6.1-16.6)	17.5 (11.3-23.7)	13.0 (7.4-18.6)	28.0 (21.8-34.3)	23.4 (17.5-29.3)	13.8 (9.0-18.6)
PASDAS LDA,[g] % (95% CI)[b]	24	18.2 (11.9-24.6)	26.3 (19.1-33.4)	9.1 (4.2-14.0)	35.0 (28.4-41.7)	33.2 (26.6-39.7)	8.8 (4.8-12.7)
	52	39.6 (31.7-47.5)	39.4 (31.5-47.3)	33.8 (26.0-41.6)	49.5 (42.6-56.5)	43.9 (37.0-50.8)	38.7 (32.0-45.4)
PASDAS VLDA,[g] % (95% CI)[b]	24	3.1 (0.1-6.2)	6.3 (2.2-10.3)	1.3 (0.0-3.4)	13.6 (8.7-18.4)	9.3 (5.2-13.5)	0.9 (0.0-2.4)
	52	8.2 (3.6-12.7)	17.5 (11.3-23.7)	9.1 (4.2-14.0)	23.4 (17.5-29.3)	21.0 (15.3-26.7)	12.9 (8.2-17.6)
MDA, % (95% CI)[b]	24	12.6 (7.1-18.0)	20.0 (13.5-26.5)	7.8 (3.2-12.4)	30.4 (24.0-36.8)	27.6 (21.3-33.8)	7.8 (4.0-11.6)
	52	29.6 (22.2-37.0)	28.8 (21.4-36.1)	26.6 (19.3-33.9)	40.7 (33.8-47.5)	32.2 (25.7-38.7)	29.0 (22.8-35.3)
vdH-S, mean (SD) change from baseline[h]	24	0.3 (2.5)	1.0 (3.2)	1.2 (2.7)	0.6 (2.4)	0.5 (1.7)	0.9 (3.5)
	52	1.2 (4.1)	1.5 (4.6)	1.5 (3.7)	0.9 (3.6)	0.5 (2.5)	1.1 (3.4)

Note: Results are pooled across DISCOVER-1 and DISCOVER-2.
Abbreviations: ACR20/50/70, ≥20/50/70% improvement in American College of Rheumatology response criteria; cDAPSA, clinical DAPSA (excludes C-reactive protein); CI, confidence interval; DAPSA, Disease Activity in Psoriatic Arthritis; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDA, low disease activity; LS, least-squares; MDA, minimal disease activity; PASDAS, Psoriatic Arthritis Disease Activity Score; PsA, psoriatic arthritis; Q4/8W, every 4/8 weeks; SD, standard deviation; SF-36 PCS/MCS, 36-item Short-Form health survey physical/mental component summary; vdH-S, PsA-modified van der Heijde-Sharp score; VLDA, very low disease activity; W, week.
[a]For binary endpoints, patients meeting treatment failure criteria and with missing data were considered nonresponders through Week 24; after Week 24 and through Week 52, patients with missing data were imputed as nonresponders and no treatment failure rules were applied. For continuous endpoints through Week 24, patients meeting treatment failure criteria were imputed as zero (no change) from baseline, and remaining missing data were assumed to be missing at random and imputed by multiple imputations; after Week 24 and through Week 52, after patients discontinued study agent for any reason, the change from baseline, if missing, was set to zero (no change), and no treatment failure rules were applied after Week 24.
[b]95% CIs based on the Wald statistic.
[c]LS mean determined using an analysis of covariance model.
[d]Defined as ≥4-point improvement in FACIT-Fatigue score.
[e]DAPSA LDA defined as score ≤ 14; DAPSA remission defined as score ≤ 4.
[f]cDAPSA LDA defined as score ≤ 13; cDAPSA remission defined as score ≤ 4.
[g]PASDAS LDA defined as score ≤ 3.2; PASDAS VLDA defined as score ≤ 1.9.
[h]Collected in DISCOVER-2 only, Read Campaign 2; scores are based on observed data. Patients with dactylitis at baseline: guselkumab Q4W, n = 114; guselkumab Q8W, n = 108; Placebo→Guselkumab Q4W, n = 92. Patients without dactylitis at baseline: guselkumab Q4W, n = 118; guselkumab Q8W, n = 130; Placebo→Guselkumab Q4W, n = 138.

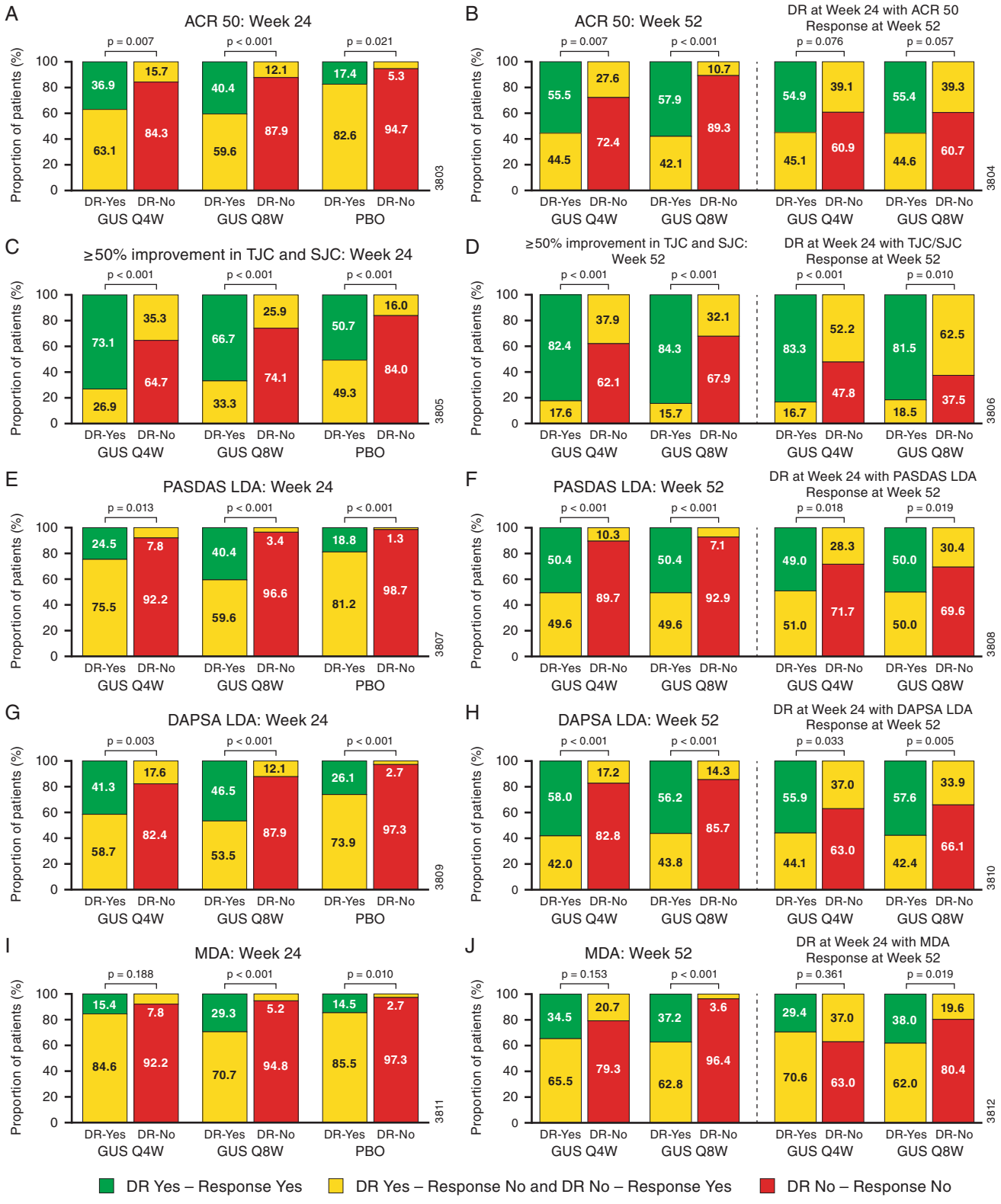


Figure 4. Clinical response at Week 24 and Week 52 by dactylitis resolution status.* Data pooled across DISCOVER-1 and DISCOVER-2. *Based on observed data; post hoc *P* values calculated based on Chi-squared statistics. ACR 50, 50% or more improvement in American College of Rheumatology response criteria; DAPSA, Disease Activity in Psoriatic Arthritis; DR, dactylitis resolution; GUS, guselkumab; LDA, low disease activity; MDA, minimal disease activity; PASDAS, Psoriatic Arthritis Disease Activity Score; PBO, placebo; Q4/8W, every 4/8 weeks; SJC, swollen joint count; TJC, tender joint count.

severity based on digit size and tenderness, with scores summed across each of the 20 digits, that has demonstrated responsiveness in PsA clinical trials (24,57,62).

Limitations. Clinical assessment of dactylitis is inherently subjective. In a clinical trial setting, assessors may have been more likely to overestimate the prevalence of dactylitis than in real-world settings, potentially contributing to the relatively high placebo response observed in these studies. Specifically, the DSS lacks objective assessments of digit size and tenderness, formal validation, and an established minimally clinically important difference. In the DISCOVER studies, the independent joint assessors were not given specific instructions not to include dactylitic digits in the SJC, so the observed differences in mean SJC in patients with versus without dactylitis (14 vs. 10) may have been due to dactylitis itself, which by definition is swelling of and swelling between the metacarpophalangeal and proximal interphalangeal and distal interphalangeal joints, such that each dactylitic digit contributes 2 or 3 swollen joints (6). Additionally, prevalent use of NSAIDs at baseline (reported by 64% of patients with and 64% of patients without dactylitis) may have reduced pain and swelling in dactylitic joints, potentially confounding DSS measurements. The high prevalence of overweight and obesity in these studies (74% of patients had a BMI ≥25 kg/m^2 at baseline) may also have confounded dactylitis diagnosis and assessment, as BMI has been shown to be a source of variability in digital subcutaneous tissue thickness, and inflammation in this tissue is a characteristic feature of dactylitis (63). Despite these limitations, the predominant focus of the current analyses was dactylitis resolution, which is a rigorous binary endpoint. The response indices of 20% or more, 50% or more, and 70% or more improvement in DSS were first used in the GO-DACT Phase 3b trial of golimumab in patients with PsA, in which these thresholds provided discrimination between treatment arms, helping confirm superiority of active treatment over placebo for the treatment of dactylitis (24). Reassuringly, guselkumab treatment effects were generally maintained across baseline demographic subgroups, including normal, overweight, and obese BMI categories.

The current analyses of dactylitis resolution in DISCOVER-1 and DISCOVER-2 were limited to a relatively short 1-year time frame. However, DISCOVER-2 continued through 2 years, and dactylitis resolution rates were maintained from Week 52 to 100 (72%-83% across treatment groups at Week 100) (22).

In conclusion, dactylitis is a PsA disease domain associated with more severe disease activity and worse patient outcomes. Guselkumab treatment is effective in resolving dactylitis in a broad range of patients with PsA, highlighting the role of IL-23 inhibition in controlling this important disease domain and emphasizing the importance of IL-23 in PsA pathophysiology and therapy. By selectively inhibiting the p19 subunit of IL-23, guselkumab promotes sustained resolution of dactylitis, which is associated with achievement of LDA, lower rates of radiographic progression, and achievement of other important treatment goals that may improve overall long-term outcomes in patients with PsA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. McGonagle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. McGonagle, McInnes, Deodhar, Schett, Shawi, Chakravarty, Kollmeier, X. Xu, Sheng, S. Xu, Ritchlin, Rahman, Mease.

Acquisition of data. McGonagle, McInnes, Deodhar, Schett, Ritchlin, Rahman, Mease.

Analysis and interpretation of data. McGonagle, McInnes, Deodhar, Schett, Shawi, Chakravarty, Kollmeier, X. Xu, Sheng, S. Xu, Ritchlin, Rahman, Mease.

ROLE OF THE STUDY SPONSOR

Employees of the funder had a role in the study design and in the collection, analysis, and/or interpretation of the data, the writing of the manuscript, and the decision to submit the manuscript for publication. The corresponding author had full access to all study data and had final responsibility to submit for publication.

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