


Composite Measures of Disease Activity in Psoriatic Arthritis: Comparative Instrument Performance Based on the Efficacy of Guselkumab in an Interventional Phase II Trial

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Objective. To assess performance of psoriatic arthritis (PsA) composite indices and evaluate guselkumab's effect on achieving low disease activity or remission.

Methods. In this phase II trial, patients with active PsA (≥ 3 tender and ≥ 3 swollen joints, C-reactive protein level ≥ 0.3 mg/dl, $\geq 3\%$ body surface-area with psoriasis involvement) were randomized 2:1 to subcutaneous guselkumab 100 mg ($n = 100$) or placebo ($n = 49$) at week 0, week 4, and every 8 weeks through week 44. At week 16, patients with $< 5\%$ improvement in swollen and tender joints could early escape to open-label ustekinumab. Patients continuing placebo crossed over to receive guselkumab 100 mg at weeks 24, 28, 36, and 44 (placebo to guselkumab). PsA composite indices (Psoriatic Arthritis Disease Activity Score [PASDAS], Group for Research and Assessment of Psoriasis and Psoriatic Arthritis composite score [GRACE], modified Composite Psoriatic Disease Activity Index [mCPDAI], and Disease Activity in Psoriatic Arthritis [DAPSA]) were analyzed as secondary outcomes (last observation carried forward for missing/post-early escape data through week 24; observed data post-week 24). Instrument performance was assessed.

Results. Baseline PASDAS, GRACE, mCPDAI, and DAPSA scores indicated moderate-to-high disease activity. At week 24, mean changes in each of these composite indices showed significant improvement with guselkumab (-2.50 , -2.73 , -3.8 , and -23.08 , respectively) versus placebo (-0.49 , 0.35 , -0.8 , and -4.98 , respectively; $P < 0.001$ for all). Significantly more guselkumab-treated patients achieved low/very low/remitted disease activity states according to PASDAS (very low + low 35% versus 4%; $P < 0.001$), GRACE (30% versus 2%; $P < 0.001$), mCPDAI (46% versus 10%; $P < 0.001$), and DAPSA (remission + low 40% versus 12%; $P < 0.001$). A total of 12% of guselkumab-treated versus no placebo-treated patients achieved DAPSA remission ($P < 0.01$). The PASDAS and GRACE instruments were more sensitive than the mCPDAI and DAPSA tools in detecting treatment effect. Residual skin disease and enthesitis were marginally more prominent in patients achieving DAPSA low disease activity versus other indices.

Conclusion. Guselkumab demonstrated efficacy in achieving low disease activity/remission based on all PsA composite indices assessed. Composite index use in PsA trials and the clinic requires careful consideration to optimize feasibility and instrument performance.

INTRODUCTION

Psoriatic arthritis (PsA) treatments have historically been evaluated using measures designed for rheumatoid arthritis (e.g., American College of Rheumatology [ACR] Disease Activity Score response criteria) and psoriasis (e.g., Psoriasis Area and Severity Index [PASI]). However, given the diverse and highly individual

nature of domain involvement in PsA (e.g., skin/nail disease, peripheral arthritis, dactylitis/enthesitis, axial disease), composite indices may more comprehensively assess disease activity and potentially identify agents with robust efficacy across all manifestations. Inclusion of indices for plaque psoriasis is of particular interest because cutaneous involvement is known to substantially influence patient well-being (1).

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SIGNIFICANCE & INNOVATIONS

- Composite indices have been developed for psoriatic arthritis (PsA) and included as secondary outcomes in clinical trials.
- All PsA composite indices evaluated in this phase II trial improved with guselkumab treatment, and significantly more guselkumab-treated patients achieved low disease activity states.
- The Psoriatic Arthritis Disease Activity Score and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis composite instruments demonstrated the largest improvement metrics in this trial.
- Residual nonarticular disease was more prominent in patients achieving Disease Activity in Psoriatic Arthritis low disease activity compared with other composite indices evaluated.

Guselkumab (Janssen Biotech), a human monoclonal antibody with high affinity for the p19 subunit of interleukin 23, demonstrated efficacy in a phase II trial of patients with active PsA and $\geq 3\%$ body surface area affected by psoriasis. Specifically, guselkumab significantly improved joint symptoms (ACR response), physical function (Health Assessment Questionnaire disability index [HAQ DI]), psoriasis (PASI), enthesitis score (Leeds Enthesitis Index [LEI]), dactylitis score, and health-related quality of life (HRQoL; 36-item Short Form health survey [SF-36]) (2). Additionally, guselkumab was generally well tolerated through ~ 1 year of treatment, similar proportions of guselkumab- and placebo-treated patients demonstrated investigator-identified infections through week 24, and no disproportional increase in adverse events with longer guselkumab exposure was observed (2).

Several composite outcome measures have been developed for PsA, including the Psoriatic Arthritis Disease Activity Score (PASDAS), the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) composite score (GRACE), the Composite Psoriatic Disease Activity Index (CPDAI), and the Disease Activity in Psoriatic Arthritis (DAPSA). In a recent report of

GRAPPA and Outcome Measures in Rheumatology, consensus was not reached on a specific continuous composite measure of disease activity. The report determined, however, that such assessments should include musculoskeletal disease, skin disease, and HRQoL, and that very low disease activity (VLDA)/minimal disease activity (MDA) should be targeted (3). In these secondary analyses of the aforementioned guselkumab phase II trial (2), we evaluated the effect of guselkumab on several different PsA composite indices and compared their performance.

PATIENTS AND METHODS

Ethics. These secondary analyses derive from a study conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by each site's governing ethics body; patients provided written informed consent.

Study design. PsA patients in this double-blind, placebo-controlled, parallel-group, 2-arm, multicenter trial were centrally randomized (2:1) to subcutaneous guselkumab or placebo (2). Study drugs were provided in identical prefilled syringes, and all patients received the same number of injections at the same time points. Patients randomized to guselkumab received guselkumab 100 mg at weeks 0, 4, 12, 20, 28, 36, and 44, and received placebo at week 24. Patients randomized to placebo received placebo at weeks 0, 4, 12, and 20 and received guselkumab 100 mg at weeks 24, 28, 36, and 44.

Patients with $< 5\%$ improvement in swollen joint count (SJC) and tender joint count (TJC) at week 16 early escaped to open-label ustekinumab (Janssen Biotech), i.e., from placebo to ustekinumab or from guselkumab to ustekinumab, at weeks 16, 20, 32, and 44, according to approved country-specific prescribing information. A final follow-up visit occurred at week 56.

Patients. Eligible patients included adults with PsA according to the Classification Criteria for Psoriatic Arthritis (4) for ≥ 6 months who had ≥ 3 tender and ≥ 3 swollen joints, C-reactive protein (CRP) level ≥ 0.3 mg/dl, $\geq 3\%$ body surface area with plaque psoriasis,

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and an inadequate response to standard therapies (2). Patients who received 1 prior tumor necrosis factor inhibitor were permitted but limited to 20% of participants, following 8–12 weeks of wash-out. Stable doses of methotrexate (≤ 25 mg/week), oral corticosteroids (≤ 10 mg/day of prednisone/equivalent), and nonsteroidal antiinflammatory drugs were permitted, but not required, through week 24. Sulfasalazine (≤ 3 gm/day) and leflunomide (≤ 20 mg/day) were permitted following week 24. Other disease-modifying antirheumatic drugs (DMARDs) and biologics were prohibited.

Procedures. Independent assessors evaluated joint tenderness ($n = 68$) and swelling ($n = 66$, excluding hips). Patients reported pain (0–100-mm visual analog scale [VAS]), global disease activity (0–100-mm VAS for arthritis, psoriasis, and both combined), and physical function (HAQ DI). Investigators completed the global assessment of disease activity (0–100-mm VAS), and serum CRP level was determined. The joint assessor evaluated dactylitis (from 0 = none to 3 = severe) for each finger and toe (total score 0–60) and enthesitis using the LEI (total score 0–6) (5). The PASI assessed skin disease severity and extent. The SF-36 assessed physical and mental HRQoL. Key efficacy assessments were performed at screening, baseline, and every 4 weeks through weeks 36, 44, and 56.

Outcomes. Patients achieved MDA if they met at least 5 of the following 7 criteria: TJC ≤ 1 of 68, SJC ≤ 1 of 66, PASI ≤ 1 , patient pain VAS ≤ 15 , patient global disease activity VAS (arthritis and psoriasis) ≤ 20 , HAQ DI ≤ 0.5 , and tender enthesal points ≤ 1 (6). Patients who met all 7 criteria achieved VLDA (6).

The PASDAS (7,8) was calculated using patient global VAS (arthritis and psoriasis, 0–100 mm), physician global VAS (0–100 mm), TJC, SJC, CRP level (mg/dl), enthesitis score (LEI), dactylitis score (scores of 0–3 recoded to 0–1, where any score >0 equaled 1) (9), and the SF-36 physical component summary (PCS) score. Disease activity cutoffs were as follows: very low (≤ 1.9), low (>1.9 to ≤ 3.2), moderate (>3.2 to <5.4), and high (≥ 5.4) (10).

The GRACE derives from the arithmetic mean of the desirability function, calculated by transforming the following variables, using predefined algorithms and expressing the total score as a mean ranging from 0 to 1, where 1 indicates a better state than 0: TJC, SJC, HAQ DI, patient's global VAS (arthritis and psoriasis, 0–100 mm), patient's assessment of skin disease activity VAS (0–100 mm), patient's global assessment VAS (arthritis, 0–100 mm), PASI, derived PsA QoL index (PsA QoL = $25.355 + [2.367 \times \text{HAQ DI}] - [0.234 \times \text{SF-36 PCS score}] - [0.244 \times \text{SF-36 mental component summary score}]$). The GRACE was then calculated as (1 minus the arithmetic mean of the desirability function) $\times 10$, with the following disease activity cutoffs: low (≤ 2.3), moderate (>2.3 to <4.7), and high (≥ 4.7) (8,10).

For the purpose of this analysis, the CPDAI was modified (mCPDAI) to exclude the axial disease domain. Thus, the mCPDAI (11) assessed 4 domains (joints, skin, entheses, and dactylitis)

and was calculated based on TJC, SJC, HAQ DI, PASI, and enthesitis/dactylitis scores. Within each domain, scores of 0–3 were assigned according to predefined cutoffs and summed to yield a total score of 0–12. Adjusted disease activity cutoffs ($[(\text{CPDAI}/15) \times 12]$) were as follows: low (≤ 3.2), moderate (>3.2 to <6.4), and high (≥ 6.4) (8).

The DAPSA was calculated as the sum of the TJC, SJC, CRP level (mg/dl), patient assessment of pain VAS (0–10), and patient global assessment VAS (arthritis, 0–10) (8). The disease activity cutoffs were as follows: remission (≤ 4), low (>4 to ≤ 14), moderate (>14 to ≤ 28), and high (>28) (12).

Statistical analysis. Details of sample size estimation have been reported (2). All efficacy analyses through week 24 included patients who received ≥ 1 administration of randomized treatment, with data handling rules applied (full analysis set). Patients who met treatment failure criteria (i.e., discontinued the study agent resulting from lack of efficacy or PsA worsening, initiated or increased the dose of methotrexate or oral corticosteroids for PsA, or initiated protocol-prohibited medications and/or therapies) were considered nonresponders for MDA and VLDA after treatment failure through week 24, as were patients who had missing data or early escaped at week 16. For continuous end points and response end points derived from continuous variables through week 24, patients with missing baseline data were excluded. Last observation carried forward methodology was employed to impute post-baseline missing data or data post-early escape. After week 24, all patients received active treatment, and no statistical comparisons were planned. Therefore, observed data were employed to summarize post-week 24 data among the 29 patients who crossed over from placebo to guselkumab and the 86 guselkumab-randomized patients who did not early escape at week 16 and did not discontinue the study drug prior to week 24 (week 24 data included as a reference). Statistical analyses were performed using SAS software, version 9.2.

To examine consistency of improvements in disease activity detected by each PsA composite index with improvements in HRQoL, mean improvements from week 0 to week 24 in the SF-36 PCS score were summarized by disease activity state among guselkumab-treated patients. Changes in composite index scores from week 0 to week 16 and from week 0 to week 24 were summarized using descriptive statistics, and between-treatment comparisons of change in composite indices were performed using analysis of variance. Between-treatment comparisons of the proportions of patients achieving very low or low disease activity or remission were performed post hoc with Fisher's exact test.

The relative performance of each index was assessed via calculation of treatment group effect size (the absolute value of the mean difference between baseline and week-24 values divided by the SD at baseline). Effect size values were used to categorize treatment effects as trivial (<0.20), small (≥ 0.20 to <0.50), moderate (≥ 0.50 to <0.80), or large (≥ 0.80) (13). Additional

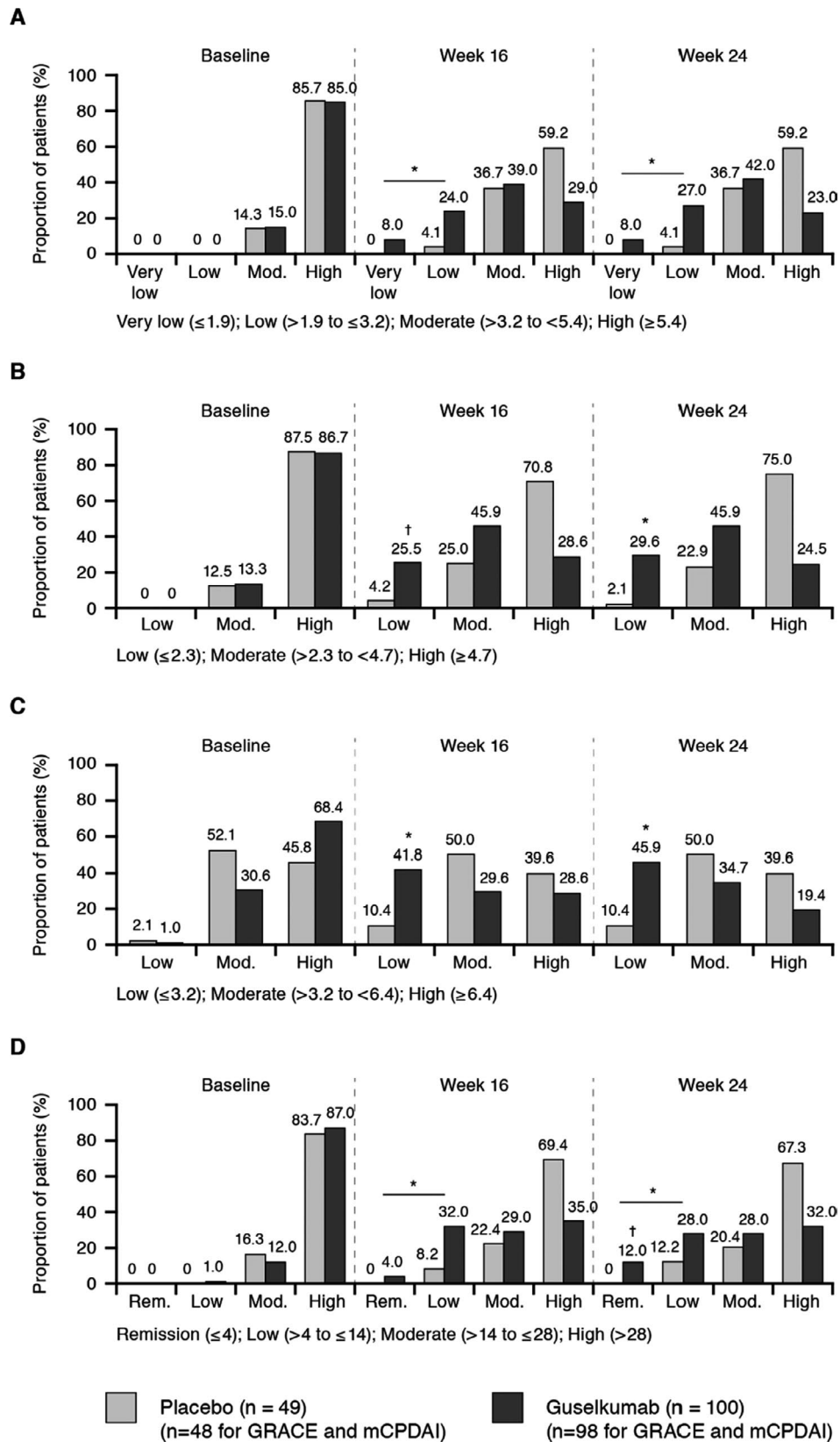


Figure 1. Proportions of patients achieving disease activity states for psoriatic arthritis-specific composite end points at week 16 and week 24 (full analysis set; last observation carried forward for missing data). **A**, Psoriatic Arthritis Disease Activity Score; **B**, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis composite score (GRACE); **C**, modified Composite Psoriatic Disease Activity Index (mCPDAI); and **D**, Disease Activity in Psoriatic Arthritis. *P* values were calculated post hoc. * = *P* ≤ 0.001; † = *P* ≤ 0.01.

comparative statistics included standardized mean differences (the absolute value of mean difference in change from baseline [guselkumab minus placebo] divided by the pooled SD of change from week 0 to week 24) and treatment group standardized response means (the absolute value of mean change from baseline divided by the SD of change from week 0 to week 24). The proportions of patients meeting no residual disease activity criteria (defined by CRP level \leq the upper limit of normal [0.287 mg/dl], dactylitis score = 0, enthesitis LEI score = 0, PASI \leq 1, TJC \leq 1 of 68, or SJC \leq 1 of 66) were assessed among patients achieving PsA-specific composite end point low, very low, or remitted states of disease activity, MDA, or VLDA at week 24.

RESULTS

Disposition and baseline characteristics. This phase II trial was conducted at 34 sites in North America and Europe. Patient screening began on March 27, 2015; the last patient visit was completed on January 17, 2017. Patient disposition has been reported (2). Briefly, 149 patients were randomized to placebo (n = 49) or guselkumab 100 mg (n = 100). Seventeen of 49 patients

(35%) receiving placebo and 10 of 100 guselkumab-treated patients (10%) qualified for early escape to ustekinumab at week 16. Twenty-nine of 49 patients (59%) in the placebo group crossed over to receive guselkumab at week 24; 28 of these patients completed treatment through week 44. Eighty-six of 100 patients (86%) in the guselkumab group completed week 24 and continued guselkumab treatment; 84 patients (84%) completed treatment through week 44. Overall, 135 randomized patients (including 23 who early escaped to ustekinumab) of 149 (91%) completed the trial at week 56.

Baseline characteristics were generally similar between randomized groups and indicated moderate-to-severe arthritis, with substantial disability (mean HAQ DI 1.39). At study outset, 72% and 54% of patients presented with enthesitis and dactylitis, respectively (2). Baseline mean scores for PASDAS (6.5), GRACE (6.1), mCPDAI (7.6), and DAPSA (46.7) also demonstrated moderate-to-high disease activity. When summarized via categorization, the proportions of patients with moderate-to-high disease activity at baseline were comparable between the placebo and guselkumab groups for each of the indices for PASDAS (both 100%), GRACE (both 100%), mCPDAI (98% and 99%, respectively), and DAPSA (100% and 99%, respectively) (Figure 1).

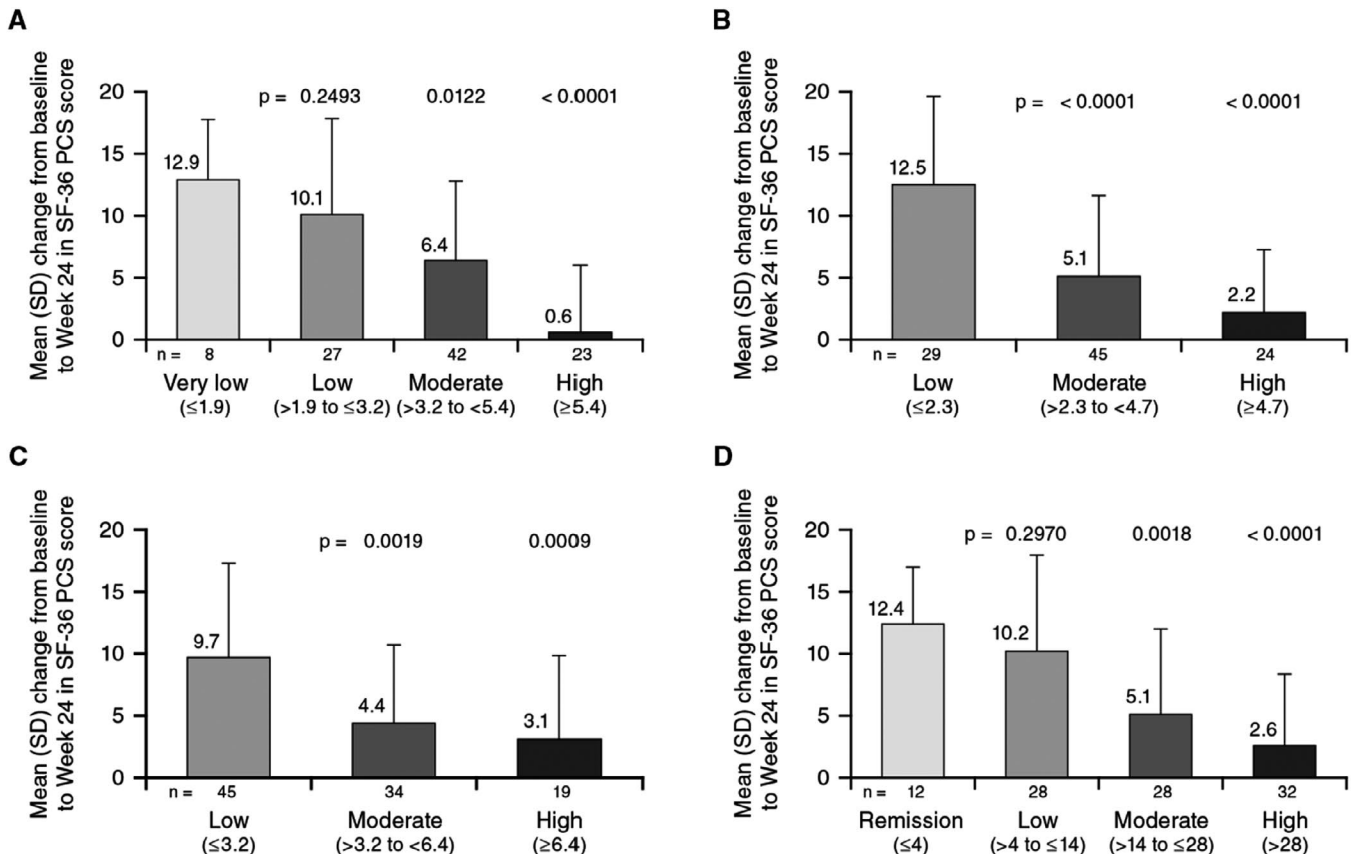


Figure 2. Mean (SD, shown as error bars) changes from baseline at week 24 in the 36-item Short Form health survey (SF-36) physical component summary (PCS) score by disease activity state according to psoriatic arthritis-specific composite end points (guselkumab-treated patients in the full analysis set; last observation carried forward for missing data). **A**, Psoriatic Arthritis Disease Activity Score; **B**, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis composite score; **C**, modified Composite Psoriatic Disease Activity Index; and **D**, Disease Activity in Psoriatic Arthritis.

Validation of PsA-specific composite indices using the SF-36 PCS score as an anchor. Changes from week 0 to week 24 in SF-36 PCS scores were consistent with disease activity states defined by each PsA composite index in guselkumab-treated patients. Specifically, the largest improvements in SF-36 PCS scores were observed in patients with low disease activity (including VLDA or remission) at week 24 (9.7–12.9 across indices), which were significantly higher than scores observed in patients with moderate (4.4–6.4; $P < 0.05$) or high (0.6–3.1; $P < 0.001$) disease activity at week 24 (Figure 2).

The effect of guselkumab on PsA-specific composite end points. *Placebo-controlled period.* Guselkumab significantly improved disease activity from week 0 to week 24, relative to placebo, when assessed using indices for PASDAS (mean changes -2.50 versus -0.49), GRACE (-2.73 versus -0.35), mCPDAI (-3.8 versus -0.8), and DAPSA (-23.08 versus -4.98) ($P < 0.001$ for all) (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.2404/abstract>). Consistently, significantly higher proportions of guselkumab-treated than placebo-treated patients achieved low disease activity (including VLDA or remission) when assessed by indices for PASDAS (very low + low 35% versus 4%; $P < 0.001$), GRACE (30% versus 2%; $P < 0.001$), mCPDAI (46% versus 10%; $P < 0.001$), and DAPSA (remission + low 40.0% versus 12%; $P < 0.01$). Further, more patients achieved VLDA based on PASDAS (8% versus 0; $P = 0.053$) and significantly more patients achieved DAPSA remission (12% ver-

sus 0; $P < 0.01$) (Figure 1). Achievement of low disease activity, based on the different composite indices, among patients with or without dactylitis or enthesitis is summarized in Supplementary Table 1, available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24046/abstract>. Comparatively, as reported previously (2), 23% versus 2% of guselkumab-treated and placebo-treated patients achieved MDA at week 24 ($P < 0.001$). A similar response pattern was observed for VLDA (6% versus 0; $P = 0.076$) (Figure 3A).

Active-treatment period. In the post-week 24 efficacy population, observed mean changes in the PsA composite indices at week 44 are shown in Supplementary Figure 2, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.2404/abstract>; week-24 data in the same population are included for reference. The improvements afforded by guselkumab at week 24 were sustained through week 44 in guselkumab-randomized patients, and similar improvements were realized in placebo-randomized patients who received guselkumab from week 24 to week 44. Also, among patients who crossed over from placebo to guselkumab at week 24, the proportions of patients with low disease activity (including VLDA or remission) were higher at week 44 than prior to the start of guselkumab at week 24 (i.e., PASDAS very low + low 39% at week 44 versus 7% at week 24, GRACE 39% versus 7%, mCPDAI 71% versus 14%, and DAPSA remission + low 50% versus 21%) and were generally consistent with those observed at week 44 among patients receiving guselkumab from week 0 forward (i.e., PASDAS very low + low 39% for placebo to guselkumab and 46% for guselkumab GRACE 39% and

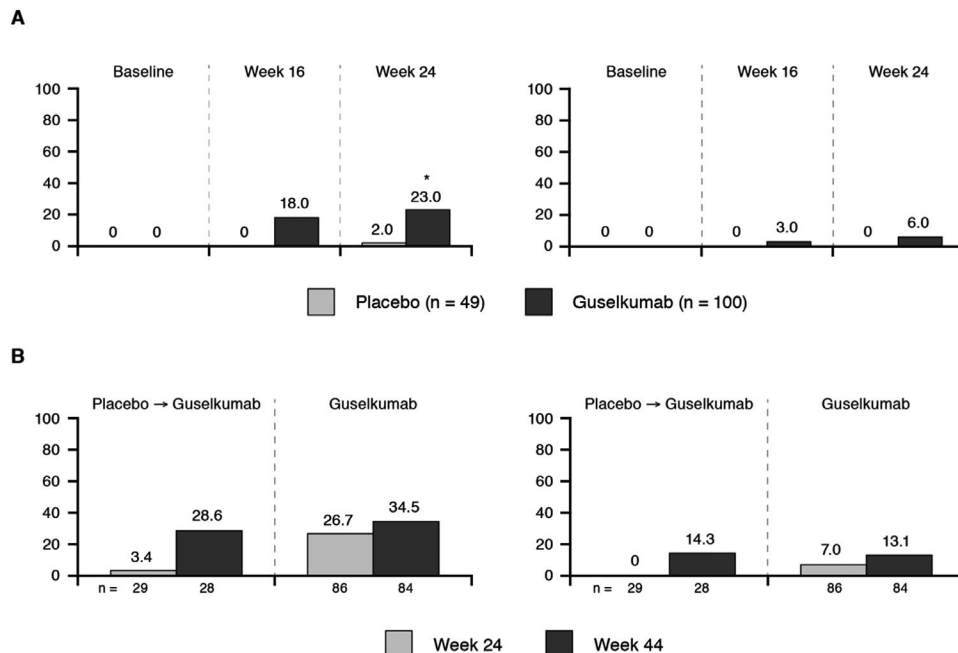


Figure 3. Proportions of patients (%) achieving minimal disease activity (MDA) and very low disease activity (VLDA). **A**, At week 16 (MDA, left) and week 24 (VLDA, right) (full analysis set; nonresponder imputation). **B**, At week 24 (MDA, left) and week 44 (VLDA, right) (post-week 24 efficacy analysis set, observed data; week-24 observed data in the same population included as a reference; P values were calculated post hoc). * = $P \leq 0.001$.

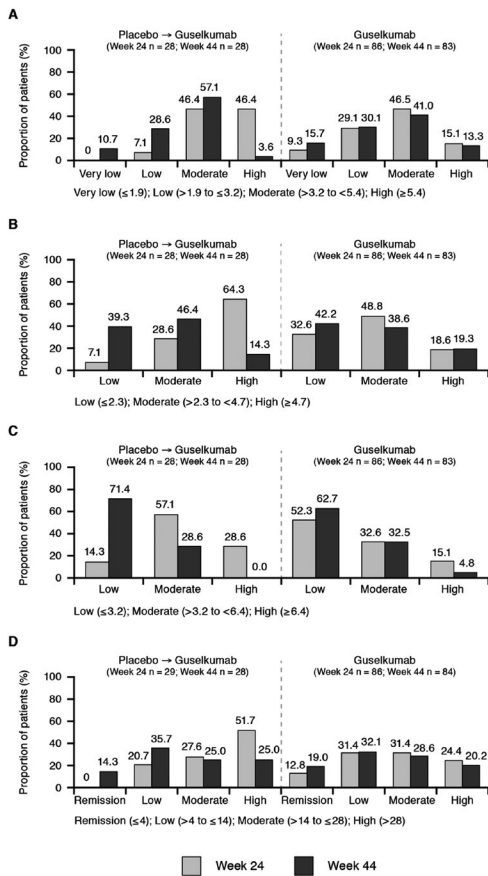


Figure 4. Proportions of patients achieving disease activity states post-week 24 for the psoriatic arthritis-specific composite end points. **A**, Psoriatic Arthritis Disease Activity Score; **B**, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis composite score; **C**, modified Composite Psoriatic Disease Activity Index; and **D**, Disease Activity in Psoriatic Arthritis. Week-44 data derived from the post-week 24 efficacy analysis set-based observed data (week-24 observed data in the same population included for reference).

42%, respectively; mCPDAI 71% and 63%, respectively; and DAPSA remission + low 50% and 51%, respectively) (Figure 4). In guselkumab-randomized patients, low disease activity (including VLDA or remission) response rates were maintained or increased from week 24 to week 44 (last on-treatment efficacy assessment, i.e., 38% going to 46% for PASDAS, 33% going to 42% for GRACE, 52% going to 63% for mCPDAI, and 44% going to 51% for DAPSA). Furthermore, PASDAS VLDA (9% going to 16%), DAPSA remission (13% going to 19%) (Figure 4), MDA (27% going to 35%), and VLDA (7% going to 13%) (Figure 3B) response rates increased from week 24 to week 44.

Performance of PsA-specific composite end points in detecting treatment effects at week 24. Statistics for the standardized mean differences (5.16–8.84), effect size (1.12–2.29, wherein effect size ≥ 0.80 represents a large treatment effect) (13), and standardized response means (1.14–1.58) indi-

cated that guselkumab elicited a substantial effect in treating the diverse manifestations of PsA relative to placebo regardless of the composite index employed (Figure 5). Based on standardized mean differences, the PASDAS (8.13) and GRACE (8.84) indices were more sensitive than the mCPDAI (7.20), and all 3 were more sensitive than the DAPSA (5.16), in distinguishing guselkumab from placebo treatment (Figure 5A). The effect size and statistics for the standardized response means also indicated that PASDAS (2.29 and 1.58, respectively) and GRACE (2.18 and 1.55, respectively) were more sensitive than mCPDAI (1.75 and 1.39, respectively), and all 3

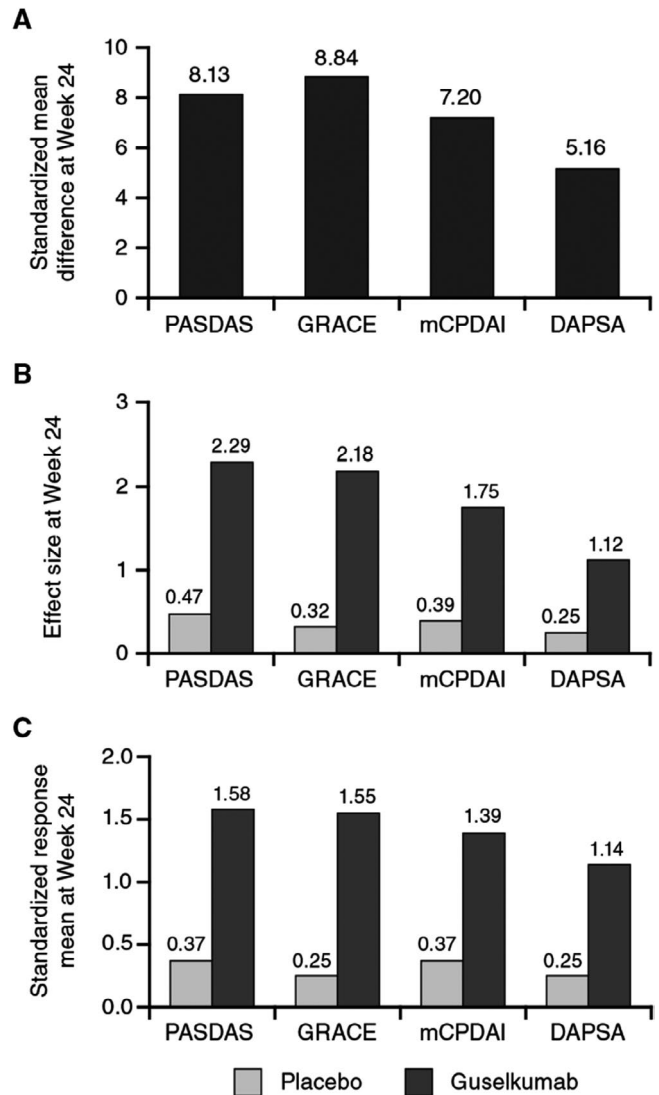


Figure 5. Comparative statistics evaluating guselkumab treatment effects detected at week 24 according to the Psoriatic Arthritis Disease Activity Score (PASDAS), Group for Research and Assessment of Psoriasis and Psoriatic Arthritis composite score (GRACE), modified Composite Psoriatic Disease Activity Index (mCPDAI), and Disease Activity in Psoriatic Arthritis (DAPSA) psoriatic arthritis-specific composite end points. **A**, standardized mean difference; **B**, effect size; and **C**, standardized response mean (full analysis set; last observation carried forward for missing data).

Table 1. Number (%) of patients meeting no residual disease activity criteria among guselkumab-treated patients achieving low disease activity states defined by psoriatic arthritis composite indices at week 24 (full analysis set)*

Measure of residual disease activity	PASI ≤1	TJC ≤1	SJC ≤1	CRP ≤ULN	LEI = 0	Dactylitis = 0	MDA	VLDA
PASDAS								
Very low: ≤1.9 (n = 8)	7 (87.5)	8 (100.0)	5 (62.5)	4 (50.0)	8 (100.0)	8 (100.0)	8 (100.0)	3 (37.5)
Low: >1.9 to ≤3.2 (n = 27)	22/26 (84.6)	20 (74.1)	12 (44.4)	12 (44.4)	23 (85.2)	25 (92.6)	12/25 (48.0)	3/25 (12.0)
GRACE								
Low: ≤2.3 (n = 29)	26 (89.7)	23 (79.3)	14 (48.3)	9 (31.0)	24 (82.8)	27 (93.1)	21/28 (75.0)	6/28 (21.4)
mCPDAI								
Low: ≤3.2 (n = 45)	37 (82.2)	37 (82.2)	19 (42.2)	16 (35.6)	42 (93.3)	42 (93.3)	22/44 (50.0)	6/44 (13.6)
DAPSA								
Remission: ≤4 (n = 12)	9 (75.0)	12 (100.0)	8 (66.7)	6 (50.0)	11 (91.7)	12 (100.0)	10/11 (90.9)	4/11 (36.4)
Low: >4 to ≤14 (n = 28)	19/27 (70.4)	22 (78.6)	10 (35.7)	11 (39.3)	22 (78.6)	22 (78.6)	12/27 (44.4)	2/27 (7.4)
MDA (n = 23)	21 (91.3)	20 (87.0)	14 (60.9)	5 (21.7)	19 (82.6)	22 (95.7)	–	6 (26.1)
VLDA (n = 6)	6 (100.0)	6 (100.0)	6 (100.0)	1 (16.7)	6 (100.0)	6 (100.0)	6 (100.0)	–

* PASI = Psoriatic Area and Severity Index; TJC = tender joint count; SJC = swollen joint count; CRP = C-reactive protein; ULN = upper limit of normal (0.287 mg/dl); LEI = Leeds Enthesitis Index; MDA = minimal disease activity; VLDA = very low disease activity; PASDAS = Psoriatic Arthritis Disease Activity Score; GRACE = Group for Research and Assessment of Psoriasis and Psoriatic Arthritis composite score; mCPDAI = modified Composite Psoriatic Disease Activity Index; DAPSA = Disease Activity in Psoriatic Arthritis.

were more sensitive than DAPSA (1.12 and 1.14, respectively) in detecting changes upon treatment (Figure 5B and C).

Evaluation of residual disease activity among guselkumab-treated patients who achieved low disease activity, VLDA, remission, or MDA at week 24 based on PsA composite indices. The criterion for no residual skin disease (PASI ≤1) was met in ≥80% of patients achieving PASDAS, GRACE, or mCPDAI low disease activity or VLDA and/or MDA; 75% and 70% of patients achieving DAPSA remission and low disease activity, respectively, also demonstrated PASI ≤1. The criterion for no residual TJC (≤1) was met in 100% of patients achieving PASDAS VLDA and DAPSA remission and/or VLDA; in 87% of patients achieving MDA; and in 74–82% of patients achieving low disease activity based on PASDAS, GRACE, mCPDAI, and DAPSA. The criterion for no residual SJC (≤1) was met in 100% of patients achieving VLDA; in ~60% of patients achieving PASDAS VLDA and DAPSA remission and/or MDA; and in ~35–48% of patients achieving low disease activity based on the PASDAS, GRACE, mCPDAI, and DAPSA instruments. The majority of patients achieving low disease activity, VLDA, or remission according to the PsA-specific indices or MDA/VLDA had no enthesitis or dactylitis, but >50% had an elevated CRP level (>0.287 mg/dl). All patients who achieved PASDAS VLDA and ~91% of those who achieved DAPSA remission also met MDA criteria, while <40% also met VLDA criteria (Table 1).

DISCUSSION

Guselkumab demonstrated efficacy in a phase II trial of patients with active PsA (2). Herein, guselkumab demonstrated superiority over placebo in improving composite scores, with significantly more guselkumab-treated than placebo-treated

patients achieving MDA and low disease activity states. Overall, the PASDAS and GRACE were more sensitive than the mCPDAI, and all were more sensitive than the DAPSA, at detecting treatment effect. For patients achieving low disease states, residual nonarticular disease was more prominent in patients achieving DAPSA low disease activity versus other indices evaluated.

The MDA and VLDA indices assess joint, skin, enthesal disease, and physical function; both can serve as response criteria (defining low disease activity and VLDA, respectively) and treatment targets. The PASDAS and GRACE instruments were developed using longitudinal observational data derived from a large international cohort of PsA patients (7). The PASDAS more heavily weights patient and physician global assessments than joint, skin, dactylitis, enthesitis, acute-phase response, and HRQoL domains, while the GRACE equally weights joints, skin, physical function, QoL, and global assessments. The domain-based CPDAI (axial/peripheral joints, skin, entheses, dactylitis) employs predefined cutoffs, derived from published literature and expert consensus, to categorize disease severity (11).

The DAPSA, deriving from a reactive arthritis measure, was further developed using a clinical cohort of PsA patients to assess joint disease, acute-phase response, and patient assessments of pain and overall disease activity (12). In this study, these PsA-specific indices were validated using the SF-36 PCS score as an anchor, which may be partly circular given that it is a component of the PASDAS. Results showed that the largest improvements in SF-36 PCS scores occurred in patients in remission or with very low or low disease activity according to each index at week 24, and these improvements were significantly higher than those observed in patients with moderate or high disease activity at the same time point. Of note, the PASDAS, GRACE, and DAPSA composite measures were also externally validated in PsA using radiographic data

from the golimumab GO-REVEAL PsA trial. In that analysis, each index was able to differentiate the progression of structural damage of peripheral joints in relation to disease outcome (14).

Based on standardized mean differences, effect size, and standardized response means statistics, the PASDAS and GRACE indices, based on the arithmetic mean of the desirability function, appear to be more sensitive than the mCPDAI, which itself is more sensitive than DAPSA, in detecting changes in disease activity afforded by guselkumab treatment and distinguishing these effects from those of placebo. Consistently, a previous analysis using data from the golimumab GO-REVEAL trial in PsA indicated that PASDAS and the arithmetic mean of the desirability function (from which the GRACE index derives) demonstrated larger effect sizes than the mCPDAI and DAPSA tools (8). The PASDAS is a weighted measure encompassing a wider spectrum of disease manifestations than, for example, the largely articular DAPSA, and this weighting may account for its larger effect size. The PASDAS was also derived from real patient data using regression analyses, and such methodology is likely to result in more emphasis (weighting) being given to domains showing the greatest changes. Both the GRACE and mCPDAI are modular measures, and despite covering many important domains, their modular construction may inhibit their responsiveness. A point to note is that most patients in this study had polyarticular disease and were treated with a drug that has demonstrated high levels of clinical efficacy; in other circumstances the relative performance of these composite indices may differ.

Regarding residual disease activity, the majority of patients who achieved remission or very low or low disease activity states after guselkumab treatment, based on the PASDAS, GRACE, mCPDAI, DAPSA, and MDA/VLDA indices, demonstrated little residual skin disease, enthesitis, dactylitis, or tender joints, although proportions of patients with residual skin disease and enthesitis were marginally higher in the group of patients who achieved low disease activity with the DAPSA. Consistent results were obtained in previous determinations based on the golimumab GO-REVEAL trial (8). Substantial proportions of patients achieving low disease activity per the GRACE, DAPSA, and mCPDAI exhibited residual swollen joints. The same was true for achievement of PASDAS low disease activity despite the relatively minor contribution of the SJC to that index versus equal weighting in the GRACE, DAPSA, and mCPDAI. Achievement of very low or remitted disease activity according to the PASDAS and DAPSA, as well as MDA or VLDA, substantially reduced the proportions of patients with residual swollen joints. Further, despite achieving remission, very low or low disease activity states, most of these patients still exhibited elevated CRP levels, indicating incomplete resolution of chronic inflammation. Clearly, none of these composite minimal targets represent total abrogation of disease activity.

Among all composite indices evaluated, VLDA appears to represent the most stringent (achieved by only 13% of guselkumab-treated patients at week 44). Achievement of VLDA, however,

resulted in the least amount of residual disease activity across all aspects of disease evaluated other than CRP level. While the small number of patients achieving VLDA in this study should be noted, consistent results were recently reported in a retrospective analysis of 347 patients with PsA who received standard or biologic DMARDs in either a tight-control clinical trial or an observational cohort study (15). Herein, all patients achieving PASDAS VLDA and 20 of 22 (91%) achieving DAPSA remission also achieved MDA, while 15 of 23 patients (65%) who met the MDA criteria did not achieve PASDAS VLDA, and 13 of 23 (57%) did not meet the DAPSA remission criteria, suggesting that PASDAS VLDA and DAPSA remission criteria are more stringent and difficult to achieve than MDA.

Future challenges for composite measures will be to strike the correct balance between comprehensiveness and feasibility, particularly in the clinic. Composite indices such as the PASDAS and GRACE can add another layer of documentation, yet complete evaluation of any patient with PsA can require assessment of all clinical domains. If the additional data for some of these indices are worth collecting, then we need to be clear about the benefit. In the clinic, simply collecting the data required for the DAPSA will encourage incomplete assessment and could give a false impression of overall disease activity. Should the new composite indices only be used in clinical trials? Currently, the answer is in the affirmative (3), but with further use and additional longitudinal cohorts, a short-hand version can possibly be developed for clinical use. Outside of dedicated centers, using composite measures might be limited to those patients exhibiting more complex clinical manifestations, while those with oligosymptomatic manifestations might readily be managed using conventional tools.

Regarding limitations, the current analyses are hampered by the small sample size of the phase II trial from which the data derive. Additionally, the SF-36 PCS score is a component of the PASDAS and thus was not an independent measure in PASDAS validation. The evaluation of residual disease is also limited by small numbers of patients achieving remission and low or very low disease activity.

In conclusion, the composite outcomes assessed are not uniform in either responses or disease domains included, and the choice of composite index for any particular study, or for use in the clinic, will depend on which domains are to be assessed. Clearly, in patients selected for active articular disease, all composite indices assessed perform well and can distinguish between placebo and active drug. However, differing populations, e.g., those exhibiting predominant axial disease or predominant enthesitis, may require careful choice of composite index; existing indices require further validation in such patient subgroups. Of interest, in our study, a lower proportion of participants with dactylitis/enthesitis at baseline achieved low disease activity assessed by PASDAS or mCPDAI versus those without dactylitis/enthesitis; however, proportions were comparable when disease activity was assessed using the GRACE or DAPSA, both of which

do not assess dactylitis/enthesitis. These exploratory data suggest that, in patients with dactylitis/enthesitis, indices assessing dactylitis/enthesitis may be more appropriate to ensure that such disease is not overlooked. Selection and use of a particular composite index requires careful consideration given their diverse properties. Future studies should aim to optimize feasibility and performance of composite tools by developing new, or adapting existing, indices.

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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 submitted for publication. Dr. Helliwell 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.

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ROLE OF THE STUDY SPONSOR

All authors, including employees of Janssen, were involved in data collection, analysis, and/or interpretation; trial design; patient recruitment; manuscript preparation; and the decision to submit for publication. Janssen provided funding to a professional medical writer who assisted with manuscript preparation and submission.

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