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Abstract
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Reference

DOI : 10.1002/acr.24046
PMID : 31421033
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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/acr.24046

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Funding: Janssen Research & Development, LLC funded this trial. All authors, including employees of Janssen (XLX, SX, YW, ECH), 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.

Disclosures: PS Helliwell has received research grants and/or payments to third parties for lectures and educational material development/events (<$10,000) from AbbVie, Amgen, Celgene, Janssen, Novartis, Pfizer, and UCB.

A Deodhar has received research grants from AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer, and UCB and has served on the advisory boards of Eli Lilly, Janssen, Novartis, Pfizer, and UCB (<$10,000).

AB Gottlieb has advisory board and/or consulting agreements with AbbVie, Allergan, Avotres Therapeutics, Beiersdorf Inc., Boeringer Ingelheim, Bristol Myers Squibb Co., Celgene Corp., Dermira, Eli Lilly, Incyte, Janssen, Leo Pharmaceuticals, Novartis, Reddy

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Labs, Sun Pharmaceutical Industries, UCB, and Valeant, Xbiotech (<$10,000), as well as research/educational grants from Boeringer Ingelheim, Incyte, Janssen, Novartis, Xbiotech, and UCB.

W-H Boehncke has received honoraria as a speaker or advisor for the following companies: AbbVie, Almirall, Biogen, BMS, Celgene, Eli Lilly, Janssen,Leo, MSD, Novartis, Pantec, Pfizer, Sanofi, and UCB (<$10,000).

XL Xu, S Xu, Y Wang, and EC Hsia are employed by Janssen Research & Development, LLC (a subsidiary of Johnson & Johnson) and own Johnson & Johnson stock or stock options.

DD Gladman has received grants and/or consultancies (<$10,000) from AbbVie, Amgen, BMS, Celgene, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, and UCB.

CT Ritchlin has received grants/or consultancies (<$10,000) from AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer, and UCB.

ABSTRACT

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

Methods. In this Phase 2 trial, patients with active PsA (≥3 tender and ≥3 swollen joints, C-reactive protein ≥0.3 mg/dL, ≥3% body-surface-area psoriasis involvement) were randomized 2:1 to subcutaneous guselkumab 100 mg (N=100) or placebo (N=49) at Week 0, Week 4 and q8w through Week44. At Week 16, patients with <5% improvement in swollen and tender joints could early escape (EE) to open-label ustekinumab. Patients continuing placebo

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crossed-over to receive guselkumab 100 mg at Weeks 24, 28, 36, and 44 (placebo→guselkumab). PsA composite indices (Psoriatic Arthritis Disease Activity Score [PASDAS], GRAppa Composite scorE [GRACE], modified Composite Psoriatic Disease Activity Index [mCPDAI], Disease Activity index for PSoriatic Arthritis [DAPSA]) were analyzed as secondary outcomes (last-observation-carried-forward for missing/post-EE 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 demonstrated significant improvement with guselkumab (-2.50, -2.73, -3.8, -23.08, respectively) vs. placebo (-0.49, 0.35, -0.8, -4.98; all p<0.001). Significantly more guselkumab-treated patients achieved low (or very-low/remission) disease activity state(s) per PASDAS (very-low+low 35.0% vs. 4.1%; p<0.001), GRACE (29.6% vs. 2.1%; p<0.001), mCPDAI (45.9% vs. 10.4%, p<0.001), and DAPSA (remission+low 40.0% vs. 12.2%; p<0.001); 12% of guselkumab-treated vs. 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.
SIGNIFICANCE & INNOVATIONS

- Composite indices have been developed for psoriatic arthritis (PsA) and included as secondary outcomes in clinical trials.
- All PsA composite indices evaluated improved with guselkumab treatment, and significantly more guselkumab-treated patients achieved low disease activity states.
- The PASDAS and GRACE instruments demonstrated the largest improvement metrics in this Phase 2 trial.
- Residual non-articular disease was more prominent in patients achieving DAPSA low disease activity compared with other composite indices evaluated.

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, since cutaneous involvement is known to substantially influence patient well-being (1).

Guselkumab (Janssen Biotech, Inc., Horsham, PA, USA), a human monoclonal antibody with high-affinity for the p19-subunit of interleukin-23, recently demonstrated efficacy in a Phase 2 trial of patients with active PsA and ≥3% body surface area (BSA) affected by psoriasis. Specifically, guselkumab significantly improved joint symptoms (ACR response), physical
function (Health Assessment Questionnaire-Disability Index [HAQ-DI]), psoriasis (PASI), enthesitis (Leeds Enthesitis Index [LEI]), dactylitis, 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 Week24, 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), GRAppa Composite scorE (GRACE), Composite Psoriatic Disease Activity Index (CPDAI), and Disease Activity index for PSoriatic Arthritis (DAPSA). In a recent report of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and Outcome Measures in Rheumatology (OMERACT), consensus was not reached on a specific continuous measure of disease activity. It was determined, however, that such assessments should include musculoskeletal disease, skin disease, and HRQoL and that very low/minimal disease activity (VLDA/MDA) should be targeted (3). In these secondary analyses of the aforementioned guselkumab Phase 2 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 (NCT02319759) conducted according to Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by each site’s governing ethical body; patients provided written informed consent.
**Study design.** PsA patients in this double-blind, placebo-controlled, parallel-group, two-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 placebo at Week 24. Patients randomized to placebo received placebo at Weeks 0, 4, 12, and 20 and guselkumab 100 mg at Weeks 24, 28, 36, and 44.

Patients with <5% improvement in swollen and tender joint counts (TJCs and SJC) at Week 16 early escaped to open-label ustekinumab (Janssen Biotech, Inc., Horsham, PA, USA), 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 (CASPAR) (4) for ≥6 months, ≥3 tender and ≥3 swollen joints, C-reactive protein (CRP) ≥0.3 mg/dL, ≥3% BSA with plaque psoriasis, and inadequate response to standard therapies (2). Patients who received one prior tumor necrosis factor-inhibitor were permitted, but limited to 20% of participants, following 8–12 weeks of washout. Stable doses of methotrexate (MTX; ≤25 mg/week), oral corticosteroids (≤10 mg/day of prednisone/equivalent), and nonsteroidal anti-inflammatory drugs were permitted, but not required, through Week 24. Sulfasalazine (≤3 g/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 was determined. The joint assessor evaluated dactylitis (0-none to 3-severe) for each finger and toe (total score 0–60) and enthesitis using the LEI (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, every 4 weeks through Week 36, Week 44, and Week 56.

**Outcomes.** Patients achieved MDA if they met at least five of the following seven criteria: TJC ≤1/68, SJC ≤1/66, 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 seven 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 (mg/L), enthesitis (LEI), dactylitis (scores of 0–3 recoded to 0–1, where any score >0 equaled 1) (9), and the SF-36 PCS score. Disease activity cutoffs were: very low (≤1.9), low (>1.9 – ≤3.2), moderate (>3.2 – <5.4), high (≥5.4) (10).

The GRACE derives from the Arithmetic Mean of the Desirability Function (AMDF), calculated by transforming the following variables, using predefined algorithms and expressing the total score as a mean ranging from 0–1, 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 PsAQoL index (PsAQoL=25.355+[2.367×HAQ-DI] –

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[0.234×SF-36 PCS score] – [0.244×SF-36 mental component summary score]). The GRACE was then calculated as (1–AMDF) x 10, with the following disease activity cutoffs: low (≤2.3), moderate (>2.3 – <4.7), 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 four domains (joints, skin, entheses, dactylitis) and was calculated based on TJC, SJC, HAQ-DI, PASI, and dactylitis/enthesitis 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 ([CPDAI/15]x12) were: low (≤3.2), moderate (>3.2 – <6.4), high (≥6.4) (8).

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

**Statistical analyses.** 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 study agent resulting from lack of efficacy or PsA worsening, initiated or increased the dose of MTX 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 endpoints and response endpoints 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→guselkumab and the 86 guselkumab-randomized patients who did not early escape at Week 16 and did not discontinue study drug prior to Week 24 (Week 24 data included as a reference). Statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA).

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 Week16 and from Week 0 to Week24 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 (ES; the absolute value of the mean difference between baseline and Week-24 values divided by the standard deviation [SD] at baseline). ES values are 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 comparative statistics included standardized mean differences (SMDs; the absolute value of mean difference in change from baseline [guselkumab minus placebo] divided by pooled SD of change from Week 0 to Week24) and treatment group standardized response means (SRMs; the absolute value of mean change from baseline divided by SD of change from Week 0 to Week24). The proportions of patients meeting no residual disease activity criteria (defined by CRP ≤ upper limit of normal [0.287 mg/dL], dactylitis score=0, enthesitis LEI score=0, PASI ≤1, TJC ≤1/68, SJC ≤1/66) were assessed

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among patients achieving PsA-specific composite endpoint low disease activity/remission states, MDA, or VLDA at Week 24.

RESULTS

disposition and baseline characteristics

This Phase 2 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 (34.7%) placebo- and 10/100 (10.0%) guselkumab-treated patients qualified for early escape to ustekinumab at Week 16. Twenty-nine of 49 (59.2%) patients 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 (86.0%) patients in the guselkumab group completed Week 24 and continued guselkumab treatment; 84 (84.0%) patients completed treatment through Week 44. Overall, 135 (including 23 who early escaped to ustekinumab) of 149 (90.6%) randomized patients 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, 71.8% and 54.4% of patients presented with enthesitis and dactylitis, respectively (2). Baseline mean PASDAS (6.5), GRACE (6.1), mCPDAI (7.6), and DAPSA (46.7) scores 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 PASDAS (both 100%), GRACE
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 very low disease activity or remission) at Week 24 (9.7–12.9 across indices), which were significantly higher than those 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 endpoints

Placebo-controlled period: Guselkumab significantly improved disease activity from Week 0 to Week 24, relative to placebo, when assessed using the PASDAS (mean changes: -2.50 vs. -0.49, respectively), GRACE (-2.73 vs. -0.35), mCPDAI (-3.8 vs. -0.8), and DAPSA (-23.08 vs.-4.98) indices (all p<0.001; Figure S1A-D). Consistently, significantly higher proportions of guselkumab- than placebo-treated patients achieved low disease activity (including very low disease activity or remission) when assessed by the PASDAS (very low+low 35.0% vs. 4.1%; p<0.001), GRACE (29.6% vs. 2.1%; p<0.001), mCPDAI (45.9% vs. 10.4%; p<0.001), and DAPSA (remission+low 40.0% vs. 12.2%; p<0.01) indices. Further, more patients achieved very low disease activity based on PASDAS (8.0% vs. 0, p=0.053) and significantly more patients achieved DAPSA remission (12.0% vs. 0; p<0.01) (Figure 1A-D).

Achievement of low disease activity, based on the different composite indices, among
patients with or without dactylitis or enthesitis is summarized in Table S1. Comparatively, as reported previously (2), 23.0% vs. 2.0% of guselkumab- and placebo-treated patients, respectively, achieved MDA at Week 24 (p<0.001). A similar response pattern was observed for VLDA (6.0% vs. 0, respectively; 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 Figure S2A-D; 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 very low disease activity or remission) were higher at Week 44 than prior to the start of guselkumab at Week 24 (i.e., PASDAS very low+low: 39.3% at Week 44 vs. 7.1% at Week 24; GRACE: 39.3% vs. 7.1%, respectively; mCPDAI: 71.4% vs. 14.3%, respectively; and DAPSA remission+low: 50.0% vs. 20.7%, respectively) and were generally consistent with those observed at Week 44 among patients receiving guselkumab from Week 0 forward (i.e., PASDAS very low+low: 39.3% for placebo→guselkumab and 45.8% for guselkumab, respectively; GRACE: 39.3% and 42.2%, respectively; mCPDAI: 71.4% and 62.7%, respectively; and DAPSA remission+low: 50.0% and 51.1%, respectively; Figure 4A-D). In guselkumab-randomized patients, low disease activity (including very low disease activity or remission) response rates were maintained or increased from Week 24 to Week 44 (last on-treatment efficacy assessment, i.e., 38.4%→45.8% for PASDAS, 32.6%→42.2% for GRACE, 52.3%→62.7% for mCPDAI, 44.2%→51.1% for DAPSA). Furthermore, PASDAS
very low disease activity (9.3%→15.7%), DAPSA remission (12.8%→19.0%) (Figure 4A-D), MDA (26.7%→34.5%), and VLDA (7.0%→13.1%) (Figure 3B) response rates increased from Week 24 to Week 44.

**Performance of PsA-specific composite endpoints in detecting treatment effects at Week 24**

The SMD (5.16–8.84), ES (1.12–2.29, wherein ES ≥0.80 represents a ‘large’ treatment effect) (13), and SRM (1.14–1.58) statistics indicated that guselkumab elicited a substantial effect in treating the diverse manifestations of PsA relative to placebo, regardless of composite index employed (Figure 5). Based on SMD, the PASDAS (8.13) and GRACE (8.84) indices were more sensitive than the mCPDAI (7.20), and all three were more sensitive than the DAPSA (5.16), in distinguishing guselkumab from placebo treatment (Figure 5A). The ES and SRM statistics also indicated that the PASDAS (2.29 and 1.58, respectively) and GRACE (2.18 and 1.55, respectively) were more sensitive than the mCPDAI (1.75 and 1.39, respectively), and all three were more sensitive the than DAPSA (1.12 and 1.14, respectively), indices in detecting changes upon treatment (Figure 5B, C).

**Evaluation of residual disease activity among guselkumab-treated patients who achieved low or very low disease activity, remission, MDA, or VLDA at Week 24 based on PsA composite indices**

The no-residual-skin-disease criterion (PASI ≤1) was met in ≥80% of patients achieving PASDAS, GRACE, or mCPDAI low or very low disease activity and/or MDA or VLDA; 75.0% and 70.4% of patients achieving DAPSA remission and low disease activity, respectively, also demonstrated PASI ≤1. The no-residual-TJC criterion (≤1) was met in 100% of patients achieving PASDAS very low disease activity, DAPSA remission, and/or VLDA; in 87.0% of patients achieving MDA; and in 74.1–82.2% of patients achieving low
disease activity based on PASDAS, GRACE, mCPDAI, and DAPSA. The no-residual-SJC criterion (≤1) was met in 100% of patients achieving VLDA; in ~60% of patients achieving PASDAS very low disease activity, 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 or very low disease activity or remission according to the PsA-specific indices or MDA/VLDA had no enthesitis or dactylitis, but >50% had elevated CRP (>0.287 mg/dL). All patients who achieved PASDAS very low disease activity 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 2 trial of patients with active PsA (2). Herein, guselkumab demonstrated superiority over placebo in improving composite scores, with significantly more guselkumab- 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 non-articular 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 and very low disease activity, 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, 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 SMD, ES, and SRM statistics, the PASDAS and AMDF-based GRACE indices 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 utilizing data from the golimumab GO-REVEAL trial in PsA indicated that PASDAS and AMDF (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 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. It should also be remembered 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, 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 patients who achieved low disease activity with the DAPSA. Consistent results were obtained in previous determinations based on the golimumab GO-REVEAL trial (8). However, residual swollen joints were observed for all of the indices. For the PASDAS, this reflects the relatively minor contribution of the SJC to the index; this does not apply to GRACE, DAPSA, or mCPDAI, however, as they give equal weight to the SJC. 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 13.1% 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. 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 PsA patients who received standard or biological DMARDs in either a tight-control clinical trial or an observational cohort study (15). Herein, all patients achieving PASDAS very low disease activity and 20 of 22 (90.9%) achieving DAPSA remission also achieved MDA, while 15 of 23 (65.2%) patients who met the MDA criteria did not achieve PASDAS very low disease activity and 13 of 23 (56.5%) did not meet the DAPSA remission criteria, suggesting PASDAS very low disease activity 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 it could be argued that complete evaluation of any patient with PsA requires assessment of all clinical domains. If it is worth collecting the additional data for some of these indices, 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, it is possible that a ‘short-hand’ version can be developed for clinic 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 2 trial from which the data derive. Additionally, the SF-36 PCS score is a component of 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 disease activity.

In conclusion, the composite scores assessed are not uniform in either responses or disease domains included, and the choice of composite score 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 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.
ACKNOWLEDGMENTS

The authors thank Michelle L Perate, MS for professional writing services funded by Janssen.

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 data integrity the accuracy of analyses.

Study conception and design. Helliwell, Deodhar, Gottlieb, Boehncke, XLXu, Wang, Hsia,

Acquisition of data. Helliwell, Deodhar, Gottlieb, XLXu, Wang, Hsia,

Analysis and interpretation of data. Helliwell, Deodhar, Gottlieb, Boehncke, XLXu, SXu, Wang, Hsia, Gladman, Ritchlin
REFERENCES


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FIGURE LEGENDS

Figure 1. Proportions of patients achieving disease activity states at Week 16 and Week 24 for the PASDAS (A), GRACE (B), mCPDAI (C), and DAPSA (D) PsA-specific composite endpoints (full analysis set; last observation carried forward for missing data; p-values were calculated post hoc). DAPSA = Disease Activity Index for Psoriatic Arthritis, GRACE = Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAapp) Composite score, mCPDAI = modified Composite Psoriatic Disease Activity Index, PASDAS - Psoriatic Arthritis Disease Activity Score, PsA = psoriatic arthritis
Figure 2. Mean changes from baseline at Week 24 in the SF-36 PCS score by disease activity state according to the PASDAS (A), GRACE (B), mCPDAI (C), and DAPSA (D) PsA-specific composite endpoints (guselkumab-treated patients in the full analysis set; last observation carried forward for missing data; p-values were calculated post hoc). DAPSA = Disease Activity index for PSoriatic Arthritis, GRACE = Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAppa) Composite scorE, mCPDAI = modified Composite Psoriatic Disease Activity Index, PASDAS = Psoriatic Arthritis Disease Activity Score, PCS = physical component summary, PsA = psoriatic arthritis, SD = standard deviation, SF-36 = 36-item Short Form health survey
Figure 3. Proportions of patients achieving MDA and VLDA (A) at Week 16 and Week 24 (full analysis set; NRI) and (B) at Week 24 and Week 44 (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). MDA = minimal disease activity, NRI = nonresponder imputation, VLDA = very low disease activity
**Figure 4.** Proportions of patients achieving disease activity states post-Week 24 for the PASDAS (A), GRACE (B), mCPDAI (C), and DAPSA (D) PsA-specific composite endpoints (post-Week 24 efficacy analysis set; observed data). Week-24 observed data in the same population included as a reference. DAPSA = Disease Activity index for Psoriatic Arthritis, GRACE = Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAppa) Composite score, mCPDAI = modified Composite Psoriatic Disease Activity Index, PASDAS - Psoriatic Arthritis Disease Activity Score, PsA = psoriatic arthritis

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Figure 5. Comparative statistics evaluating guselkumab treatment effects detected at Week 24 according to the PASDAS, GRACE, mCPDAI, and DAPSA PsA-specific composite endpoints: standardized mean difference (A), effect size (B), and standardized response mean (C) (full analysis set; last observation carried forward for missing data). DAPSA = Disease Activity index for Psoriatic Arthritis, GRACE = Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAppa) Composite score, mCPDAI = modified Composite Psoriatic Disease Activity Index, PASDAS = Psoriatic Arthritis Disease Activity Score, PsA = psoriatic arthritis.
**Table 1.** Number (%) of patients meeting no residual disease activity criteria among guselkumab-treated patients achieving low disease activity states defined by PsA composite indices at Week 24 (full analysis set)*

<table>
<thead>
<tr>
<th>Measure of residual disease activity</th>
<th>PASI ≤1</th>
<th>TJC ≤1</th>
<th>SJC ≤1</th>
<th>CRP ≤ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PASDAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low (≤1.9); N=8</td>
<td>7 (87.5)</td>
<td>8 (100.0)</td>
<td>5 (62.5)</td>
<td>4 (50.0)</td>
</tr>
<tr>
<td>Low (&gt;1.9≤3.2), N=27</td>
<td>22/26 (84.6)</td>
<td>20 (74.1)</td>
<td>12 (44.4)</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td><strong>GRACE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (≤2.3), N=29</td>
<td>26 (89.7)</td>
<td>23 (79.3)</td>
<td>14 (48.3)</td>
<td>9 (31.0)</td>
</tr>
<tr>
<td><strong>mCPDAI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (≤3.2), N=45</td>
<td>37 (82.2)</td>
<td>37 (82.2)</td>
<td>19 (42.2)</td>
<td>16 (35.6)</td>
</tr>
<tr>
<td><strong>DAPSA</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Remission (≤4), N=12</td>
<td>9 (75.0)</td>
<td>12 (100.0)</td>
<td>8 (66.7)</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td>Low (&gt;4≤14), N=28</td>
<td>19/27 (70.4)</td>
<td>22 (78.6)</td>
<td>10 (35.7)</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td><strong>MDA, N=23</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>21 (91.3)</td>
<td>20 (87.0)</td>
<td>14 (60.9)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td><strong>VLDA, N=6</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>6 (100.0)</td>
<td>6 (100.0)</td>
<td>6 (100.0)</td>
<td>1 (16.7)</td>
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<tr>
<td><strong>LEI=0</strong></td>
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<tr>
<td><strong>Dactylitis=0</strong></td>
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<tr>
<td><strong>MDA</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>VLDA</strong></td>
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<table>
<thead>
<tr>
<th>Category</th>
<th>Low (≤3.2), N=45</th>
<th>42 (93.3)</th>
<th>42 (93.3)</th>
<th>22/44 (50.0)</th>
<th>6/44 (13.6)</th>
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<tbody>
<tr>
<td><strong>DAPSA</strong></td>
<td>Remission (≤4), N=12</td>
<td>11 (91.7)</td>
<td>12 (100.0)</td>
<td>10/11 (90.9)</td>
<td>4/11 (36.4)</td>
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<td></td>
<td>Low (&gt;4–≤14), N=28</td>
<td>22 (78.6)</td>
<td>22 (78.6)</td>
<td>12/27 (44.4)</td>
<td>2/27 (7.4)</td>
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<tr>
<td><strong>MDA, N=23</strong></td>
<td></td>
<td>19 (82.6)</td>
<td>22 (95.7)</td>
<td>-</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td><strong>VLDA, N=6</strong></td>
<td></td>
<td>6 (100.0)</td>
<td>6 (100.0)</td>
<td>6 (100.0)</td>
<td>-</td>
</tr>
</tbody>
</table>

*CRP = C-reactive protein, DAPSA = Disease Activity index for Psoriatic Arthritis, GRACE = Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRApPa) Composite score, LEI = Leeds enthesis index, mCPDAI = modified Composite Psoriatic Disease Activity Index, MDA = minimal disease activity, PASDAS = Psoriatic Arthritis Disease Activity Score, PASI = Psoriatic Area and Severity Index, PsA = psoriatic arthritis, SJC = swollen joint count, TJC = tender joint count, ULN = upper limit of normal (0.287 mg/dL), VLDA = very low disease activity*