

ORIGINAL RESEARCH

Comparative performance of composite measures from two phase III clinical trials of ixekizumab in psoriatic arthritis

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ABSTRACT

Background/objective The aim of this study was to evaluate relative performance of composite measures in psoriatic arthritis and assess the impact of structural damage and functional disability on outcomes during ixekizumab treatment.

Methods Data from SPIRIT-P1 and SPIRIT-P2 were analysed to evaluate the effect of ixekizumab on achievement of low disease activity (LDA) and remission with the minimal disease activity (MDA) and very low disease activity (VLDA) composite, Disease Activity index for Psoriatic Arthritis (DAPSA), Psoriatic Arthritis Disease Activity Score, GRAPPA Composite Score and modified Composite Psoriatic Disease Activity Index (mCPDAI). Performance was compared by quantifying residual symptom burden and the impact of structural damage and functional disability.

Results Significantly more ixekizumab-treated patients achieved treatment targets at week 24 versus placebo assessed with all composites. More patients achieved targets assessed by mCPDAI and DAPSA than other composites. Residual disease activity was similar between composites, but residual high patient-reported outcomes (PROs) and functional disability were more frequent when assessed with mCPDAI and DAPSA. Achievement of treatment targets was reduced by high baseline levels of structural damage and functional disability.

Conclusion Residual disease activity was similar in patients achieving treatment targets assessed with all composites, but residual high PROs and functional disability were more common when assessed with mCPDAI and DAPSA, most likely due to the absence/attenuated functional assessment in these composites. High baseline levels of structural damage and functional disability attenuated response rates with all composites, affecting MDA/VLDA most prominently; LDA may be the most appropriate target in these patients.

Trial registration number NCT01695239.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, clinically heterogeneous, inflammatory condition. Disease domains include peripheral arthritis, spondylitis, enthesitis, dactylitis,

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Psoriatic arthritis (PsA) is a multidimensional disease that can be evaluated by composite measures that assess disease activity and/or achievement of treatment targets such as low disease activity (LDA) and remission.
- ⇒ Ixekizumab, an interleukin-17A antibody, is an effective treatment for the multiple domains of PsA.

WHAT THIS STUDY ADDS

- ⇒ Significant proportions of patients with PsA treated with ixekizumab achieved LDA and remission, but there was variability in the performance of composite measures. More patients achieved treatment targets when assessed with modified Composite Psoriatic Disease Activity Index (mCPDAI) and Disease Activity index for Psoriatic Arthritis (DAPSA) than other composites. Residual disease activity was similar in treatment target achievers between composites, but residual high patient-reported outcomes (PROs) and functional disability were higher in patients achieving targets when assessed with mCPDAI and DAPSA than other composites.
- ⇒ Differences in composite performance may be, in part, driven by differences in the inclusion and role of functional assessments and other PROs between composites. Achievement of treatment targets was significantly reduced in patients with high baseline levels of structural damage and functional disability with all composites.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Low disease activity may be the most appropriate treatment target for patients with high levels of structural damage and functional disability. Binary achievement of treatment targets assessed with any of the composite measures should not be used alone to inform treatment decisions. In a multidimensional disease, such as PsA, clinicians should assess all disease domains even if they are not included in the composite used, and outcomes should always be interpreted with respect to the modifiable and non-modifiable aspects of PsA.



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plaque psoriasis and nail psoriasis. Treatment decisions for PsA are guided, in part, by the disease manifestations present in a patient.^{1–3} Recommendations by the EULAR, the American College of Rheumatology, and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) include a treat-to-target approach with either low disease activity (LDA) or remission as a treatment goal,^{1–3} as suggested by the Treat-to-Target task force in the original and updated recommendations.⁴ It is also recommended that physicians consider all major clinical domains of PsA when developing treatment strategies for patients. Importantly, the impact of disease on pain, function, quality of life (QoL), and structural damage is determined by specific manifestations individually or in combination.^{1 5 6}

Several composite measures have been developed to assess PsA disease outcomes in a single instrument. Most composite measures are considered multidimensional because they combine assessments of multiple disease domains to quantify total disease activity or a disease activity state, such as LDA or remission. Of the multidimensional composite measures, the minimal disease activity (MDA) composite differs from the others in that it is binary and, thus, can only inform if a patient is in LDA or remission.⁷ The other multidimensional composites (the Psoriatic Arthritis Disease Activity Score (PASDAS),⁸ GRAPPA Composite score (GRACE)⁸ and Composite Psoriatic Disease Activity Index (CPDAI)⁹) are continuous measures with defined cut-off points for LDA and remission and can also quantify changes in disease activity during treatment. The multidimensional measures include assessments of joint disease and function but differ in other symptom domains that are directly assessed, including skin, enthesitis, dactylitis, pain and axial disease. The major unidimensional composite measure, the Disease Activity index for Psoriatic Arthritis (DAPSA),¹⁰ is a continuous measure with cut-off points defined for LDA and remission. The DAPSA contains a narrower range of symptom domain assessments than the multidimensional composites as it focuses on articular disease and does not include any assessments of function. Given these disparities in the components and constructs of the composite measures, understanding the similarities and differences in assessing clinical outcomes is important for effective use in clinical trials and routine practice.

Currently, MDA (multidimensional) and DAPSA (unidimensional) are both recommended as targets for PsA treatment,⁴ but the other instruments are also considered. One point of view is that only multidimensional measures can adequately quantify the cumulative disease activity of a multifactorial disease like PsA. This view also asserts unidimensional measures may underestimate disease activity by focusing on only one aspect of the disease.¹¹ Others argue that condensing a multifactorial disease into a single disease activity score will obscure the differences between activity in individual domains and emphasise that individual domains

may respond differentially to treatment.¹² Therefore, it may be better for a composite to focus on core disease activity, with individual extra articular domains assessed separately. These may be items already included within the composite where individual components can be used to support individual decision-making, or they may be additional measures that are not included within the composite. Thus, residual disease activity must be accurately quantified in patients who achieve LDA and remission targets using multidimensional and unidimensional composites.

An additional controversy is whether physical function and QoL should be included in composite measures (as opposed to assessing them separately) because they are outcomes of disease, not measures of disease activity.¹³ Physical function in PsA depends on both modifiable (disease activity) and irreversible (joint damage) components. Functional impairment due to joint damage is resistant to improvement during treatment, meaning the presence of significant joint damage may limit the responsiveness of composites that include assessment of physical function despite there being a reduction in core disease activity.^{6 14} The relative performance of these composites must, therefore, be quantified in patients with varying degrees of pre-existing structural damage and functional disability. Newer measures, such as the Psoriatic Arthritis Impact of Disease (PsAID), have been developed and validated to assess disease impact or QoL in PsA. These measures are typically not included in composite measures of disease activity but are very helpful alongside disease activity measure to support shared decision-making in clinical practice.

Previous analyses have demonstrated variability in the performance of composite measures, including in the proportions of patients achieving treatment targets and their residual symptoms. However, the severity of residual symptoms has not been quantified and the relative performance of composites in patients with varying degrees of functional disability and structural damage has not been assessed. Gaining a better understanding of the relative performance of composite measures in such populations will help inform on the most appropriate choice for clinical trials and clinical practice.

We report results of prespecified and post-hoc analyses from the SPIRIT-P1 and SPIRIT-P2 trials,^{15–18} evaluating the effects of ixekizumab (IXE), a high-affinity monoclonal antibody that selectively targets interleukin-17A, on five disease-specific composite measures. The aim was to assess the concordance and variability in performance of the composite measures in patients with PsA, including those with pre-existing joint damage and functional disability. An additional aim was to provide greater granularity than previous analyses to the frequency and severity of residual symptoms in patients who achieve treatment targets.

MATERIALS AND METHODS

Study design and patients

The analyses reported here include data from two randomised, double-blind, phase III trials in patients with active PsA: SPIRIT-P1 (NCT01695239)^{15,16} and SPIRIT-P2 (NCT02349295).^{17,18} Details of these clinical trials have been published previously. Briefly, SPIRIT-P1 enrolled biological-naïve patients, and SPIRIT-P2 enrolled patients with an inadequate response or intolerance to one or two tumour necrosis factor inhibitors (TNFi) (TNFi-inadequate responders, TNFi-IR). For both trials, patients were at least 18 years of age, had a PsA diagnosis of at least 6 months, met classification criteria for PsA (Classification for Psoriatic ARthritis, (CASPAR) criteria), had ≥ 3 tender joints and ≥ 3 swollen joints, and either currently had or had a history of plaque psoriasis. In SPIRIT-P1, patients were randomised to placebo (N=106), 80 mg IXE every 2 weeks (IXE Q2W; N=103) or 4 weeks (IXE Q4W; N=107) after a 160 mg starting dose, or adalimumab (ADA) (N=101). In SPIRIT-P2, patients were randomised to placebo (N=118), IXE Q2W (N=123) or IXE Q4W (N=122).^{15–18} Patients who remained on placebo and ADA were re-randomised (1:1) to receive (after 8-week washout for patients on ADA) IXE Q2W or IXE Q4W, beginning with a starting dose of 160 mg (given as two injections).

Assessments

Composite endpoint measures used in this analysis were MDA,⁷ very low disease activity (VLDA),¹⁹ DAPSA,¹⁰ PASDAS,⁸ GRACE⁸ and modified CPDAI (mCPDAI).⁹ Their components, formulas and cut-off points for LDA and remission are shown in online supplemental table 1. As the Dermatology Life Quality Index (DLQI) was only collected up to 24 weeks in the SPIRIT trials, mCPDAI outcomes are only reported to week 24. DAPSA, PASDAS and GRACE scores were calculated post hoc. Structural damage was measured by the van der Heijde modified Total Sharp Score (mTSS) and was only collected in SPIRIT-P1.

Statistical analyses

Composite measures were calculated at various time points, per protocol for each measure (online supplemental table 2), through week 52 (mCPDAI through week 24). Treatment comparisons (IXE Q4W and IXE Q2W vs placebo) were made using a logistic regression model for categorical data with missing values imputed by non-responder imputation. A mixed model for repeated measures analysis was used for treatment comparisons for continuous data. Data from patients who were inadequate responders at week 16 were censored after week 16 and up to week 24.

Patients on active biological treatment (ie, patients treated with IXE and ADA in SPIRIT-P1 and IXE in SPIRIT-P2) were pooled for post-hoc comparisons between the composite measures at weeks 24 and 52. Comparisons between the composite measures were made for the

complete integrated data set to explore the impact of baseline functional impairment and structural damage on composite outcomes and in subgroups defined by baseline Health Assessment Questionnaire-Disability Index (HAQ-DI) (HAQ-DI <1; HAQ-DI ≥ 1 and <1.5; HAQ-DI ≥ 1.5) and from patients in SPIRIT-P1 only in tertiles defined by baseline mTSS. The percentage decrease from baseline for the continuous composites was calculated from the population mean changes in the structural damage and functional disability subgroups.

The effect size and standardised response mean (SRM) were estimated for all continuous composite measures (DAPSA, PASDAS, GRACE and mCPDAI) from the complete integrated data set.

The effect size values were calculated using the following definition:

$$\text{Effect Size} = \frac{(\text{mean at baseline} - \text{mean at Week X})}{SD(\text{baseline})}$$

The SRM values were calculated using the following definition:

$$\text{Standardized Response Mean} = \frac{(\text{mean at baseline} - \text{mean at Week X})}{SD(\text{change from baseline at Week X})}$$

Effect size or SRM values >0.8 were considered large.

Comparisons between the binary composite measures for LDA (MDA, PASDAS ≤ 3.2 , DAPSA ≤ 14 , GRACE ≤ 2.3 and mCPDAI ≤ 3) and remission (VLDA, DAPSA remission ≤ 4 , PASDAS near remission (NR) ≤ 1.9 and mCPDAI VLDA ≤ 1) were analysed separately. Residual disease activity in LDA and remission achievers were calculated as the percentage of patients experiencing symptoms above the defined cut-off point for each domain. The cut-off points used are those required for the achievement of MDA. For components not included in MDA, the cut-off points were the percentage with static physician global assessment (PGA) >1 , PGA visual analogue scale (VAS, 0–100 mm) >20 , Dactylitis >0 , C reactive protein (CRP) ≥ 5 mg/L, DLQI ≥ 3 and 36-item short-form health survey (SF-36) physical component summary (PCS) ≤ 40 . To further examine the severity of residual symptoms disease activity, the domain scores at the median, 60th, 70th, 80th and 90th percentiles were calculated. The post-hoc analyses were performed only in patients with no missing values. For post-hoc comparisons between composite measures, observed data are reported, and inadequate responder data are included.

The statistical analyses were performed using SAS V.9.2.

RESULTS

Patient disposition

Baseline demographics for SPIRIT-P1 (biological-naïve) and SPIRIT-P2 (TNFi-IR) have been published previously.^{11,13} Baseline DAPSA, mCPDAI, PASDAS and GRACE scores were well balanced between treatment arms. Baseline DAPSA scores were numerically higher in SPIRIT-P2 than SPIRIT-P1, PASDAS and mCPDAI scores were numerically higher in SPIRIT-P1 patients and were similar for GRACE across both studies (online

supplemental table 3). For patients on biological treatment in SPIRIT-P1, the mTSS tertiles were calculated as lower tertile (mTSS ≤ 2 , n=83), middle tertile (mTSS >2 and <17.5 , n=136) and upper tertile (mTSS ≥ 17.5 , n=75). Mean baseline mTSS in the tertiles were 1.1, 7.2 and 51.7, respectively. The median mTSS in the upper tertile was 36.5 with a range of 17.5–218.5. Patients in the upper mTSS tertile had a significantly longer time since PsA onset and a greater number of swollen joints than patients in the lower mTSS tertile. HAQ-DI was similar across the tertiles (online supplemental table 4). Time since PsA onset, tender joint counts (TJCs) and swollen joint counts (SJC), patient assessment of pain using VAS (0–100 mm), patient global assessment (PtGA) and high-sensitivity CRP concentration were significantly greater in patients with a baseline HAQ-DI ≥ 1.5 compared with the subgroup with HAQ-DI ≤ 1 (online supplemental table 5). Overall, at week 16, 15.5% of patients (121 of 780) were inadequate responders and were censored to week 24.

Composite measure outcomes during treatment with IXE

In patients with active PsA who were biological naïve (SPIRIT-P1) or TNFi-IR (SPIRIT-P2), IXE treatment resulted in rapid and statistically significant improvements from baseline in composite scores versus placebo at all time points (online supplemental table 3), as well as similar proportions of patients achieving LDA and remission in the two patient populations (figure 1). Significantly greater proportions of IXE-treated versus placebo patients achieved LDA and remission, defined by all composites, at week 24 (figure 1A–I); for the labelled dose of IXE (80 mg Q4W), improvements were either sustained or further improved through week 52. At week 24, for the targets of LDA and remission, MDA/VLDA was achieved by the lowest proportion of patients (figure 1A,B) and mCPDAI LDA and remission by the greatest proportion (figure 1I).

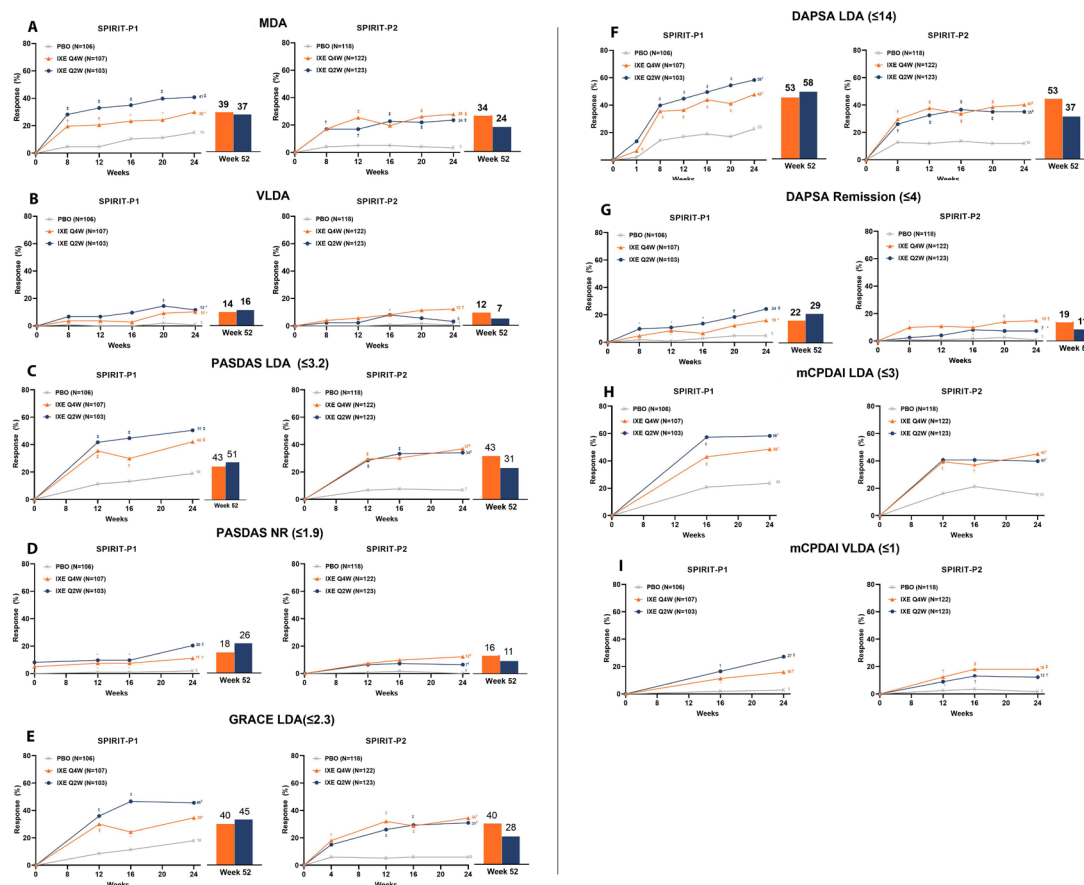


Figure 1 Proportion of patients treated with ixekizumab who achieved composite measure endpoints in SPIRIT-P1 (left panels) and SPIRIT-P2 (right panels) for MDA (A), VLDA (B), PASDAS LDA (C), PASDAS NR (D), GRACE LDA (E), DAPSA LDA (F), DAPSA Remission (G), mCPDAI LDA (H), mCPDAI VLDA (I). * $P < 0.05$ vs PBO; † $p < 0.01$ vs PBO; ‡ $p < 0.001$ vs PBO. Missing time points for the various composite scores are due to the data collection schedule within the studies. Missing data were imputed using a non-responder imputation method. DAPSA, Disease Activity index for Psoriatic Arthritis; GRACE, GRAppa Composite score; IXE Q2W, 80 mg ixekizumab every 2 weeks; IXE Q4W, 80 mg ixekizumab every 4 weeks; LDA, low disease activity; mCPDAI, modified Composite Psoriatic Disease Activity Index; MDA, minimal disease activity; N, number of patients in treatment group; NR, near remission; PASDAS, Psoriatic Arthritis Disease Activity Score; PBO, placebo; VLDA, very low disease activity.

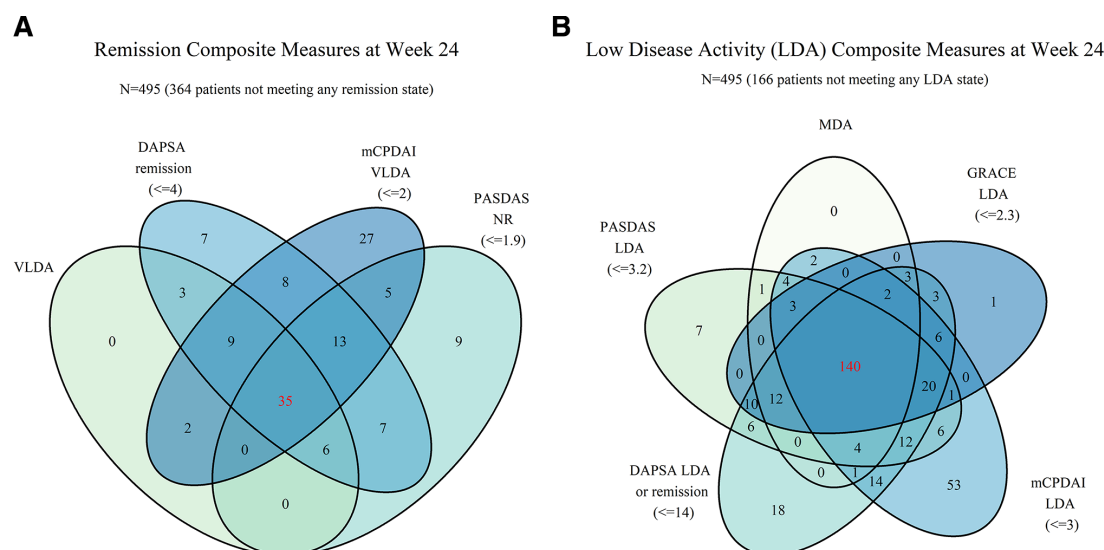


Figure 2 Venn diagrams representing the number of patients treated with biologics meeting different criteria for remission (A) or LDA (B) at week 24. DAPSA, Disease Activity index for Psoriatic Arthritis; GRACE, GRAppa Composite scorE; mCPDAI, modified Composite Psoriatic Disease Activity Index; MDA, minimal disease activity; N, number of patients in the analysis population; NR, near remission; PASDAS, Psoriatic Arthritis Disease Activity Score; VLDA, very low disease activity.

Comparisons of composite measures

At week 24, 66.5% (n=329 of 495) and 26.5% (n=131 of 495) of patients randomised to active treatment (IXE and ADA) achieved at least one of the LDA (figure 2A) and remission (figure 2B) criterion, respectively. For LDA, the fewest patients achieved MDA (n=172, 34.7%), followed by GRACE (n=201, 40.6%), PASDAS (n=226, 45.7%), DAPSA (n=251, 50.7%) and mCPDAI LDA (n=268, 54.1%). At week 24, 140 patients met LDA criteria for all composites. All patients who met MDA also met LDA criteria for at least one other composite. The mCPDAI LDA alone was met by 53 patients, DAPSA LDA alone by 18, PASDAS LDA alone by 7 and GRACE LDA alone by 1. For the target of remission, VLDA was achieved by the fewest patients (n=55, 11.1%) followed by PASDAS NR (n=75, 15.2%), DAPSA remission (n=88, 17.8%) and mCPDAI VLDA (n=99, 20.0%). At week 24, 35 patients met remission criteria for all four composites. All patients who achieved VLDA also achieved remission criteria for at least one other composite. A total of 27 patients achieved mCPDAI VLDA, 9 patients achieved PASDAS NR and 7 patients achieved DAPSA without achieving remission criteria for any other composite. The number of patients on active treatment meeting different LDA and remission criteria at week 52 is presented in online supplemental figure 1.

Achieving LDA or remission criteria for any composite measure endpoint led to a substantial reduction in the proportion of patients exhibiting residual disease activity after 24 and 52 weeks of treatment (tables 1 and 2). Achievement of MDA and VLDA was associated with the lowest proportions of patients experiencing symptoms above the defined cut-off points for the vast majority of the symptom and outcome domains (tables 1 and 2; figure 3). Achievement of LDA and VLDA assessed by mCPDAI was associated with the greatest proportion of

patients with residual symptoms above the cut-off points for the majority of symptom and outcome domains, particularly for joint counts (LDA only (online supplemental figure 2A,B)); patient pain (figure 3A) and PtGA (figure 3B). The greatest proportion of patients who achieved the target of remission scoring above the cut-off points for TJC was associated with PASDAS NR, and SJC was associated with both PASDAS NR and mCPDAI VLDA (online supplemental figure 2A,B, respectively). DAPSA was associated with the greatest proportion of patients with an HAQ-DI >0.5 for both LDA (37.5%, table 2) and remission (17.0%, table 1) at week 24. However, residual enthesitis, dactylitis and skin disease, which are not directly assessed in the DAPSA, occurred in similar proportions of patients as other composites (tables 1 and 2). Although there was some variation, outcomes were generally similar at week 52. Residual disease activity in patients who did not achieve at least LDA and remained in high disease activity at weeks 24 and 52 can be found in online supplemental tables 6 and 7. Despite not achieving treatment targets, the frequencies of patients scoring above the cut-off points for each domain were lower for the majority of composites compared with baseline.

The mean severity of residual symptoms for patients achieving LDA or remission was similar between composites; any differences were small and unlikely to be clinically significant (online supplemental tables 8 and 9). Residual joint disease was uncommon and similar between all composites for patients who achieved remission. For patients who only achieved LDA, residual joint disease was marginally greater in those assessed with mCPDAI. For example, 10% of patients who achieved LDA when assessed with the mCPDAI had at least 10 TJCs and/or 6 SJCs (online supplemental figure 2A,B, respectively). Residual enthesitis, dactylitis, and skin disease were uncommon and similar in patients who achieved

Table 1 Residual disease activity in patients who achieved remission at week 24 based on VLDA, PASDAS and mCPDAI and at week 52 based on VLDA, PASDAS and DAPSA

| | Week 24 (N=495)* | | | | | Week 52 (N=327)† | | | | |
|-----------------|------------------------|-----------------------------|---------------------------------|-----------------------------|---------------------------------|------------------------|-----------------------------|---------------------------------|---------------------------------|--|
| | Percentage of patients | | | | | Percentage of patients | | | | |
| | VLDA (n=55) | PASDAS NR ≤1.9 (n=75) | DAPSA remission ≤4 (n=88) | mCPDAI VLDA <1 (n=99) | Baseline measures (N=495) | VLDA (n=55) | PASDAS NR ≤1.9 (n=80) | DAPSA remission ≤4 (n=92) | Baseline measures (N=325) | |
| TJC >1 | 0.0‡ | 18.7 | 10.2 | 15.2 | 100.0 | 0.0 | 23.8 | 12.0 | 100.0 | |
| SJC >1 | 0.0‡ | 14.7 | 4.5 | 10.1 | 100.0 | 0.0 | 8.8 | 2.2 | 100.0 | |
| PASI >1 | 10.9 | 8.0 | 13.6 | 9.1 | 77.9 | 5.5 | 6.3 | 6.6 | 80.8 | |
| BSA >3 | 1.8 | 5.3 | 5.7 | 4.0 | 58.4 | 0.0 | 2.5 | 3.3 | 60.3 | |
| sPGA >1 | 5.5 | 5.3 | 8.0 | 4.0 | 76.7 | 1.8 | 2.5 | 4.3 | 79.3 | |
| Pt pain VAS >15 | 0.0‡ | 8.0 | 5.7 | 27.3 | 97.7 | 0.0 | 10.0 | 5.4 | 97.8 | |
| PtGA VAS >20 | 0.0‡ | 1.3 | 1.1 | 18.2 | 97.3 | 0.0 | 2.5 | 0.0 | 98.1 | |
| PGA VAS >20 | 5.5 | 0.0 | 5.7 | 9.1 | 97.0 | 3.6 | 0.0 | 3.3 | 96.5 | |
| HAQ-DI >0.5 | 0.0‡ | 13.3 | 17.0 | 15.2 | 84.0 | 0.0 | 13.8 | 17.4 | 83.5 | |
| LEI >1 | 0.0‡ | 0.0 | 2.3 | 0.0 | 47.3 | 0.0 | 2.5 | 9.8 | 48.0 | |
| Dactylitis >0 | 7.3 | 8.0 | 9.1 | 0.0 | 24.9 | 5.5 | 3.8 | 5.4 | 28.0 | |
| CRP ≥5 mg/L | 25.5 | 21.3 | 20.5‡ | 22.2 | 58.7 | 23.6 | 13.8 | 22.8‡ | 56.8 | |
| DLQI ≥3 | 9.1 | 4.0 | 11.4 | 14.1 | 64.3 | – | – | – | 67.1 | |
| SF-36 PCS >40 | 1.8 | 8.0 | 10.2 | 13.1 | 76.9 | 3.6 | 3.8 | 8.7 | 79.0 | |

SF-36 MCS not used in any composite measure estimating remission. Observed data are reported.

*Patients initially randomised to ADA or IXE.

†Patients initially randomised to IXE.

‡Cut-off was lower than 0.

ADA, adalimumab; BSA, body surface area; CRP, C reactive protein; DAPSA, Disease Activity index for Psoriatic Arthritis; DLQI, Dermatology Life Quality Index; HAQ-DI, Health Assessment Questionnaire-Disability Index; IXE, ixekizumab; LEI, Leeds Enthesitis Index; mCPDAI, modified Composite Psoriatic Disease Activity Index; MCS, mental component summary; n, number of patients in the specified category; N, number of patients in the analysis population; NR, near remission; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, Psoriasis Area and Severity Index; PCS, physical component summary; PGA, physician global assessment; Pt, patient; PtGA, patient global assessment; SF-36, 36-item short-form health survey; SJC, swollen joint count; sPGA, static physician global assessment; TJC, tender joint count; VAS, visual analogue scale; VLDA, very low disease activity.

LDA or remission with any of the composite measures (tables 1 and 2). PGA VAS scores were below the cut-off point of 20 for all patients who achieved remission with any composite (online supplemental figure 2F, right panel); scores were only above the cut-off point of 20 in the 90th percentile of LDA achievers, and where the highest score was only 23 (DAPSA) (online supplemental figure 2F, left panel). CRP concentrations above the upper limit of normal were similar in LDA and remission achievers between composites, and only approximately 10% of patients for any composite were above the normal limit of 5 mg/L (online supplemental figure 2I).

There were greater differences between composites for the patient-reported outcomes (PROs) than other composite measures, particularly in patients who only achieved at least LDA. In patients who achieved remission at week 24, residual patient pain was below the cut-off point of 15 for all patients assessed with VLDA for which it is a requirement and only 8.0% assessed with PASDAS and 5.7% assessed with DAPSA scored >15 (table 1). However, 27.3% of patients achieving remission assessed with the mCPDAI scored >15 on patient pain (table 1)

with at least 10% having a score of at least 30 (figure 3A, right panel). Residual pain was more prevalent with all composites in patients who only achieved LDA but was most prevalent with mCPDAI and DAPSA, where 47.8% and 37.8% of LDA achievers, respectively, scored >15 (table 2). At least 20% and 10% of patients achieving LDA with mCPDAI and DAPSA, respectively, scored at least 35 (figure 3A, left panel). At week 24, PtGA was below the cut-off point of 20 for most patients who met remission criteria with any composite (figure 3B, right panel); excess scores were found most commonly when assessed with the mCPDAI where 18.2% of achievers scored >20 (table 1). For LDA achievers, 38.1% of those assessed with the mCPDAI exceeded the cut-off point (table 2) and at least 10% had a score of 50 or greater (figure 3B, left panel). Regarding the functional assessments in patients who achieved remission, 17.0%, 15.2%, 13.3%, and 0.0% scored >0.5 on the HAQ-DI with DAPSA, mCPDAI, PASDAS, and VLDA, respectively, at week 24 (table 1). At the 90th percentile of remission achievers assessed with DAPSA and mCPDAI, the HAQ-DI score was 0.8 (figure 3C, right panel). A greater proportion of

Table 2 Residual disease activity in patients who achieved low disease activity at week 24 based on MDA, PASDAS, DAPSA and GRACE and at week 52 based on MDA, PASDAS, DAPSA and GRACE

| | Week 24* | | | | | Week 52† | | | | | |
|-----------------|------------------------|------------------------|----------------------|----------------------|-----------------------|---------------------------------|----------------|------------------------|----------------------|-----------------------|---------------------------------|
| | Percentage of patients | | | | | Percentage of patients | | | | | |
| | MDA (n=172) | PASDAS ≤3.2 (n=226) | DAPSA ≤14 (n=251) | mCPDAI ≤3 (n=268) | GRACE ≤2.3 (n=201) | Baseline measures (N=495) | MDA (n=149) | PASDAS ≤3.2 (n=189) | DAPSA ≤14 (n=228) | GRACE ≤2.3 (n=171) | Baseline measures (N=325) |
| TJC >1 | 33.7 | 45.1 | 45.8 | 50.7 | 39.3 | 100.0 | 33.6 | 45.0 | 49.6 | 39.8 | 100.0 |
| SJC >1 | 20.3 | 27.9 | 24.7 | 36.2 | 22.4 | 100.0 | 12.8 | 19.0 | 19.3 | 16.4 | 100.0 |
| PASI >1 | 12.2 | 15.0 | 19.1 | 14.2 | 15.4 | 77.9 | 8.7 | 10.6 | 14.0 | 9.9 | 80.8 |
| BSA >3‡ | 8.8 | 10.7 | 13.2 | 10.9 | 11.4 | 58.4 | 2.0 | 4.8 | 7.0 | 4.1 | 60.3 |
| sPGA >1 | 7.0 | 6.6 | 9.2 | 9.0 | 7.5 | 76.7 | 3.4 | 3.7 | 5.7 | 4.7 | 79.3 |
| Pt pain VAS >15 | 16.9 | 30.1 | 37.8 | 47.8 | 27.4 | 97.7 | 18.1 | 32.8 | 43.4 | 28.7 | 97.8 |
| PtGA >20 | 7.0 | 18.6 | 25.9 | 38.1 | 14.4 | 97.3 | 6.7 | 18.0 | 30.3 | 14.0 | 98.1 |
| PGA >20 | 11.0 | 9.3 | 15.1 | 24.3 | 10.4 | 97.0 | 6.0 | 3.2 | 10.1 | 5.8 | 96.5 |
| HAQ-DI >0.5 | 19.2 | 29.6 | 37.5 | 33.6 | 23.4 | 84.0 | 15.4 | 26.5 | 36.0 | 19.3 | 83.5 |
| LEI >1 | 1.7 | 7.5 | 11.6 | 4.9 | 9.0 | 47.3 | 7.4 | 9.0 | 11.8 | 10.5 | 48.0 |
| Dactylitis >0 | 8.1 | 4.9 | 6.8 | 3.4 | 7.5 | 24.9 | 5.4 | 5.3 | 4.8 | 5.3 | 28.0 |
| CRP ≥5 mg/L | 21.5 | 22.6 | 26.3 | 22.8 | 22.9 | 58.7 | 25.5 | 25.4 | 27.6 | 26.3 | 56.8 |
| DLQI ≥3§ | 12.8 | 15.0 | 18.7 | 17.5 | 14.4 | 64.3 | – | – | – | – | 67.1 |
| SF-36 PCS >40 | 14.0 | 16.4 | 24.7 | 28.4 | 16.9 | 76.9 | 14.8 | 21.7 | 31.6 | 16.4 | 79.0 |
| SF-36 MCS >40 | 8.1 | 9.3 | 10.4 | 11.6 | 6.0 | 27.9 | 4.7 | 5.8 | 7.0 | 2.9 | 26.1 |

Observed data are reported.

*Patients initially randomised to ADA or IXE.

†Patients initially randomised to IXE.

‡One patient had a missing BSA measure at week 24.

§DLQI not collected after week 24.

ADA, adalimumab; BSA, body surface area; CRP, C reactive protein; DAPSA, Disease Activity Index for Psoriatic Arthritis; DLQI, Dermatology Life Quality Index; GRACE, GRAPPA Composite score; HAQ-DI, Health Assessment Questionnaire-Disability Index; IXE, ixekizumab; LEI, Leeds Enthesitis Index; mCPDAI, modified Composite Psoriatic Disease Activity Index; MCS, mental component summary; MDA, minimal disease activity; n, number of patients in the specified category; N, number of patients in the analysis population; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, Psoriasis Area and Severity Index; PCS, physical component summary; PGA, physician global assessment; Pt, patient; PtGA, patient global assessment; SF-36, 36-item short-form health survey; SJC, swollen joint count; sPGA, static physician global assessment; TJC, tender joint count; VAS, visual analogue scale.

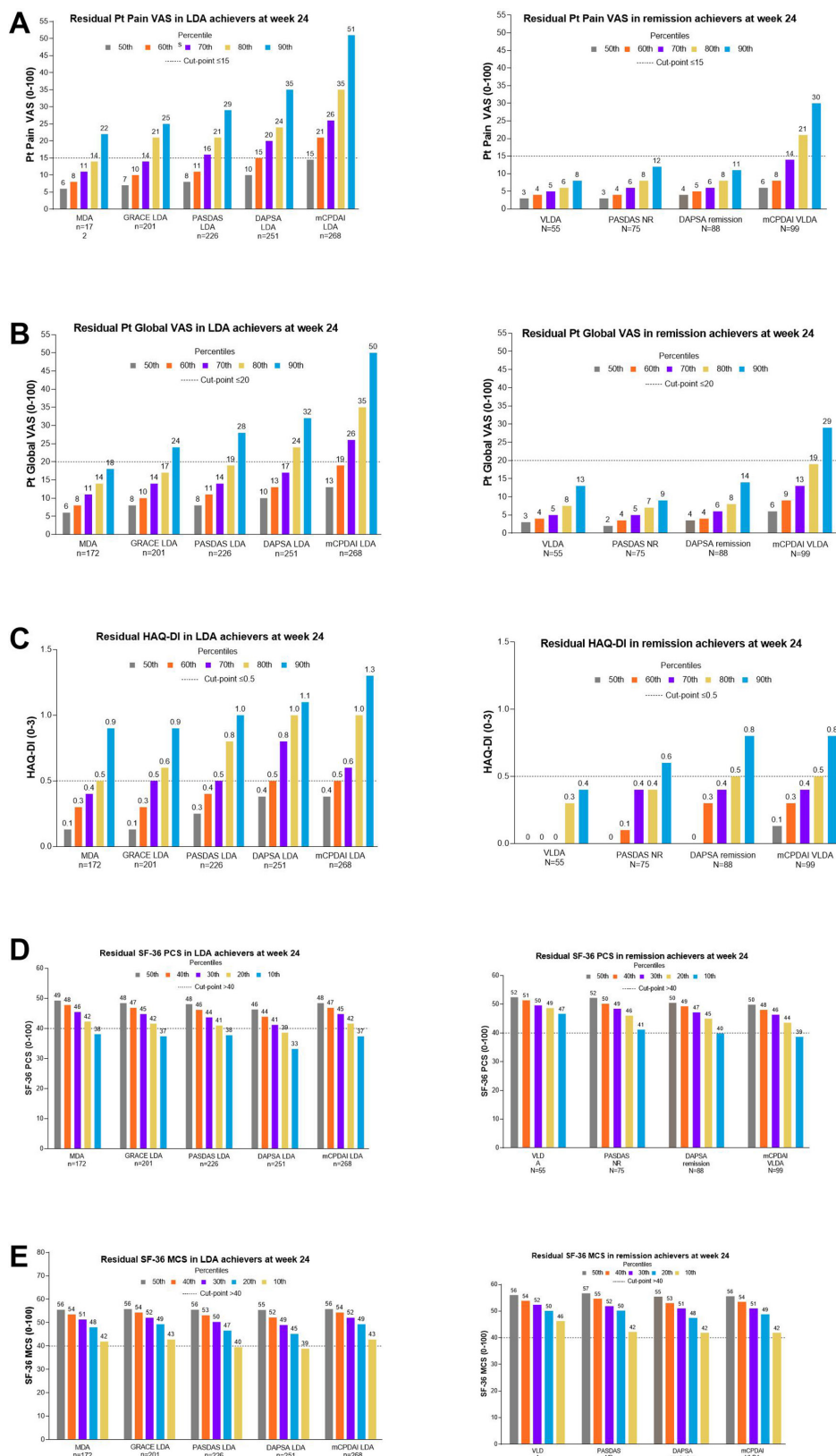


Figure 3 Residual disease activity by percentile for LDA achievers (left panels) and remission achievers (right panels) for patient pain VAS (A), patient global VAS (B), HAQ-DI (C), SF-36 PCS (D) and SF-36 MCS (E). DAPSA, Disease Activity index for Psoriatic Arthritis; GRACE, GRAppa Composite score; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDA, low disease activity; mCPDAI, modified Composite Psoriatic Disease Activity Index; MCS, mental component summary; MDA, minimal disease activity; n, number of patients in the specified category; NR, near remission; PASDAS, Psoriatic Arthritis Disease Activity Score; PCS, physical component summary; Pt, patient; SF-36, 36-item short-form health survey; VAS, visual analogue scale; VLDA, very low disease activity.

patients who only achieved at least LDA scored above the HAQ-DI cut-off point, which occurred most frequently in patients assessed by the DAPSA (37.5%) and mCPDAI (33.6%), in line with the partly irreversible nature of the HAQ-DI in patients with higher joint damage. At the 80th percentile of LDA achievers with these composites, the HAQ-DI score was 1.0 (figure 3C, left panel). Residual high HAQ-DI scores >1 occurred in fewer than 10% of patients achieving MDA or GRACE LDA. Residual poor function assessed with the SF-36 PCS followed a similar pattern as with HAQ-DI (figure 3D). In general, for all domain scores, the results should be seen in the context of circularity for those items included in the composite measure (online supplemental table 1) but not the other items, and especially when cut-off points defined by MDA are applied. There were some differences in outcomes at week 52 compared with week 24, but these were small and unlikely clinically significant with similar patterns between composites.

In patients who did not achieve LDA or remission, there was a high percentage of patients with residual activity in TJC, SJC, patient pain, PtGA, HAQ-DI, enthesitis, and SF-36 PCS at both week 24 and week 52 (online supplemental tables 6 and 7). However, relative to the baseline number of patients with disease activity, there were improvements in SJC, skin responses, PGA VAS and dactylitis by 52 weeks in patients treated with IXE.

Comparisons of composite measures by severity of baseline structural damage and impaired physical function

Baseline composite scores and reduction from baseline on treatment were numerically greater in the upper versus lower mTSS tertile for all composites, but no differences were statistically significant (figure 4A–D). A numerically lower proportion of patients in the upper versus lower mTSS tertile achieved LDA or remission at week 24 for each composite (figure 4E–I). The differences between the lower and upper tertiles were statistically significant for DAPSA remission (figure 4F), PASDAS LDA (figure 4G), GRACE LDA (figure 4H) and MDA (figure 4I), suggesting that baseline structural damage had a greater impact on these composites. The impact of structural damage on remission achievement appeared similar between composites, with the proportions of patients achieving remission amounting to about half in the upper compared with the lower mTSS tertiles for VLDA, PASDAS and DAPSA, but the difference was only statistically significant for the DAPSA (figure 4F).

Baseline composite scores also increased with increasing baseline HAQ-DI score (figure 5A–D), and showed a significantly greater reduction from baseline in all composite scores in patients with lower versus higher baseline physical disability (HAQ-DI ≤1 vs HAQ-DI >1.5) at week 24 (figure 5A–D) and week 52 (online supplemental figure 3A–C). At week 24, the

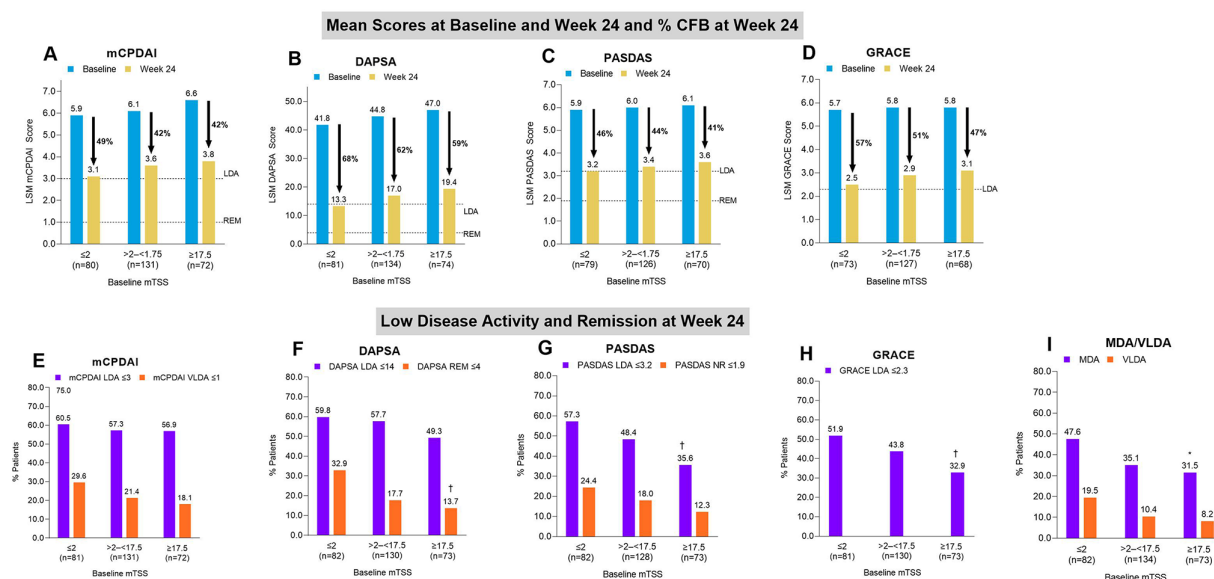


Figure 4 Composite performance by baseline structural damage at week 24. LSM change from baseline and per cent mean change from baseline for mCPDAI (A), DAPSA (B), PASDAS (C) and GRACE (D) by baseline mTSS subgroup and proportion of patients achieving mCPDAI LDA/REM (E), DAPSA LDA/REM (F), PASDAS LDA/NR (G), GRACE LDA (H) and MDA/VLDA (I) by baseline mTSS subgroup. Horizontal dotted lines represent the cut-off points LDA and REM. Text within vertical arrows indicates per cent change from baseline values. * $P < 0.05$ mTSS ≥ 17.5 vs mTSS ≤ 2 ; † $p \leq 0.01$ mTSS ≥ 17.5 vs mTSS ≤ 2 .

Response rates are shown as observed cases. LSM is based on an ANCOVA model which includes baseline mTSS group, time since onset of PsA and baseline value as covariate. ANCOVA, analysis of covariance; CFB, change from baseline; DAPSA, Disease Activity index for Psoriatic Arthritis; GRACE, GRAppa Composite score; LDA, low disease activity; LSM, least squares mean; mCPDAI, modified Composite Psoriatic Disease Activity Index; MDA, minimal disease activity; n, number of patients in the specified category; mTSS, van der Heijde modified Total Sharp Score; NR, near remission; PASDAS, Psoriatic Arthritis Disease Activity Score; PsA, psoriatic arthritis; REM, remission; VLDA, very low disease activity.

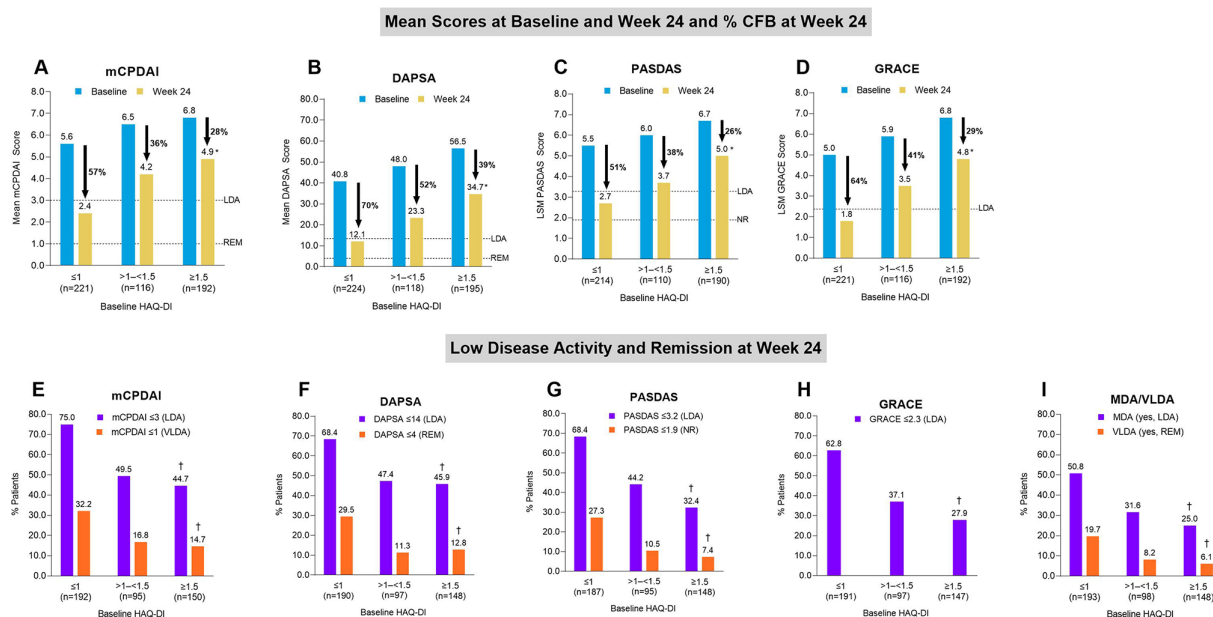


Figure 5 Composite performance by baseline functional disability based on HAQ-DI subgroup at week 24. (A–D) Mean score at baseline and LSM score at week 24 with per cent mean change from baseline (vertical arrows) for mCPDAI (A), DAPSA (B), PASDAS (C) and GRACE (D). (E–I) Proportion of patients achieving mCPDAI LDA/REM (E), DAPSA LDA/REM (F), PASDAS LDA/NR (G), GRACE LDA (H), and MDA/VLDA (I). Horizontal dotted lines in panels A–D represent the cut-off points LDA and REM. Text within vertical arrows indicates per cent change from baseline values. * $P < 0.001$ for LSM change from baseline for subgroup HAQ-DI ≤ 1 vs HAQ-DI ≥ 1.5 ; † $p \leq 0.001$ for response rate subgroup HAQ-DI ≥ 1.5 vs subgroup HAQ-DI ≤ 1 . Response rates are shown as observed cases. LSM is based on an ANCOVA model which includes baseline HAQ-DI group, time since onset of PsA and baseline value as covariate. ANCOVA, analysis of covariance; CFB, change from baseline; DAPSA, Disease Activity index for Psoriatic Arthritis; GRACE, GRAppa Composite scoreE; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDA, low disease activity; LSM, least squares mean; mCPDAI, modified Composite Psoriatic Disease Activity Index; MDA, minimal disease activity; n, number of patients in the specified category; NR, near remission; PASDAS, Psoriatic Arthritis Disease Activity Score; PsA, psoriatic arthritis; REM, remission; VLDA, very low disease activity.

percentage reduction from baseline in composite score was also lower in the high HAQ-DI subgroup compared with the low HAQ-DI subgroup. Few patients from the middle and upper HAQ-DI subgroups achieved remission assessed with any composite (online supplemental figure 3D–G). Significantly fewer patients with a baseline HAQ-DI ≥ 1.5 achieved LDA or remission for every composite at weeks 24 and 52 compared with those with a baseline HAQ-DI ≤ 1 (figure 5E–I (week 24), online supplemental figure 3D–G (week 52)). At week 24, the greatest proportion of patients achieved LDA and remission across all HAQ-DI subgroups when assessed with mCPDAI (figure 5E) and DAPSA (figure 5F) and the lowest with MDA/VLDA (figure 5I). The differences in the proportions of patients achieving LDA between the lower and higher HAQ-DI subgroups were smaller for mCPDAI and DAPSA, suggesting that achievement of LDA assessed with these measures was relatively less impacted by baseline functional disability than with the other composites. The proportion of patients who achieved remission increased between weeks 24 and 52 in the HAQ-DI ≥ 1.5 subgroup when assessed with DAPSA (figure 5F and online supplemental figure 3D) but not when assessed with VLDA (online supplemental figure 3G) or PASDAS (online supplemental figure 3E). Remission achievement improved with all composites

for the other HAQ-DI subgroups (figure 5E–G and online supplemental figure 3).

Effect sizes and standardised response means

Data from our analysis of the summary of effect size for disease activity scores and SRM at weeks 24 and 52 indicated that all measures had large effect sizes and SRM (table 3). The highest values were associated with GRACE and PASDAS.

DISCUSSION

In this analysis, we examined the efficacy of IXE for the treatment of PsA in the SPIRIT-P1 and SPIRIT-P2 trials as assessed by a number of composite measures. Post-hoc analyses were performed to identify the concordance and variability in the achievement of LDA and remission states defined by the different composites. IXE rapidly and significantly reduced composite scores, and significantly more patients achieved LDA and remission compared with placebo at week 24. The response rates were maintained or increased through week 52.

We observed variation between composites in the numbers of patients who achieve LDA and remission, which is consistent with findings in previous analyses.^{20–25} Substantially more patients achieved targets assessed with mCPDAI and DAPSA than other composites (figure 2 and

Table 3 Summary of effect size and standardised response mean

| | Effect size | | Standardised response mean | |
|--------|---------------------|---------------------|----------------------------|---------------------|
| | Week 24* (N=451) | Week 52† (N=193) | Week 24* (N=451) | Week 52† (N=193) |
| PASDAS | 2.37 | 3.09 | 1.63 | 2.36 |
| DAPSA | 1.24 | 1.64 | 1.36 | 1.75 |
| mCPDAI | 1.31 | 1.95 | 1.09 | 1.58 |
| GRACE | 2.40 | 3.05 | 1.61 | 2.30 |

Observed data are reported.

Scores ≥ 0.8 were considered large treatment effects.

*Patients initially randomised to adalimumab or ixekizumab.

†Patients initially randomised to ixekizumab.

DAPSA, Disease Activity index for Psoriatic Arthritis; GRACE, GRAppa Composite score; mCPDAI, modified Composite Psoriatic Disease Activity Index; N, number of patients in the analysis population; PASDAS, Psoriatic Arthritis Disease Activity Score.

online supplemental figure 2). Post-hoc analyses found few clinically significant differences between composites in the proportions of patients who experienced residual symptoms in the core domains of PsA (joints, enthesitis, dactylitis and skin disease) when treatment targets were achieved. However, a greater proportion of patients who achieved LDA or remission assessed with mCPDAI and DAPSA than with the other composites experienced residual high PROs: patient pain, PtGA, HAQ-DI and SF-36 PCS. Although achievement of remission and LDA with all composites was reduced in patients with higher levels of baseline functional disability and structural damage, the composites that include functional assessments, PtGA, and/or patient pain (MDA, PASDAS, GRACE) were impacted to a greater degree than the composites that included only either a functional assessment or patient pain and PtGA assessments (mCPDAI, DAPSA). Worse outcomes in patients with high disease activity and functional disability at baseline are consistent with a previous study where greater disease activity, patient pain, PtGA, and baseline HAQ-DI were all negative predictors of achieving remission and LDA during anti-TNF treatment.²⁶ All these factors were more prevalent in the high baseline functional disability group.

In this analysis, fewer patients in the highest HAQ-DI subgroup achieved LDA and remission than those in the higher mTSS subgroup, suggesting high levels of functional disability from all causes had a greater impact on composite outcomes than structural damage. Although structural damage contributes to functional disability in PsA, the contribution is relatively modest, with an increase in mTSS of 50 estimated to add just 0.1 to the HAQ-DI score.⁶ The mean mTSS in the upper tertile was only 51.7, and the HAQ-DI score was only 0.1 greater than in the lower mTSS tertile, which may explain the relatively small impact of structural damage on composite performance.

Because of how the HAQ-DI influences mCPDAI, where it only contributes to a domain if that domain is involved, more patients with residual functional impairment were still able to achieve LDA assessed with mCPDAI than with other composites. DAPSA does not include a functional measure and, as disease activity improves during treatment, the score is decreased enough for more patients to achieve the cut-off points for LDA and remission than with other composites. Residual non-modifiable functional disability, such as that associated with structural damage, does not directly influence the treatment target. However, achievement of DAPSA treatment targets was still reduced in patients with high levels of functional disability and structural damage. This result is likely due to the relationship between patient pain, TJC, PtGA and function.^{27 28} Patients with high levels of functional disability assessed with PASDAS and GRACE are less likely to achieve LDA and remission, likely because these measures include functional assessments and PtGA, and GRACE additionally patient pain. Reduction in these composite scores during treatment will be limited to those associated with disease activity and the modifiable components of functional disability and pain. For VLDA, the requirement of an HAQ-DI ≤ 0.5 would limit achievement in patients with high HAQ-DI scores. For MDA, the HAQ-DI score ≤ 0.5 is not a requirement, but if not met, patients would be required to meet five out of six of the other domains. As two of these domains are patient pain and PtGA, which will likely be correlated with functional disability,^{27 28} this likely accounts for the more limited achievement of MDA.

All continuous scoring composites demonstrated good sensitivity to detect changes in disease activity during biological treatment, with large effect sizes and SRMs that increased from week 24 to week 52. Consistent with previous analyses, PASDAS and GRACE had the largest values.^{21 29 30 31} The high PASDAS values are explained by how this composite was developed, which entailed using statistical methods to identify components most likely to change with treatment.⁸ PASDAS and GRACE also assess more domains than DAPSA; thus, they may be more responsive to the totality of changes in disease activity during treatment, including skin disease. Changes in mCPDAI may have been blunted by omission of the axial component as well as how it was designed, which included prespecified cut-off points for severity in each domain coupled with functional and QoL assessments. Interestingly, despite the fact that DAPSA focuses primarily on the joints, DAPSA remission and DAPSA LDA were associated with similar good outcomes for enthesitis, dactylitis or skin disease, even though these other scores comprise these items in their formulas.

Our analyses have some potential limitations. First, given these data are from randomised clinical trials with specific entry criteria, generalising the results to a real-world population may be limited and results should be interpreted in this context. Some of the composite measures and all the treat-to-target comparisons were analysed post

hoc, and the SPIRIT trials were not designed as treat-to-target studies. Additionally, these are descriptive analyses so it is not clear if differences in proportions are statistically significant. The post-hoc analyses were performed only in patients with no missing values. Although some of the composites were modified, their performance should not have been substantially impacted. Furthermore, axial disease was not incorporated into any of the composite measures analysed. As the patients in these analyses were from clinical trial populations, almost all of them had polyarthritis; thus, it is unclear if these results pertain to patients with oligoarthritis. In the analyses performed in functional disability and structural damage subgroups, there was no assessment of comorbidities that may impact changes in functional disability during treatment, and the levels of structural damage were also relatively low. Finally, when interpreting these findings, the fact that patients in these analyses were primarily treated with IXE should be considered. That patients who achieved treatment targets had similar levels of residual musculoskeletal and skin symptoms despite differences between composites in their assessment may be caused by the consistent efficacy of IXE across these domains of PsA.

In conclusion, we found that more patients achieved targets assessed by mCPDAI and DAPSA than with other composites. Residual disease activity levels were similar between composites, but residual high PROs and functional disability were more frequent in treatment target achievers assessed by mCPDAI and DAPSA. This may be due in part to the absence or attenuated functional assessment or other PROs in these composites meaning some patients can still achieve treatment targets despite having greater residual levels of functional disability and pain. MDA/VLDA is most difficult to achieve due to its construction and strict cut-off points of all domains. All composites were affected by higher levels of structural damage or functional impairment, but this was less prevalent in those composite measures without direct measures of functional impairment and other PROs. As joint damage may lead to irreversible disability, patients with joint damage may be left at a higher floor of functional impairment even if they reach clinical remission, meaning they are less likely to achieve all treatment targets. For patients with high baseline functional disability, including structural damage, LDA/MDA may be a more appropriate treatment target than remission as recognised in previous recommendations.⁴ The most important implication for clinical practice is that binary achievement of treatment targets assessed with any of the composite measures should not be used alone to inform treatment decisions. In a multidimensional disease such as PsA, clinicians should assess all disease domains and functional and QoL outcomes even if they are not included in the composite used. This approach will enable identification of disease activity and functional disability from any cause (even though a treatment target is achieved) and avoid undertreatment. Clinicians can then tailor drug treatments and other interventions

(such as exercise, physiotherapy and psychological therapies) appropriately to ensure the best outcomes for patients.

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Patient consent for publication Not required.

Ethics approval This study involves human participants. SPIRIT-P1 and SPIRIT-P2 were conducted in accordance with Good Clinical Practice, the principles of the Declaration of Helsinki, and local laws and regulations. SPIRIT-P1 was approved by the Western Institutional Review Board (approval #1-838258-1), and SPIRIT-P2 was approved by the Bellberry Human Research Ethics Committee (application #2015-01-049-AA). For both studies, approval was also obtained from each additional site. All patients in both studies gave written informed consent.

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Data availability statement Data are available upon reasonable request. Data are available on reasonable request. Lilly provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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