

# Rapid and sustained improvements in patient-reported signs and symptoms with ixekizumab in biologic-naïve and TNF-inadequate responder patients with psoriatic arthritis

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## Abstract

### Objective

To analyse the onset and sustainability of patient-reported improvements in symptoms of psoriatic arthritis (PsA) following treatment with ixekizumab (IXE) up to Week 108.

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### Methods

In patients with active PsA, either naïve to biological DMARDs (SPIRIT-P1) or having inadequate response or intolerance to 1 or 2 prior TNF-inhibitors (TNFi-experienced; SPIRIT-P2), we analysed the change from baseline in joint pain visual analogue scale (VAS; 0–100 scale), patient global assessment (PatGA VAS; 0–100 scale), fatigue numerical rating scale (NRS; 0 [no fatigue] to 10 [worst imaginable]), and Health Assessment Questionnaire-Disability Index (HAQ-DI; 0–3), up to Week 108.

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### Results

IXE-treated patients compared to placebo reported rapid and statistically significant improvement in pain VAS, PatGA, and HAQ-DI as early as Week 1 and this benefit was sustained or increased through Week 108. Fatigue scores improved in IXE-treated patients compared to placebo in both studies; results were statistically significant at Week 24 only in SPIRIT-P2. Improvements in fatigue with IXE were sustained over 2 years. The improvements observed in these patient-reported outcomes (PROs) were consistent in biologic-naïve or TNFi-experienced patients.

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### Conclusion

Patients treated with IXE versus PBO achieved significantly greater improvements and showed faster onset of improvements in patient-reported outcomes measuring symptoms and impact of PsA. Responses were sustained over 2 years and were generally consistent regardless of prior TNFi experience.

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### Key words

ixekizumab, anti-IL-17, pain, fatigue, patient-reported outcomes, TNF-inhibitors

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## Introduction

Psoriatic arthritis (PsA) is a chronic, progressive, heterogeneous, musculo-skeletal disease which can have a profound effect on patients' health-related quality of life (HRQoL) because of the combined burden of pain, fatigue, and other physical impairments (1-3). In surveys assessing the relative importance of PsA symptoms, patients with PsA consistently prioritised pain and fatigue, which subsequently impact physical functioning, HRQoL, and productivity in addition to musculoskeletal disease activity (2, 4, 5). Additionally, residual pain can persist despite treatment with currently available biologic therapies, representing an unmet need (6).

Clinical trials most often focus on the composite American College of Rheumatology (ACR) response criteria when assessing rapidity of onset and sustained improvements in PsA signs and symptoms (7). While clinical trials for biologic DMARDs (bDMARD) or targeted synthetic DMARDs (tsDMARD) have increasingly reported more information on the patient-centric components of these response criteria (8-16), there are relatively few publications detailing onset and longer-term effects of the individual components of the ACR measure. However, patient survey data suggest the patient-reported outcomes (PROs) within the ACR composite measure may be more important and relevant to patients with PsA than a single composite score (17).

PROs measuring pain, physical function, patient global assessment, and HRQoL (e.g. SF-36) are part of the core domains GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) and OMERACT (Outcome Measures in Rheumatology) recommended for PsA assessment in clinical trials and longitudinal observational studies (18, 19). The significance of these PROs (pain, physical function, patient global assessment, and HRQoL assessment) is further emphasised by their variable inclusion in composite endpoints, such as the psoriatic arthritis disease activity score (PASDAS) (20). However, HRQoL assessments (specifically SF-36) are underrepresented

in current composite measures (21, 22). Further, recent updates to the PsA core domains have added patient-reported fatigue (4, 23).

Ixekizumab (IXE), an approved treatment for patients with PsA and/or psoriasis, is a high-affinity monoclonal antibody which selectively targets IL-17A and has demonstrated significant efficacy in biologic-naïve (SPIRIT-P1) and TNF inhibitor-experienced (SPIRIT-P2) patients with PsA (24-26). SPIRIT-P1 and SPIRIT-P2 are 2 phase III randomised clinical studies demonstrating IXE improved signs and symptoms of PsA, including PROs, compared to placebo (PBO) up to Week 24, and these improvements were sustained through 52 weeks of treatment (25-29). Here, we examine the effect of IXE treatment on patient-centric measures including fatigue, pain, patient global assessment, and physical function in patients from SPIRIT-P1 and SPIRIT-P2 clinical trials receiving treatment for up to 2 years.

## Methods

### Study design

Data were obtained from SPIRIT-P1 (completed; NCT01695239) and SPIRIT-P2 (completed; NCT02349295). These are phase III, randomised, double-blind, and placebo-controlled trials in patients with active PsA. In SPIRIT-P1, patients were biologic-naïve, whereas in SPIRIT-P2, patients were required to have an inadequate response ( $\geq 12$  weeks on therapy) or intolerance to 1 or 2 prior TNF inhibitors (TNFi-experienced) (25, 26). In both studies, patients were randomised to 80 mg IXE every 2 weeks (Q2W), 80 mg IXE every 4 weeks (Q4W), or PBO; SPIRIT-P1 included 40 mg adalimumab Q2W as an active reference arm. Patients randomised to IXE Q4W or IXE Q2W received a starting dose of 160 mg given as 2 injections at Week 0. Inadequate responders (defined as  $<20\%$  improvement from baseline in both tender and swollen joint counts) were required to add or modify concomitant medications at Week 16. Patients on PBO or ADA who were inadequate responders were re-randomised to either IXE Q4W or Q2W at Week 16, and any remaining

**Table I.** Summary of change from baseline in individual clinical responses through Week 24 using MMRM analysis.

Visit		LSM change from baseline					
		SPIRIT-P1 (bDMARD-naïve)			SPIRIT-P2 (TNFi-experienced)		
		PBO (n=106)	IXE Q4W (n=107)	IXE Q2W (n=103)	PBO (n=118)	IXE Q4W (n=122)	IXE Q2W (n=123)
Joint pain VAS <sup>a</sup>	Baseline	58.5 (22.95)	60.1 (19.41)	58.4 (21.66)	63.9 (20.11)	63.9 (21.40)	62.7 (20.87)
	Week 1	-6.1 (1.94)	-14.5 (1.94) <sup>†</sup>	-19.3 (2.00) <sup>‡</sup>	-8.4 (2.70)	-19.7 (2.69) <sup>‡</sup>	-19.1 (2.62) <sup>‡</sup>
	Week 24	-14.0 (2.68)	-29.6 (2.51) <sup>‡</sup>	-31.6 (2.54) <sup>‡</sup>	-21.4 (3.97)	-36.9 (3.74) <sup>‡</sup>	-33.5 (3.58) <sup>‡</sup>
Fatigue NRS <sup>a,b</sup>	Baseline	5.4 (2.22)	5.8 (2.29)	5.5 (2.44)	5.9 (2.28)	5.9 (2.48)	6.0 (2.49)
	Week 4	-0.6 (0.20)	-1.5 (0.20) <sup>†</sup>	-1.5 (0.20) <sup>†</sup>	-0.4 (0.28)	-1.6 (0.28) <sup>‡</sup>	-1.4 (0.28) <sup>‡</sup>
	Week 24	-1.3 (0.25)	-1.6 (0.24)	-1.9 (0.24)	-0.7 (0.37)	-2.0 (0.35) <sup>‡</sup>	-2.1 (0.34) <sup>‡</sup>
HAQ-DI <sup>c</sup>	Baseline	1.2 (0.60)	1.2 (0.54)	1.2 (0.57)	1.2 (0.66)	1.2 (0.61)	1.2 (0.63)
	Week 1	-0.1 (0.03)	-0.2 (0.03) <sup>†</sup>	-0.2 (0.03) <sup>‡</sup>	-0.1 (0.05)	-0.3 (0.05) <sup>‡</sup>	-0.2 (0.05)
	Week 24	-0.2 (0.05)	-0.4 (0.05) <sup>‡</sup>	-0.4 (0.05) <sup>‡</sup>	-0.2 (0.08)	-0.6 (0.07) <sup>‡</sup>	-0.4 (0.07) <sup>‡</sup>
PatGA VAS <sup>a</sup>	Baseline	61.1 (22.67)	62.7 (19.07)	62.5 (19.93)	64.1 (21.48)	66.4 (20.49)	66.0 (20.52)
	Week 1	-8.2 (1.99)	-16.8 (1.99) <sup>†</sup>	-19.2 (2.06) <sup>‡</sup>	-9.0 (2.87)	-22.0 (2.86) <sup>‡</sup>	-22.7 (2.78) <sup>‡</sup>
	Week 24	-14.8 (2.65)	-33.8 (2.48) <sup>‡</sup>	-35.6 (2.50) <sup>‡</sup>	-19.0 (3.91)	-40.7 (3.68) <sup>‡</sup>	-37.3 (3.53) <sup>‡</sup>

Data presented here are LS mean (SE).

<sup>†</sup> $p < 0.01$ ; <sup>‡</sup> $p < 0.001$  vs. PBO. <sup>a</sup> 0–100 scale, higher=worse; <sup>b</sup> 0–3 scale, higher=worse; <sup>c</sup> 0–10 scale, higher=worse.

<sup>†</sup>For SPIRIT-P1, the earliest time point measured was Week 4; for SPIRIT-P2 an additional time point was measured at Week 2 [PBO: -0.5 (0.27); IXE Q4W: -1.6 (0.27)<sup>‡</sup>; IXE Q2W: -1.3 (0.26)<sup>†</sup>].

bDMARD: biologic disease-modifying anti-rheumatic drug; HAQ-DI: Health Assessment Questionnaire-Disability Index; IR: inadequate responder; IXE: ixekizumab; IXE Q4W: IXE 80 mg every 4 weeks; IXE Q2W: IXE 80 mg every 2 weeks; LSM: least squares mean; MMRM: mixed models for repeated measures; n: number of patients in the analysis population; NRS: numeric rating scale; PatGA: patient global assessment; PBO: placebo; SE: standard error; TNFi: tumour necrosis factor inhibitors; VAS: visual analogue scale.

patients were re-randomised at Week 24. Patients initially receiving IXE remained on their original dose during the extension period (from Week 24 to 108) (25, 26).

Both studies were conducted in accordance with the consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethics Guidelines, the International Conference on Harmonization Good Clinical Practice Guidelines, and applicable laws and regulations. Protocols were reviewed and approved by the institutional ethical review board and all participants provided written informed consent.

#### Eligibility criteria

Males and females  $\geq 18$  years old with an established diagnosis of active PsA  $\geq 6$  months according to the Classification Criteria for Psoriatic Arthritis were eligible for enrolment. Patients were also required to have active PsA, defined as the presence of  $\geq 3$  tender and  $\geq 3$  swollen joints, and either active psoriatic skin lesions or a documented history of plaque psoriasis. Patients in

SPIRIT-P1 were required to be naïve to bDMARD treatment, while patients in SPIRIT-P2 were required to have an inadequate response or intolerance to 1 or 2 TNF inhibitors. Detailed information on the inclusion and exclusion criteria for SPIRIT-P1 and SPIRIT-P2 have been published (25, 26).

#### Assessments

We measured change from baseline through week 108 for the following PROs: joint pain visual analogue scale (VAS), fatigue numeric rating scale (NRS), patient global assessment (PatGA VAS), and Health Assessment Questionnaire-Disability Index (HAQ-DI) (30–32). In both studies changes from baseline were measured starting at Week 1 for joint pain VAS, PatGA and HAQ-DI. In SPIRIT-P1, the fatigue NRS was measured starting at Week 4, while in SPIRIT-P2 the fatigue NRS was measured starting at Week 2.

Joint pain VAS is a patient-reported, single-item, 100-mm scale anchored between 0 and 100. Higher scores correspond to greater pain intensity (30). A clinically meaningful improvement (MCID) in pain VAS was defined as  $\geq 10$  mm/100 improvement in patients with

baseline pain score  $\geq 10$ , and the number and percentages of patients achieving MCID were reported (33, 34).

Fatigue NRS is a patient-reported, single-item, 11-point horizontal scale anchored at 0 and 10, with 0 representing “no fatigue” and 10 representing “as bad as you can imagine” (31). The number and percentage of patients achieving a MCID in fatigue NRS were reported according to a  $\geq 3$  points/10 improvement in patients with baseline fatigue score  $\geq 3$  (31).

The HAQ-DI is a patient-reported standardised questionnaire commonly used in PsA to measure disease-associated disability. It consists of 24 questions referencing 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities. The scores range from 0 to 3, with higher scores reflecting greater disability (32). An improvement of 0.35 has been defined as the minimum important improvement in PsA (35).

PatGA is the patient’s overall assessment of PsA activity recorded using the 100 mm horizontal VAS. The left anchor (0 mm) represents “very well” and the right anchor (100 mm) represents “very poor” (36).

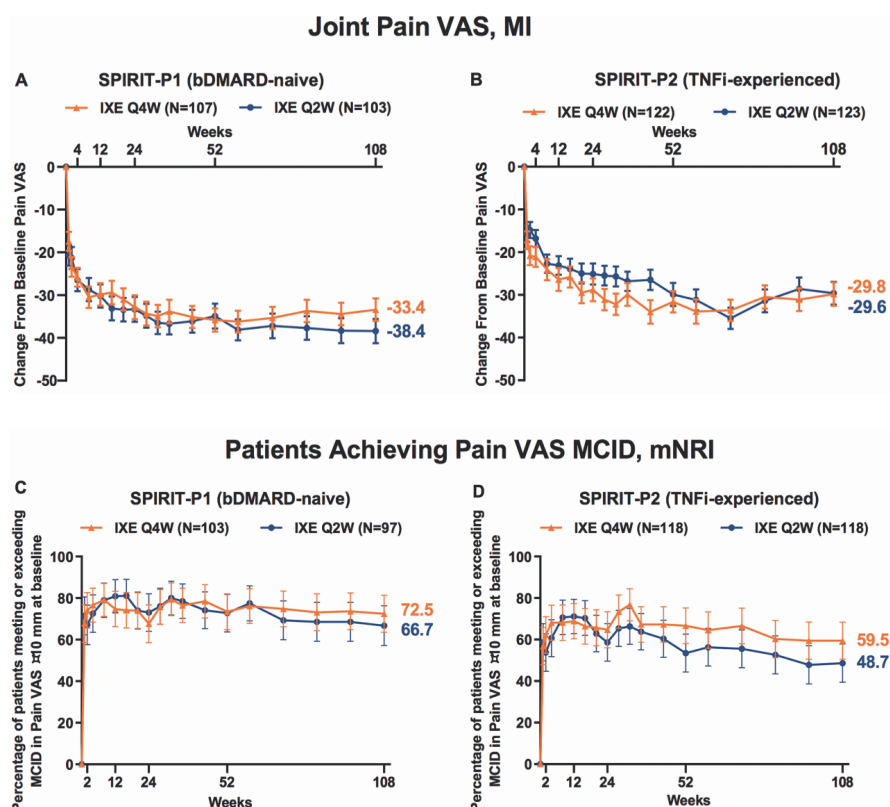
### Statistical analysis

Efficacy analyses were conducted on the intent-to-treat population defined as an all randomised population. During Weeks 0–24, mean change from baseline in pain VAS, fatigue NRS, PatGA VAS, and HAQ-DI were analysed using a pre-specified mixed-effects model for repeated measures (MMRM). The detailed description of the MMRM model is described in previous publications (25, 26). Additionally, in patients randomised to IXE at baseline, the mean change from baseline in pain VAS, fatigue NRS, patient global VAS, and HAQ-DI were also reported post hoc through Week 108, with missing data imputed using the multiple imputation (MI) method.

The number and percentage of patients achieving a MCID in pain VAS and fatigue NRS up to Week 24 were analysed *post hoc*. Treatment comparisons were conducted using logistic models. Observed data at Weeks 20 and 24 were excluded for patients classified as inadequate responders at Week 16. Patients who had missing data, who were deemed inadequate responders at Week 16, or who discontinued treatment early were imputed using non-responder imputation (NRI). Detailed descriptions of the statistical methods for continuous measures were described in Mease *et al.* and Nash *et al.* (25, 26). Response rates up to Week 108 were also reported among patients initially randomised to IXE, with missing data imputed using modified NRI.

### Results

In total, 780 patients (SPIRIT-P1, n=417; SPIRIT-P2, n=363) were included in the analyses. As previously reported, the mean patient age was 49.5 years in SPIRIT-P1 and 51.9 years in SPIRIT-P2; ≥91% were white and 46% were male in both studies (25, 26). The mean (SD) baseline scores in SPIRIT-P1 trial for tender joint count (TJC) were PBO=19.2 (13.0), IXE Q4W=20.5 (13.7) and IXE Q2W=21.5 (14.1), whereas, in the SPIRIT-P2 trial values were: PBO=23.0 (16.2), IXE Q4W=22.0 (14.1), and IXE Q2W=25.0 (17.3). The mean (SD) baseline scores in SPIRIT-P1 trial for swollen joint count



**Fig. 1.** Mean change from baseline in pain VAS score through Week 108 in SPIRIT-P1 (A) and SPIRIT-P2 (B) by MI method. Percentage of patients meeting or exceeding MCID of pain VAS ≥10 mm at baseline through Week 108 in SPIRIT-P1 (C) and SPIRIT-P2 (D) by mNRI method.

IXE: ixekizumab; IXE Q4W: ixekizumab 80 mg every 4 weeks; IXE Q2W: ixekizumab 80 mg every 2 weeks; MI: Multiple Imputation; mNRI: modified non-responder imputation; VAS: visual analogue scale.

(SJC) values were PBO=10.6 (7.3), IXE Q4W=11.4 (8.2), and IXE Q2W=12.1 (7.2), whereas, in the SPIRIT-P2 trial values were PBO=10.3 (7.4), IXE Q4W=13.1 (11.2) and IXE Q2W=13.5 (11.5). At baseline, the percentage of patients with enthesitis (defined as LEI>0) in SPIRIT-P1 were PBO=53.8%, IXE Q4W=65.4% and IXE Q2W=57.3% and in -P2 were PBO=58.5%, IXE Q4W=55.7% and IXE Q2W=68.3%. The baseline percentage of patients with dactylitis (defined as LDI-B>0) in SPIRIT-P1 were PBO=36.8%, IXE Q4W=50.5%, and IXE Q2W=39.8% and in -P2 were PBO=11.9%, IXE Q4W=23.0% and IXE Q2W=16.3%. Mean baseline scores for joint pain VAS, fatigue NRS, PatGA, and HAQ-DI were similar across study arms but slightly higher in SPIRIT-P2 compared to SPIRIT-P1 (Table I).

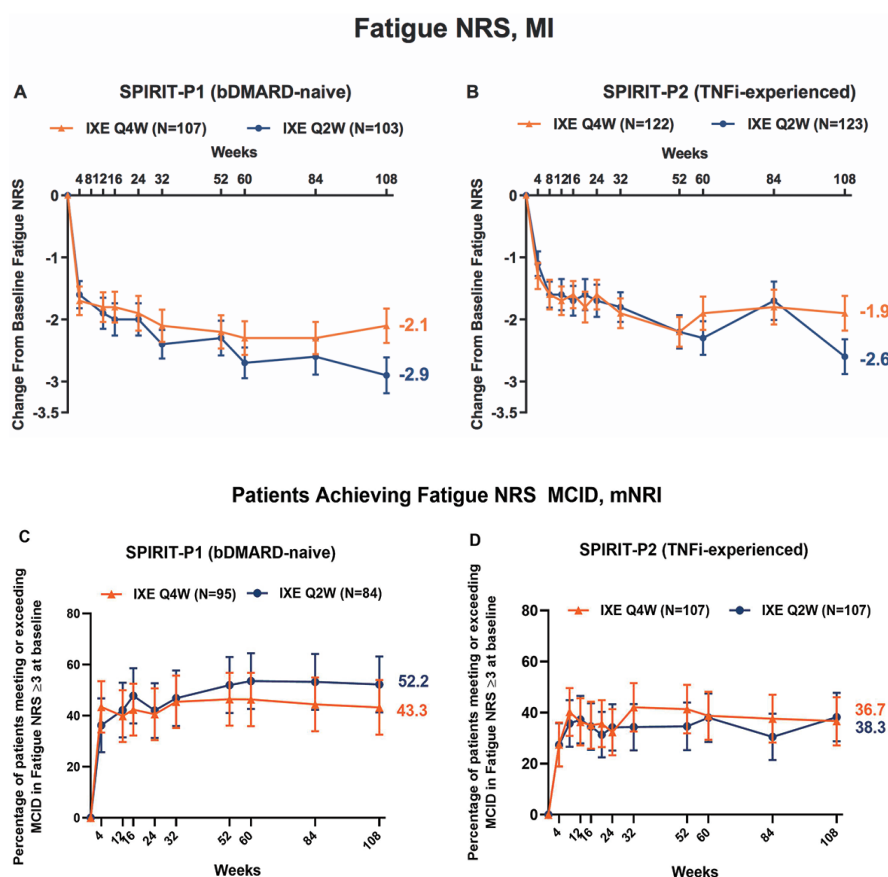
Treatment with IXE was associated with a rapid and sustained reduction in pain with statistically significant improvement as early as Week 1 in both

studies (Table I). At Week 1, patients treated with both IXE doses in SPIRIT-P1 and -P2 showed statistically significant reductions in mean change from baseline in pain VAS score *versus* PBO (Table I). At Week 24, further improvement in pain VAS scores continued in both studies ( $p<0.001$  vs. PBO for both IXE doses) (Table I). The improvement in pain VAS scores was sustained to Week 108 in patients on continuous IXE treatment (Fig. 1A-B).

A greater percentage of IXE-treated patients reported clinically meaningful improvement in pain MCID compared with PBO-treated patients as early as Week 1 (Table II). With continuous IXE treatment, the percentage of patients achieving the pain VAS MCID was sustained until Week 108 in both the studies (Fig. 1C-D).

Significant improvements in fatigue occurred at the earliest time point measured in both studies: Week 4 for SPIRIT-P1 and Week 2 for SPIRIT-P2 (Table I). In both studies, the mean





**Fig. 2.** Mean change from baseline in fatigue NRS score through Week 108 in SPIRIT-P1 (A) and SPIRIT-P2\* (B) by MI method. Percentage of patients meeting or exceeding MCID of fatigue NRS  $\geq 3$  at baseline through Week 108 in SPIRIT-P1 (C) and SPIRIT-P2\*\* (D) by mNRI method.

\*For SPIRIT-P1, the earliest time point measured was Week 4; for SPIRIT-P2 an additional time point was measured at Week 2 [IXE Q4W: -1.4 (0.20); IXE Q2W: -1.1 (0.20)].

\*\*For SPIRIT-P1, the earliest time point measured was Week 4; for SPIRIT-P2 an additional time point was measured at Week 2 [IXE Q4W: 31.7%; IXE Q2W: 25.4%].

IXE: ixekizumab; IXE Q4W: ixekizumab 80 mg every 4 weeks; IXE Q2W: ixekizumab 80 mg every 2 weeks; MI: Multiple Imputation; mNRI: modified non-responder imputation; NRS: numeric rating scale.

change from baseline in the fatigue NRS at Week 4 was statistically significant for both IXE doses *versus* PBO (Table I). Fatigue NRS scores continued to improve up to Week 24 for both IXE groups in both studies, only SPIRIT-P2 demonstrated statistically significant improvement with both IXE doses compared to PBO at Week 24. In patients continuously treated with IXE, improvement in fatigue persisted through Week 108 in both studies (Fig. 2A-B). At the earliest time point commonly assessed in both studies (Week 4), a greater number of IXE-treated patients compared with PBO-treated patients reported clinically meaningful improvement in fatigue (Table II). In patients continuously treated with IXE, the percentage of patients achieving the fatigue NRS MCID (SPIRIT-P1: IXE Q4W=43.3%, IXE Q2W=52.2%; SPIRIT-P2: IXE Q4W=36.7%, IXE Q2W=38.3%) was sustained to Week 108 (Fig. 2C-D).

Patients had a significant reduction in HAQ-DI score as early as Week 1 with both IXE doses in SPIRIT-P1 ( $p < 0.001$  vs. PBO) and with IXE Q4W in SPIRIT-P2 ( $p < 0.001$  vs. PBO). Improvement in physical functioning continued up to Week 24 with statistically significant improvement *versus* PBO with both IXE doses in both studies (Table I). In patients continuously treated with IXE, improvements in physical functioning

**Table II.** Percentage of patients achieving MCID response levels for Pain VAS and Fatigue NRS through Week 24 using NRI analysis in ITT population.

		Percentage of the patients with MCID or higher level response					
		SPIRIT-P1 (bDMARD-naïve)			SPIRIT-P2 (TNFi-experienced)		
		PBO (n=104)	IXE Q4W (n=103)	IXE Q2W (n=97)	PBO (n=117)	IXE Q4W (n=118)	IXE Q2W (n=118)
Joint pain VAS <sup>a</sup>	Week 1	47 (45.2)	69 (67.0) <sup>†</sup>	66 (68.0) <sup>†</sup>	40 (34.2)	66 (55.9) <sup>‡</sup>	69 (58.5) <sup>‡</sup>
	Week 24	37 (35.6)	63 (61.2) <sup>‡</sup>	69 (71.1) <sup>‡</sup>	37 (31.6)	73 (61.9) <sup>‡</sup>	66 (55.9) <sup>‡</sup>
Fatigue NRS <sup>a, b</sup>	Week 4	15 (16.1)	40 (42.1) <sup>‡</sup>	28 (33.3) <sup>†</sup>	10 (9.3)	28 (26.2) <sup>†</sup>	29 (27.1) <sup>†</sup>
	Week 24	19 (20.4)	35 (36.8) <sup>#</sup>	34 (40.5) <sup>†</sup>	6 (5.6)	33 (30.8) <sup>‡</sup>	36 (33.6) <sup>‡</sup>

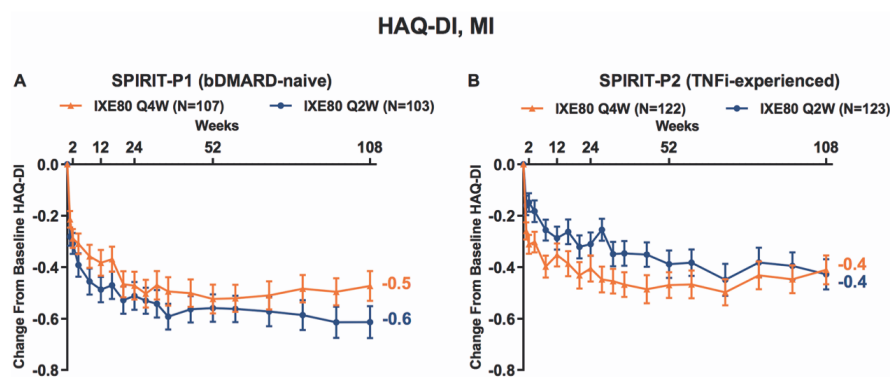
Data presented here are n (%).

<sup>†</sup> $p < 0.01$ ; <sup>‡</sup> $p < 0.001$ ; <sup>#</sup> $p < 0.05$  vs. PBO.

<sup>a</sup>0–100 scale, higher=worse; <sup>b</sup>0–10 scale.

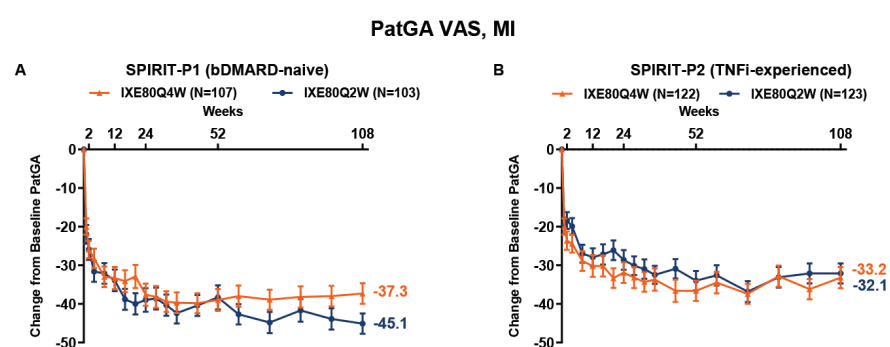
\*For SPIRIT-P1, the earliest time point measured was Week 4; for SPIRIT-P2 an additional time point was measured at Week 2 [PBO: 11 (10.2); IXE Q4W: 33 (30.8)<sup>‡</sup>; IXE Q2W: 27 (25.2)<sup>†</sup>].

IXE: ixekizumab; IXE Q4W: IXE 80 mg every 4 weeks; IXE Q2W: IXE 80 mg every 2 weeks; n: number of responders; N: number of patients in the analysis population; NRI: non-responder imputation; NRS: numeric rating scale; PBO: placebo; VAS: visual analogue scale.



**Fig. 3.** Mean change from baseline in HAQ-DI score through Week 108 in SPIRIT-P1 (A) and SPIRIT-P2 (B) by MI method.

HAQ-DI: Health Assessment Questionnaire-Disability Index; IXE: ixekizumab; IXE Q4W: ixekizumab 80 mg every 4 weeks; IXE Q2W: ixekizumab 80 mg every 2 weeks; MI: Multiple Imputation; mNRI: modified non-responder imputation.



**Fig. 4.** Mean change from baseline in PatGA VAS Score through Week 108 in SPIRIT-P1 (A) and SPIRIT-P2 (B) by MI method.

IXE: ixekizumab; IXE Q4W: ixekizumab 80 mg every 4 weeks; IXE Q2W: ixekizumab 80 mg every 2 weeks; MI: Multiple Imputation; mNRI: modified non-responder imputation; PatGA: patient global assessment.

measured by HAQ-DI, which persisted through Week 108; patients receiving IXE Q4W had improvements from baseline of -0.5 and -0.4 at Week 108 in SPIRIT-P1 and -P2, respectively (Fig. 3A-B).

Both IXE-treated groups showed statistically significant improvement in PatGA VAS as early as Week 1 with continued improvement through Week 24 ( $p < 0.001$  vs. PBO) in SPIRIT-P1 and SPIRIT-P2 (Table I). In patients continuously treated with IXE, improvement in PatGA VAS persisted through Week 108; SPIRIT-P1 and -P2 patients on IXE Q4W treatment had improvement from baseline of -37.3 and -33.2 points, respectively (Fig. 4A-B).

## Discussion

Pain, physical function, patient global assessment, and fatigue are the prominent patient-reported symptoms in-

cluded in the PsA core domain set endorsed by GRAPPA and OMERACT (19, 20). It is important to demonstrate that clinical improvement is associated with reduction in fatigue, as well as improved quality of life and function. Results from the 2 phase III (SPIRIT-P1 and SPIRIT-P2) trials have shown IXE-treated patients had rapid and statistically significant improvement in pain, physical function, patient global assessment, and fatigue. In SPIRIT-P1 there was a numerically higher response for the Q2W dose across the PRO endpoints, except for the Pain VAS MCID, possibly related to the definition of the MCID as a 10% improvement. In SPIRIT-P2 no dose response was seen because of the smaller sample size; however, the SPIRIT studies were not powered to detect a difference between the two doses. The early improvements were sustained until Week 108 and con-

sistent in both bDMARD-naïve and TNFi-experienced patients.

While early onset of effect may be a specific attribute of a therapy, it can only be assessed relative to the earliest time point measured within a clinical trial. Earlier onset ( $\leq 4$  weeks after initiation of therapy) of pain relief, fatigue, patient global, and physical function have been reported for only a limited number of clinical trials, and the time points reported are variable, making comparison across therapies difficult. Likewise, association of early improvement in PROs to improvement in clinical status is also not often reported (8-13, 37-39). Data from the SPIRIT trials show patients treated with IXE Q4W versus PBO reported statistically significant improvement in pain, patient global assessment, and physical function as early as Week 1, with more than 50% of patients in both studies reporting clinically meaningful improvement in pain ( $\geq 10$ -point improvement) after 1 week of therapy. Patients also reported a significant improvement in fatigue at the earliest time point measured (Week 4 in SPIRIT-P1; Week 2 in SPIRIT-P2), with 26-42% of IXE Q4W treated patients reporting clinically meaningful improvement in fatigue ( $\geq 3$  points) at Week 4. Statistically significant improvement in fatigue at Week 24 was seen in SPIRIT-P2 only, while a similar numerical improvement was seen across the two studies, the smaller sample size in SPIRIT-P1 may have contributed to the lack of statistical significance achieved in this study.

Rapid onset of symptom relief may be the most important treatment goal for some patients. But long-term maintenance of therapeutic efficacy, particularly for disease symptoms which are of greatest importance to patients, could have implications for patient adherence to treatment regimens and persistence on therapy over time. Similar to early onset of therapy, few trials have reported long-term effects ( $\geq 2$  years) of bDMARD or tDMARDs on individual PROs (4). Data from the SPIRIT trials showed sustained improvement in PROs up to Week 108 in IXE Q4W-treated patients, with 59.4% (SPIRIT-P2) to 72.5% (SPIRIT-P1) of

patients reporting clinically meaningful improvement in pain, and 37–43% of IXE Q4W-treated patients reporting clinically meaningful improvement in fatigue after 2 years of treatment.

Reduced efficacy, specifically with TNFis, has been reported as patient's progress from first-line therapy to later lines of therapy (40–42). Limited data exist on whether prior biologic experience affects PROs in PsA patients to a similar extent, with the analyses which have been done showing mixed results. Data from the RAPID-PsA study found certolizumab's effect on pain and physical function was slightly greater in patients with prior TNFi experience compared to patients who were TNFi-naïve (8). Results from the FUTURE 2 study show patients treated with secukinumab who were TNFi-naïve reported a greater effect on physical function and pain compared to secukinumab-treated patients who had prior TNFi experience (39). OPAL-Broaden and OPAL-Beyond studies showed that tofacitinib 5 mg twice daily had a greater effect on pain, PatGA, HAQ-DI, and FACIT-fatigue in TNFi-experienced patients while TNFi-naïve patients experienced a greater effect on those 4 PROs when taking 10 mg twice daily tofacitinib (37, 38). Regardless of whether the population was bDMARD-naïve or TNFi-experienced, IXE Q4W demonstrated a similar effect on pain, patient global, physical function, and fatigue. Limitations of this study include that although the change from baseline analyses for all PRO assessments presented here were prespecified, they were not adequately protected from increases in type I error due to multiplicity of testing because they were not included within the predefined hierarchical testing procedure, the MCID analyses for pain VAS and fatigue NRS were conducted post hoc, and the lack of an active comparator or placebo-control after Week 24.

PROs are important to study in order to understand the full effect of a treatment for PsA (19, 42). As new molecules become available to treat PsA, studies should consider investigating which attributes of a therapy are most important to patients (e.g. onset of effect

and maintenance of effect), and how they affect patient satisfaction, treatment persistence, or patient preference across pharmacologic therapies (3).

## Conclusion

Patients treated with IXE achieved significantly greater improvements *versus* PBO as early as Week 1 in joint pain, HAQ-DI, and PatGA. Fatigue also improved significantly at the earliest time point measured (Week 4 for SPIRIT-P1 and Week 2 for SPIRIT-P2). Improvements for pain, PatGA, fatigue, and physical function persisted to Week 108, and were generally consistent in both SPIRIT-P1 (bDMARD-naïve) and SPIRIT-P2 (TNFi-experienced) populations.

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