Ixekizumab improves patient-reported outcomes in patients with active psoriatic arthritis and inadequate response to tumour necrosis factor inhibitors: SPIRIT-P2 results to 52 weeks

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Abstract Objective

To report patient-reported outcomes (PROs) of ixekizumab-treated patients with psoriatic arthritis (PsA) and an inadequate response (IR) or intolerance to tumour necrosis factor inhibitors (TNFi) to 52 weeks.

Methods

In SPIRIT-P2, patients with active PsA and an IR or intolerance to TNFi were randomised to ixekizumab 80 mg every 4 weeks (IXEQ4W; N=122) or every 2 weeks (IXEQ2W; N=123), or placebo (PBO; N=118) during the initial 24-week double-blind treatment period. At Week 16, background therapy was modified for IRs; additionally, IRs in the placebo group were re-randomised (1:1) to IXEQ2W or IXEQ4W. Patients receiving ixekizumab at Week 24 received the same dose during the study remainder. Patients completed several PROs for PsA disease activity, skin, health-related quality of life (HRQOL, and work through Week 52.

Results

Ixekizumab-treated patients reported significant improvements versus PBO in 36-Item Short Form Health Survey version 2, European Quality of Life 5 Dimensions visual analogue scale, Bath Ankylosing Spondylitis Disease Activity Index (total score and question 2), and Work Productivity and Activity Impairment Questionnaire-Specific Health Problem (3 of 4 domains) through Week 24. At Week 24, 9% (PBO), 52% (IXEQ4W), and 50% (IXEQ2W) of patients reported Dermatology Life Quality Index scores of 0 or 1; 0% (PBO) and 24% (IXEQ4W and IXEQ2W) reported Itch Numeric Rating Scale score of 0. Where data were collected, improvements persisted through Week 52.

Conclusion

In patients with PsA and an IR or intolerance to TNFi, ixekizumab significantly improved disease activity, skin symptoms, HRQOL, and work productivity to 52 weeks.

Key words ixekizumab, quality of life, psoriatic arthritis, clinical trial, IL-17

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Introduction

Psoriatic arthritis (PsA) is a progressive, destructive disease causing deformities, impaired physical function, loss of health-related quality of life (HRQOL), and increased mortality (1). This disease negatively impacts multiple physical and emotional aspects of patients' lives (1-3). Patients with PsA reported poorer HRQOL relative to the general population and to patients with psoriasis (2, 4). Although patients with PsA and rheumatoid arthritis report reduced HRQOL, there are some differences on the impact of these conditions on HRQOL with the presence of psoriasis perhaps causing unique disabilities among patients with PsA (5).

The current standard of care for PsA includes non-steroidal anti-inflammatory drugs, glucocorticoids, conventional disease-modifying anti-rheumatic drugs (cDMARDs), and biologic agents such as tumour necrosis factor alpha inhibitors (TNFi) (6-8). TNFi are effective in reducing the signs and symptoms of PsA (6-9), but some patients may experience an inadequate response, and others may be intolerant. The success of TNFi has increased physician and patient expectations for new agents that can be used in patients that do not respond well to TNFi.

The interleukin-17 (IL-17) pathway is involved in normal and pathological function of the immune system and plays a role in inflammatory disorders such as psoriasis and PsA (10). This led to the development of IL-17A inhibitors for treatment of psoriasis and PsA. Proof-of-concept was demonstrated in successful phase 3 clinical trials in psoriasis or PsA involving the IL-17A inhibitors secukinumab (11-13), brodalumab (14), and ixekizumab (15-18).

Ixekizumab is a high-affinity monoclonal antibody that selectively targets IL-17A (19). Ixekizumab treatment improved the signs and symptoms in patients with active PsA who were biologic-naïve (SPIRIT-P1) (15) and in patients with an inadequate response or intolerance to TNFi (SPIRIT-P2) through 24 weeks (16). The objective of this study was to assess patient-reported outcomes (PROs) up to 52 weeks in ixekizumab-treated patients who had prior inadequate response or intolerance to TNFi from the SPIRIT-P2 trial (NCT 02349295).

Materials and methods

Patients

Detailed enrolment and exclusion criteria for SPIRIT-P2 were previously reported (16). Key enrolment criteria included age \geq 18 years, active psoriatic skin lesions (plaque) or a documented history of plaque psoriasis, active PsA for \geq 6 months and meeting the CIASsification criteria for Psoriatic ARthritis (CASPAR) (20), and \geq 3 of 68 tender joint counts and of 66 swollen joint counts (16). Other key criteria were prior treatment with \geq 1 cDMARD and 1 or 2 TNFi with either an inadequate response to at least 1 TNFi due to lack of efficacy or TNFi intolerance.

Ethics

SPIRIT-P2 was conducted in accordance with the standards of the responsible local committee or with the Helsinki Declaration of 1975/83. All patients provided written informed consent.

Study design

SPIRIT-P2 was a randomised, doubleblind, placebo-controlled phase 3 trial (16). Patients were randomised 1:1:1 to ixekizumab 80 mg every 4 weeks (IXEQ4W), ixekizumab 80 mg every 2 weeks (IXEQ2W), or placebo (Supplementary Fig. 1). Patients receiving ixekizumab were given a 160-mg starting dose at Week 0. Randomisation was stratified by country and TNFi experience (inadequate response to 1 TNFi, inadequate response to 2 TNFi, or intolerance to TNFi).

Using predefined tender and swollen joint criteria, patients with an inadequate response at Week 16 were required to add or modify concomitant drugs (16). Inadequate responders who were originally assigned ixekizumab continued their originally assigned dose of ixekizumab, whereas patients initially assigned to placebo were re-randomised 1:1 to IXEQ2W or IXEQ4W. After Week 24, patients still receiving placebo at the completion of the double-blind treatment period were re-randomised 1:1 to either IXEQ4W or IXEQ2W. Patients receiving ixekizumab at Week 24 received the same dose during the study remainder. The data through Week 52 are reported.

Assessments

The PRO domains that are the focus of this report include assessment of disease activity (arthritis, axial symptoms, and skin), quality of life, and work productivity. Arthritis-related disease activity was assessed using a Joint Pain and a Patient Global Assessment (PtGA) 100-mm horizontal visual analogue scale (VAS) (21). Axial disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; 0-10; higher score more severe) (22). The BASDAI was developed to assess axial spondyloarthritis (22) and is not specific for axial involvement in PsA. To more specifically assess potential axial symptoms, a subset analysis of patients having a score of >4 on Item 2 (neck, back, or hip pain) was performed. Skin-specific disease activity was assessed using an Itch 0-10 Numeric Rating Scale (NRS), including assessment of itch resolution (Itch NRS = 0) (23, 24).

Health-related quality of life was assessed by the 36-item Short Form Health Survey version 2 - acute (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, and the 8 domain scores (25, 26). Age- and gender-matched normative values for the SF-36 were derived from the general 1998 US population (27). In addition, the European Quality of Life 5 Dimension 5 Level (EQ-5D 5L) Health Questionnaire VAS (0-100 scale; higher scores indicate better health) also measured generic HRQOL (28). Skinspecific qualify of life was assessed by the Dermatology Life Quality Index (DLQI), with a total score ranging from 0 to 30 (less to more impairment) and scores of 0 or 1 defined as no impact of disease on HRQOL (29-31). Work productivity was measured by the Work Productivity and Activity Impairment Questionnaire-Specific Health Problem (WPAI-SHP) (32, 33).

The time course plots show all time points for which data for each measure were collected through Week 24. Data Table I. Baseline demographics and characteristics*.

	PBO	ITT Population IXEQ4W	IXEQ2W
	IN=110	IN=122	N=125
Age, years, mean (SD)	51.5 (10.4)	52.6 (13.6)	51.7 (11.9)
Male, n (%)	56 (47.5)	63 (51.6)	50 (40.7)
Weight, kg, mean (SD)	91.0 (22.1)	89.9 (22.0)	85.2 (20.7)
BMI (kg/m ²), mean (SD)	31.6 (7.6)	30.9 (7.1)	30.1 (6.8)
Race, n (%)			
Asian	7 (5.9)	7 (5.7)	7 (5.7)
Black or African American	1 (0.8)	1 (0.8)	1 (0.8)
White	108 (91.5)	111 (91.0)	113 (92.6)
Multiple or other	2 (1.7)	3 (2.4)	1 (0.8)
Previous TNFi treatment, n (%)			
Inadequate response to 1	68 (57.6)	71 (58.2)	65 (52.8)
Inadequate response to 2	41 (34.7)	41 (33.6)	46 (37.4)
Intolerance	9 (7.6)	10 (8.2)	12 (9.8)
Current MTX use n (%)	40 (33.9)	48 (39 3)	61 (49.6)
Current cDMARD use $n(\%)$	52 (44.1)	60 (49.2)	73 (59.3)
Time since PsA diagnosis years mean (SD)	92(73)	11.0 (9.6)	99 (74)
Tender joint count (68 joints) mean (SD)	23.0(16.2)	22.0(14.1)	250(173)
Swollen joint count (66 joints), mean (SD)	10.3(7.4)	131(112)	135(115)
Patients with current psoriasis n (%)	10.8 (91.5)	118 (967)	113 (91.9)
% Body surface area >3% n $(\%)^{\text{F}}$	67 (62.6)	68 (61.8)	68 (63.0)
PASI score mean (SD) [¶]	71(71)	93 (91)	8.8 (10.3)
SE-36 PCS mean (SD)	33.9 (9.0)	34.8 (8.8)	34 3 (9 1)
SF-36 MCS, mean (SD)	48.0 (13.1)	49.6 (11.3)	49.1 (11.5)
SE-36 domain scores mean (SD)			
Physical functioning	41.2 (26.0)	43 2 (26 7)	44.8 (26.4)
Role physical	41.2(20.0) 41.6(24.1)	47.4(25.7)	42.9 (26.3)
Bodily pain	37.1(19.0)	39.5(20.1)	37.2(19.5)
General health	45.3 (19.8)	46.8 (20.3)	45.2(19.9)
Vitality	36.9 (21.9)	38.8(21.2)	39.9 (22.0)
Social functioning	62.6(29.1)	67 1 (27 5)	65.5(27.2)
Role emotional	72.0 (29.6)	75.6 (26.6)	73.3 (26.7)
Mental health	66.1 (22.6)	69.0 (21.0)	68.0 (20.6)
EQ-5D VAS, mean (SD)	53.6 (20.0)	53.9 (22.4)	53.9 (19.7)
Joint pain VAS, mean (SD)	63.9 (20.1)	63.9 (21.4)	62.7 (20.9)
PtGA VAS, mean (SD)	64.1 (21.5)	66.4 (20.5)	66.0 (20.5)
BASDAI, mean (SD)§	6.8 (1.4)	6.5 (1.4)	6.6 (1.4)
BASDAI-neck, back, or hip pain, mean (SD)**	7.3 (1.5)	7.2 (1.4)	7.2 (1.4)
WPAI-SHP, mean (SD)			
% absenteeism, mean (SD)	11.9 (28.1)	11.6 (26.6)	8.8 (23.2)
% presenteeism, mean (SD)	40.4 (28.8)	45.0 (25.7)	36.9 (25.0)
% overall work impairment, mean (SD)	41.5 (29.6)	46.9 (26.7)	38.8 (26.6)
% activity impairment, mean (SD)	54.0 (25.8)	53.9 (24.9)	49.3 (26.5)
DLOI, mean (SD) ^g	9.6 (8.1)	9.1 (7.4)	9.2 (7.8)
Itch NRS, mean (SD) [¶]	5.7 (2.8)	5.5 (2.5)	5.6 (3.0)

*Some data from Nash et al. (16).

[¥]Among patients with plaque psoriasis.

⁹Evaluated among ITT patients with psoriatic lesions involving ≥3% of the body surface area. N=67, N=68, and N=68 for PBO, IXEQ4W, and IXEQ2W, respectively.

[§]Evaluated among ITT patients with baseline BASDAI >4. N=96, N=100, and N=99 for PBO, IX-EQ4W, and IXEQ2W, respectively.

**Among patients with baseline BASDAI Individual Component #2 (neck, back, or hip pain) score >4. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BMI: body mass index; cDMARD: conventional disease-modifying anti-rheumatic drugs; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life–5 Dimensions 5 Level; ITT: intent-to-treat; IXEQ2W: ixekizumab 80 mg every 2 weeks; IXEQ4W: ixekizumab 80 mg every 4 weeks; MCS: Mental Component Summary; MTX: methotrexate; N: population size; n: number in group; NRS: Numeric Rating scale; PASI: Psoriasis Area Severity Index; PBO: placebo; PCS: Physical Component Summary; PsA: psoriatic arthritis; PtGA: Patient Global Assessment of Disease Activity; SD: standard deviation; SF-36: 36-Item Short Form Health Survey; TNFi: tumour necrosis factor inhibitor; VAS: visual analogue scale; WPAI-SHP: Work Productivity and Activity Impairment–Specific Health Problem. Table II. Efficacy to Week 52 using multiple imputation method*.

	Week 12		Week 24		Week 52	
	IXEQ4W N=122	IXEQ2W N=123	IXEQ4W N=122	IXEQ2W N=123	IXEQ4W N=122	IXEQ2W N=123
SF-36 PCS [¥]	5.8 (0.8)	5.9 (0.8)	6.2 (0.9)	5.9 (1.0)	7.6 (0.8)	7.6 (0.9)
SF-36 MCS [¥]	4.0 (1.0)	4.3 (0.9)	3.6 (1.0)	4.1 (1.0)	4.5 (1.0)	3.6 (1.0)
SF-36 Domains						
Physical functioning	13.8 (2.1)	11.6 (1.8)	17.1 (2.3)	12.0 (2.1)	18.8 (2.3)	13.6 (2.4)
Role physical	15.1 (2.2)	17.5 (2.6)	12.6 (2.3)	16.1 (2.6)	18.7 (2.1)	18.3 (2.7)
Bodily pain	14.7 (2.1)	16.6 (1.9)	17.1 (2.2)	16.1 (2.2)	19.6 (2.1)	22.0 (2.4)
General health	7.3 (1.4)	7.5 (1.3)	7.0 (1.4)	7.0 (1.6)	8.4 (1.6)	7.0 (1.5)
Vitality	11.2 (1.6)	12.5 (2.0)	12.0 (2.0)	12.7 (2.1)	14.7 (2.0)	15.0 (2.2)
Social functioning	12.3 (2.2)	12.6 (2.3)	10.7 (2.4)	12.9 (2.4)	15.2 (2.4)	14.3 (2.6)
Role emotional	9.6 (2.2)	10.6 (2.1)	10.6 (2.1)	9.7 (2.2)	10.8 (2.4)	8.8 (2.1)
Mental health	7.6 (1.7)	7.1 (1.5)	6.7 (1.7)	7.1 (1.6)	9.3 (1.6)	6.5 (1.6)
EQ-5D VAS	11.3 (2.4)	11.1 (1.9)	12.3 (2.4)	11.2 (2.1)	12.8 (2.2)	12.1 (2.2)
Joint pain VAS ⁹	-26.5 (2.6)	-23.2 (2.2)	-29.0 (2.6)	-25.0 (2.6)	-31.6 (2.5)	-29.8 (2.7)
PtGA VAS ⁹	-30.4 (2.8)	-28.1 (2.3)	-32.1 (2.7)	-28.6 (2.6)	-36.7 (2.6)	-34.1 (2.5)
BASDAI [§]	-2.2 (0.2)	-2.0 (0.2)	-2.4 (0.2)	-2.3 (0.2)	-2.8 (0.2)	-2.8 (0.3)
BASDAI – neck, back, or hip pain**	-1.9 (0.3)	-2.0 (0.3)	-2.3 (0.3)	-2.4 (0.3)	-2.7 (0.3)	-3.1 (0.3)
WPAI-SHP						
% absenteeism	1.1 (3.3)	2.6 (3.2)	2.1 (3.3)	6.1 (3.9)	-6.9 (3.1)	-1.8 (4.2)
% presenteeism	-23.3 (3.1)	-16.4 (3.6)	-19.0 (4.1)	-17.3 (3.8)	-27.3 (3.8)	-22.2 (3.7)
% overall work impairment	-20.5 (3.8)	-14.5 (4.0)	-18.7 (4.2)	-12.2 (3.7)	-26.5 (4.1)	-17.1 (3.9)
% activity impairment	-20.9 (2.4)	-14.7 (2.5)	-21.5 (2.8)	-16.0 (2.8)	-25.7 (2.6)	-19.2 (2.5)
Itch NRS ^{\$}	-3.2 (0.4)	-3.1 (0.4)	-2.9 (0.4)	-3.1 (0.4)	-3.5 (0.4)	-3.5 (0.4)
Itch NRS=0, % ^{\$}	30.2	24.6	26.8	27.7	32.8	30.6

*Mean change from baseline (SE) is reported unless indicated.

^vMMRM analyses of Week 12 and 24 data were reported in Nash et al. (16), and Week 52 mBOCF data were reported in Kavanaugh et al. (34).

⁹Data to 24 weeks (MMRM) were previously reported in Nash et al. (16).

[§] Evaluated among ITT patients with baseline BASDAI >4. n=100 and n=99 for IXEQ4W and IXEQ2W, respectively.

**Among patients with baseline BASDAI Individual Component #2 (neck, back, or hip pain) score >4. N=83 and N=83 for IXEQ4W and IXEQ2W, respectively. ^sEvaluated among ITT patients with psoriatic lesions involving ≥3% of the body surface area. N=68 and N=68 for IXEQ4W and IXEQ2W, respectively. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; EQ-5D: European Quality of Life–5 Dimensions 5 Level; ITT: intent-to-treat; IXEQ2W: ixekizumab 80 mg every 2 weeks; IXEQ4W: ixekizumab 80 mg every 4 weeks; mBOCF: modified baseline observation carried forward; MCS: Mental Component Summary; MMRM: mixed models repeated measures analysis; N: population size; NRS: Numeric Rating scale; PCS: Physical Component Summary; PtGA: Patient Global Assessment; SE: standard error; SF-36: 36-Item Short Form Health Survey; VAS: visual analogue scale; WPAI-SHP: Work Productivity and Activity Impairment–Specific Health Problem.

were not collected after Week 24 for the DLQI. Some data to Week 24 (Joint Pain VAS, PtGA VAS, SF-36 PCS, SF-36 MCS) were previously reported in the SPIRIT-P2 primary analysis (16) and are presented here for completeness, in addition to previously unreported Week 52 data.

Statistics

Health outcomes were analysed using the intention-to-treat (ITT) population, defined as all randomly assigned patients. Skin-specific PROs (*e.g.* itch NRS, DLQI) were assessed in the subset of patients with $\geq 3\%$ body surface area (BSA) at baseline affected by psoriasis. During the first 24 weeks, categorical data were analysed using a logistic regression model adjusting for geographical region, and previous TNFi use (inadequate responder to 1 TNFi, inadequate responder to 2 TNFi, or intolerance to a TNFi). Fisher's exact test was used for secondary comparisons. For categorical analyses, patients with missing data at Week 24 or those deemed Week 16 inadequate responders, or those who discontinued treatment on or prior to Week 24 were imputed as non-responders.

For the first 24 weeks, changes in continuous data were analysed using a mixed models repeated measures analysis (MMRM). This model used treatment, visit, geographical region, previous TNFi, treatment-by-visit interaction, geographical region-by-visit interaction, and TNFi use-by-visit interaction as factors and with baseline and baseline value-by-visit interactions as continuous, fixed covariates. For patients classified as Week 16 inadequate responders, data after Week 16 were not

included. Data are expressed as least squares mean (LSM) change from baseline. Mean SF-36 domain scores were presented using spydergrams and the missing data were imputed using the modified baseline observation carried forward method. The study was only designed and powered to compare the ixekizumab treatment groups with placebo, not the ixekizumab groups with each other.

For Week 52 data, *post-hoc* analyses were conducted; these were based on patients who were randomised to ixekizumab treatment at study initiation. The multiple imputation method was used to impute missing data. Using this method, missing observations are imputed multiple times (m-times), and the final estimate is calculated after pooling information from these m-imputed datasets. Observed data for Week 16



Fig. 1. Dermatology Life Quality Index and Itch.

The graphs show a subset of the ITT population consisting of patients with psoriatic arthritis and psoriatic skin lesions affecting $\geq 3\%$ BSA at baseline. A, LSM change from baseline in DLQI to Week 24; B, Percentage of patients reporting DLQI = 0,1 to Week 24 C, LS mean change from baseline in Itch NRS to Week 24; D, Percentage of patients reporting Itch NRS = 0 to Week 24.

* $p \le 0.001$ active vs. PBO; $^{\dagger}p \le 0.005$ active vs. PBO; $^{\Psi}p \le 0.05$ active vs PBO.

In **Panel A and C**, baseline was the last non-missing value on or before the date of first injection of study treatment at Week 0. Observed data at Weeks 20 and 24 for Week 16 inadequate responders were excluded. The *p*-values are from an MMRM model.

In Panels B and D, NRI was applied for inadequate responders at Week 16 and patients who discontinued on or before Week 24. Observed data after at Weeks 20 and 24 for Week 16 inadequate responders were excluded. *p*-values are from logistic model or Fisher's exact test.

BSA, body surface area; DLQI, Dermatology Life Quality Index; ITT, intent-to-treat; IXEQ2W, ixekizumab 80 mg every 2 weeks; IXEQ4W, ixekizumab 80 mg every 4 weeks; LSM, least squares mean; MMRM: mixed models repeated measures analysis; N: population size; NRI: non-responder imputation; NRS: numeric rating scale; PBO: placebo.

inadequate responders were included in the analysis. For comparison with Week 52, data from Week 12 and 24 were also calculated using multiple imputation.

Results

Patients and baseline demographics The ITT population was comprised of 363 patients (118 placebo; 122 IX-EQ4W; 123 IXEQ2W) (16). Betweenarm baseline characteristics were mostly similar except current methotrexate use and swollen joint counts, which were all higher in the IXEQ2W group (Table I).

Disease activity

Ixekizumab-treated patients reported significant improvement relative to placebo in both the joint pain VAS and the PtGA VAS through Week 24 (Supplementary Table I) (16), persisting



Fig. 2. SF-36. The spydergrams depict mean SF-36 scores in the ITT population during the Placebo-controlled Period (baseline and Week 24) compared with age- and gender- matched normative values. mBOCF was applied for inadequate responders at Week 16 and patients who discontinued at or before Week 24.

BP: bodily pain; GH, general health; ITT: intentto-treat; IXEQ2W: ixekizumab 80 mg every 2 weeks; IXEQ4W: ixekizumab 80 mg every 4 weeks; mBOCF: modified baseline observation carried forward; MH: mental health; Norm: normative value; PF: physical functioning; RE: role emotional; RP: role physical; SF: social functioning; SF-36: 36-Item Short Form Health Survey version 2; VT: vitality; W24: Week 24.

through Week 52 (Table II). Among the subgroup of ITT patients with baseline BASDAI >4, ixekizumab-treated patients reported significant improvements in their BASDAI total score relative to placebo through Week 24 (Supplementary Table I; Supplementary Fig. 2), persisting through Week 52 (Table II). In the subset of patients with a score >4 for question 2 of the BASDAI (neck, back, or hip pain), the ixekizumab groups reported significantly improved neck, back, and hip pain at Week 12 and 24 relative to placebo (Supplementary Table I), persisting through Week 52 (Table II).

Skin-related PROs

Among patients with baseline BSA \geq 3%, ixekizumab-treated patients reported significant improvement in the DLQI compared to those treated with placebo as early as Week 2 through Week 24 (Fig. 1A; Supplementary Table I). Likewise, higher proportions of ixekizumab-treated patients reported a DLQI of 0 or 1, indicating skin symptoms had no impact on patient quality of life, through Week 24 (Fig. 1B; Supplementary Table I). Patients did not complete the DLQI after Week 24.

Concomitant with improvements in DLQI, ixekizumab-treated patients with baseline BSA $\geq 3\%$ reported statistically significant improvement in itch compared to that reported by the placebo group though Week 24 (Fig. 1C; Supplementary Table I). Improvement persisted through Week 52 (Table II). Likewise, higher proportions of patients in the ixekizumab groups compared to the placebo group reported no itch through Week 24 (Fig. 1D; Supplementary Table I), persisting through Week 52 (Table II).

Quality of life

Patients in the ixekizumab groups reported significant improvements relative to those in the placebo group in SF-36 PCS and SF-36 MCS at Week 12 and 24 (Supplementary Table I) (16), persisting through Week 52 (Table II) (34). Likewise, patients reported statistically significant improvement relative to placebo in all SF-36 domain scores at Week 12 and 24 (Supplementary Table I), persisting through Week 52 (Table II), persisting through Week 52 (Table II), persisting through Week 52 (Table II). Figure 2 shows mean SF-36 domain scores at baseline and Week 24 relative to age-and gender-matched normative scores. At baseline, patients had SF-36



Fig. 3. EQ-5D VAS.

The graph shows the EQ-5D 5L VAS to Week 24. Observed data at Week 24 for Week 16 inadequate responders were excluded. LSM change from baseline is reported and based on an MMRM model. $*p \le 0.001$ active vs. PBO; $^{\dagger}p \le 0.005$ active vs. PBO

EQ-5D VAS: European Quality of Life – 5 Dimensions 5 Level visual analogue scale; IXEQ2W: ixekizumab 80 mg every 2 weeks; IXEQ4W: ixekizumab 80 mg every 4 weeks; LSM: least squares mean; MMRM: mixed models repeated measures analysis; N: population size; PBO: placebo.

domain scores below age- and gendermatched normative scores. By Week 24, all domains had improved *versus* baseline with both ixekizumab dosing regimens but not with placebo (Fig. 2). Consistent with the SF-36 results, ixekizumab-treated patients reported significant improvement in their EQ-5D 5L VAS scores through Week 24, achieving maximal improvement by Week 8 (Fig. 3). Improvement persisted through Week 52 (Table II).

Work productivity

Ixekizumab-treated patients reported significant improvement in 3 of 4 WPAI-SHP domains (presenteeism, activity impairment, and work impairment) through Week 24 (Fig. 4; Supplementary Table I). Improvement persisted to Week 52 (Table II).

Discussion

Previous results from the SPIRIT-P2 study demonstrated that treatment with ixekizumab provided clinically meaningful and sustained (up to 52 weeks) improvements in joint, skin, and physical function in active PsA patients with prior inadequate response or intolerance to TNFi (16, 34). These analyses extend

the findings by reporting on the patientreported benefit across a broad range of outcome domains. As previously reported, ixekizumab-treated patients had significantly greater improvements in patient-reported pain, global disease activity, and generic measures of HRQOL (i.e. SF-36 PCS and MCS) at Week 24 when compared with that of the placebo group in SPIRIT-P2 (16). This report expands the assessment of HRQOL showing statistically significant improvement in ixekizumab-treated patients compared with that of placebo in all 8 domains of the SF-36 at Week 24. The domains of Physical Functioning, Role Physical, Bodily Pain, and General Health were the most impacted (i.e. lowest scores) compared to ageand gender-matched norms at baseline. At Week 24, the domains showing the largest improvement (at least 15 points in both treatment groups) after ixekizumab treatment were Physical Functioning, Role Physical, Bodily Pain, and Social Functioning. Statistically significant improvement was also seen in the other SF-36 domains, which include those more mental/emotionally-related; this could be related to improvement of skin symptoms, as psoriasis improve-



Fig. 4. Work Productivity and Activity Index.

A: Absenteeism; B: Presenteeism (reduced productivity while at work); C: Activity impairment (outside of work); D: Work impairment (combines Absenteeism and Presenteeism). The original scores were calculated as percentages. Baseline was defined as the last non-missing assessment recorded on or before the date of first study drug injection at Week 0. Observed data at Week 24 for Week 16 inadequate responders were excluded. LSM change from baseline is reported and based on an MMRM model. * $p \le 0.001$ active vs. PBO; $^{\dagger}p \le 0.005$ active vs. PBO.

IXEQ2W: ixekizumab 80 mg every 2 weeks; IXEQ4W: ixekizumab 80 mg every 4 weeks; LSM: least squares mean; MMRM: mixed models repeated measures analysis; N: population size; PBO: placebo.

ment has been shown in other studies to have a greater impact on the mentalrelated scores (35). Complementary results were also seen with the EQ-5D VAS.

Improvement related to skin symptoms was demonstrated by patient-reported benefit as measured by the Itch NRS and DLQI. Almost one-quarter of the ixekizumab-treated patients (placebo = 0%) reported complete resolution of itch symptoms at Week 24. Improvement in overall skin symptoms translated to HRQOL benefit with approximately 50% of patients treated with ixekizumab reporting a DLQI of 0 or 1 at Week 24, compared with 9% in the placebo group. In patients with PsA, optimal improvements in HRQOL are dependent on successful treatment of both joint and skin symptoms (36).

In *post-hoc* analyses, the subgroup of patients with neck, back, or hip pain at baseline (score of ≥ 4 on question 2 of the BASDAI), reported significant improvements relative to placebo in neck, back, or hip pain at Week 24, suggesting that ixekizumab may also work on axial symptoms of PsA. However, this is a non-specific assessment, so a defi-

nite conclusion can only come from ongoing axial spondyloarthritis trials comparing ixekizumab to placebo.

As spondyloarthropathies including PsA commonly affect individuals during their prime working years, work disability is an important functional outcome (37). Data from the Multinational Assessment of Psoriasis and Psoriatic Arthritis survey (conducted between June and August 2012) of 712 patients with PsA identified that 32% of patients reported missing work during the past year from their disease, another 32% reported that PsA impacted their ability to work full-time, and approximately 25% reported that PsA impacted their ability to get a job, keep a job, or their career choice (38). In the SPIRIT-P2 study, patients reported considerable work and activity impairment at baseline. At Week 24, ixekizumab-treated patients reported statistically significant improvement in work activities (presenteeism and work impairment), as well as activities outside of work (activity impairment), relative to that reported by placebo-treated patients. Absenteeism did not improve in patients treated with ixekizumab versus those treated with placebo, possibly due to the low baseline scores and low number of patients with non-zero absenteeism. Improvement in work productivity is important because in addition to direct medical costs, the financial (and psychosocial) burden of PsA is shared by patients' employers, patients' families, and society in terms of costs related to impaired ability to perform both paid work and unpaid work (such as participating in household chores).

In this study, the clinically meaningful improvement in PROs seen during ixekizumab treatment at Week 24, including global disease activity, pain, itch, axial symptoms, generic and skin-specific measures of HRQOL, and work productivity were also sustained or improved further at Week 52.

Improvements in PROs seen with ixekizumab treatment in the SPIRIT-P2 trial are similar, and in some cases higher, than those reported in the biologic-naïve population from SPIRIT-P1 (15). In other studies that have made the comparison between biologic-naïve

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and TNF-experienced using a biologic agent, some have shown a similar treatment effect on PROs between patient populations naïve to *versus* experienced with TNFi (39), whereas others have shown that patients with prior inadequate response to TNFi had relatively smaller improvements in PROs relative to patients naïve to TNFi therapies (40, 41).

Limitations of this study include that it was not powered to detect differences between the IXEQ4W and IXEQ2W groups, although the doses seem to provide comparable efficacy. Additionally, there was no placebo comparator after Week 24. The trial results cannot be generalised beyond the patient population studied in the trial.

In conclusion, treatment with ixekizumab up to 52 weeks improved patientreported measures of disease activity, generic and skin-specific HRQOL, and work impact of PsA on productivity in patients with active PsA and a prior history of TNFi therapy. These improvements in PROs were comparable to those seen in biologic-naïve patients from the SPIRIT-P1 trial (15).

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