Efficacy and Safety of Ixekizumab in Patients with Active Psoriatic Arthritis: 52-week Results from a Phase III Study (SPIRIT-P1)

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ABSTRACT. ***Objective.*** To evaluate the efficacy and safety of ixekizumab (IXE), an interleukin 17A antagonist, in patients with psoriatic arthritis (PsA) after 52 weeks in a phase III study.

Methods. Patients were initially randomly assigned to IXE 80 mg every 2 weeks (IXEQ2W) or every 4 weeks (IXEQ4W) after a 160-mg starting dose, placebo (PBO), or adalimumab (ADA) 40 mg Q2W. At Week 24 (Week 16 for inadequate responders), ADA (8-week washout before starting IXE) and PBO patients were rerandomized to IXEQ2W or IXEQ4W. Six treatment groups were evaluated in the extension period (weeks 24-52): IXEQ2W/IXEQ2W, IXEQ4W/IXEQ4W, ADA/IXEQ2W, ADA/IXEQ4W, PBO/IXEQ2W, and PBO/IXEQ4W. The extension period population (EPP) included patients who received ≥ 1 dose of study medication during the extension period.

Results. There were 381/417 (91.4%) patients who entered the extension period. In the IXEQ4W/IXEQ4W and IXEQ2W/IXEQ2W groups (EPP), respectively, American College of Rheumatology (ACR)20 (69.1% and 68.8%), ACR50 (54.6% and 53.1%), and ACR70 (39.2% and 39.6%) response rates were sustained at Week 52. Patients rerandomized to IXE also demonstrated efficacy measured by ACR response rates at Week 52. A similar pattern was observed for Psoriasis Area and Severity Index outcomes. Radiographic progression in all 6 groups was minimal. The most frequently reported treatment-emergent adverse events (≥ 4%) were nasopharyngitis, injection site reaction, injection site erythema, upper respiratory tract infection, and back pain. No deaths were reported, and serious adverse event frequency was 0–4% with IXE.

Conclusion. During the extension period, IXEQ4W or IXEQ2W treatment demonstrated sustained efficacy in key PsA domains with a safety profile consistent with other studies investigating IXE. Clinical trial number: NCT01695239; EudraCT 2011-002326-49. (J Rheumatol First Release December 15 2017; doi:10.3899/jrheum.170429)

Key Indexing Terms:
BIOLOGIC DMARD PSORIATIC ARTHRITIS SPONDYLOARTHRITIS TREATMENT

Psoriatic arthritis (PsA) is an inflammatory musculoskeletal disease that occurs in about 30% of patients with psoriasis[1]. It is a complex disease that presents with peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail manifestations. Multiple studies have shown that the proinflammatory cytokine interleukin 17A (IL-17A) is implicated in the pathophysiology of PsA[2,3,4,5,6,7]. Targeted IL-17A inhibition is a current approach for management of PsA[8].

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Ixekizumab (IXE) is a high-affinity monoclonal antibody that selectively targets IL-17A[9] and is an approved treatment for moderate to severe psoriasis. In a 24-week placebo-controlled phase III study (SPIRIT-P1), biologic disease-modifying antirheumatic drugs (bDMARD)–naive patients with active PsA showed improvements in manifestations of PsA after IXE treatment[10]. These patients demonstrated significant improvements in signs and symptoms, quality of life, physical function, and inhibition of radiographic progression[10]. IXE also showed a safety profile that was consistent with that observed in patients with psoriasis[10,11].

We evaluated the efficacy and safety of IXE over 52 weeks in patients with active PsA who were naive to bDMARD.

MATERIALS AND METHODS

Study design. SPIRIT-P1 (NCT01695239, EudraCT 2011-002326-49) is a phase III, multicenter, double-blind, randomized study in bDMARD-naive patients with active PsA. Detailed methodology of the initial double-blind treatment period has been published[10]. Patients were randomized (1:1:1:1) to receive subcutaneous injections of placebo (PBO), adalimumab 40 mg every 2 weeks (ADA; active reference), and IXE 80 mg every 2 weeks (IXEQ2W) or 80 mg every 4 weeks (IXEQ4W; Supplementary Figure 1A, available with the online version of this article). Both IXE dose regimens included an initial 160-mg starting dose. At Week 16, inadequate responders (IR; defined by blinded, predefined criteria for changes in tender joint count and swollen joint count compared to baseline) were required to add or modify concomitant medications. IR remained on their originally assigned IXE dose or, if receiving PBO or ADA, were rerandomized 1:1 to IXEQ2W or IXEQ4W.

At the start of the extension period (weeks 24–52), any patients continuing ADA or PBO were rerandomized to either IXEQ4W or IXEQ2W at Week 24. Dosing regimens remained blinded to patients and site personnel during the extension period. Patients initially assigned to PBO received a 160-mg starting IXE dose at Week 24 (Week 16 if they were IR during the double-blind period). Patients initially assigned to ADA entered an 8-week PBO washout before receiving their first IXE dose at Week 32 (160 mg IXE at Week 24 if they were IR during the double-blind period). Patients starting IXE at Week 32 did not receive a 160-mg starting dose. Starting at Week 32, and at all subsequent visits during the extension period, all patients were evaluated for lack of efficacy using predefined mandatory discontinuation criteria (i.e., patients were discontinued if they failed to demonstrate ≥ 20% improvement from baseline in both tender and swollen joint counts).

Our study was conducted in accordance with Good Clinical Practice, the principles of the Declaration of Helsinki, and local laws and regulations, and was approved by the Western Institutional Review Board (approval #1-838258-1). Approval was also obtained from each additional site. All patients gave written informed consent.

Patients. Detailed patient eligibility criteria have been reported previously[10]. Enrolled patients were ≥ 18 years with a documented PsA diagnosis for ≥ 6 months, fulfilled Classification Criteria for Psoriatic Arthritis[12], had ≥ 3 tender and ≥ 3 swollen joints, had either ≥ 1 PsA-related hand or foot joint erosion on centrally read radiographs or C-reactive protein (CRP) > 6 mg/l, and had evidence of plaque psoriasis (current or personal history). Principal exclusion criterion was any history of biologic treatment for psoriasis or PsA.

Assessments. Efficacy endpoints included the percentage of patients achieving improvement from baseline on the American College of Rheumatology index of 20% (ACR20), 50% (ACR50), and 70% (ACR70)[13], and the percentage achieving improvements from baseline on the Psoriasis Areas and Severity Index of 75% (PASI 75), 90% (PASI 90), and 100% (PASI 100)[14]. PASI responses were evaluated in patients with a baseline body surface area (BSA)[15] ≥ 3%. Additional predefined secondary efficacy endpoints analyzed up to Week 52 were the Health Assessment Questionnaire–Disability Index[16,17] [HAQ-DI; mean change from baseline (MCB) and percentage improving by the minimally clinically important difference (MCID; ≥ 0.35[18])], 28-joint Disease Activity Score–CRP (DAS28-CRP[19]; MCB), Psoriatic Arthritis Response Criteria (PsARC[20]; percentage meeting criteria), Leeds Enthesitis Index in patients with enthesitis (LEI[21]; MCB and percentage with complete resolution of enthesitis), Leeds Dactylitis Index–Basic in patients with dactylitis (LDI-B[22,23]; MCB and percentage with complete resolution of dactylitis), van der Heijde modified total Sharp score (mTSS) for PsA[24] [MCB and percentage (posthoc) with change from baseline ≤ 0, ≤ 0.5, and ≤ the smallest detectable change (SDC) at Week 52], and Nail Psoriasis Severity Index (NAPSI; fingernails only[25]; MCB and percentage with complete resolution of fingernail psoriasis).

Most efficacy variables were assessed at each visit during the extension period (weeks 28, 32, 36, 44, and 52). LEI, LDI-B, and NAPSI were assessed only at weeks 32, 44, and 52. Radiographic images of hands and feet taken at the screening visit (used as baseline image), Week 24, and Week 52 were assessed for the mTSS centrally by 2 expert readers independently who were blinded to treatment allocation, timepoint, and patient clinical data. Individual scores were summed to create a total erosion score and joint space narrowing score for the hands/wrists and feet. The total mTSS is the sum of the erosion and joint space narrowing scores. If there were discrepancies between the 2 readers, the images were submitted to a third reader for adjudication. Average scores of 2 readers were used for the analyses.

Safety was assessed by adverse events (AE), laboratory monitoring, physical examinations, electrocardiograms, and immunogenicity testing. AE of special interest included, but were not limited to, cerebro-cardiovascular events, injection site reactions, and infections (including serious *Candida* and tuberculosis infections).

Statistical analysis. All randomized patients comprised the intent-to-treat (ITT) population. All patients who entered the extension period and received ≥ 1 dose of study medication during that period comprised the extension period population (EPP). All patients who received ≥ 1 IXE dose at any time during the 52-week study period comprised the all-IXE exposure safety population (AIESP). Efficacy and safety data were summarized according to 6 treatment groups in the extension period (PBO/IXEQ2W, PBO/IXEQ4W, ADA/IXEQ2W, ADA/IXEQ4W, IXEQ4W/IXEQ4W, and IXEQ2W/IXEQ2W) and 2 total IXE treatment groups, where all arms receiving the same IXE dosing regimen were pooled (Total IXEQ4W and Total IXEQ2W).

There were no treatment group comparisons in the extension period. For all categorical efficacy measures, missing data were imputed using a nonresponder imputation (NRI). NRI was used for analyses of ACR or PASI maintenance rates (response rates at each visit from Week 28 to Week 52 among the patients who already had a response at Week 24), and persistence rates (response rates at each visit from Week 0 to 52 among the ITT population, or from Week 28 to 52 among the EPP population). For analyses of a persistent effect (defined as an improvement from baseline observed during the 52 weeks for both placebo-controlled and extension periods in the ITT population) and maintained effect [defined as the continued response over time (weeks 24–52) in the patients from the ITT population who met the respective ACR or PASI response criteria at Week 24], an NRI was used. For continuous efficacy measures, except for mTSS, a modified baseline observation carried forward approach was used for imputing missing data. Typically, baseline values are carried forward when patients discontinue for any reason. In this modification, baseline values were carried forward when patients discontinued because of an AE, whereas the last nonmissing postbaseline observation up to Week 52 (Week 16 for patients eligible for rescue therapy) was carried forward when patients discontinued for any other reason. Linear extrapolation was used to impute missing mTSS data. For patients in the IXE/IXE groups, missing data at Week 52 were extrapolated

from baseline and the last available postbaseline value prior to Week 52. For patients in the ADA/IXE or PBO/IXE groups, missing data at Week 52 were extrapolated from baseline and the last available postbaseline value at or prior to Week 24. All radiographic data collected after the planned visit date were excluded from the Week 52 prespecified mTSS analysis. For the posthoc mTSS analysis, radiographic data from patients who had radiographs collected ≥ 1 day after the scheduled visit were included, and an interpolation method was used to prorate the change from baseline at the scheduled visits, assuming the progression rate was linear over time. A cumulative probability plot was created to visualize observed patient-level data using mTSS change from baseline at Week 52. The percentages of patients without radiographic progression at Week 52 (i.e., mTSS change from baseline at Week 52 ≤ 0.0, ≤ 0.5, and ≤ 1.32 cutoff values) were also summarized. The 1.32 cutoff was the SDC from baseline to Week 52 for this study[26].

Safety analyses were conducted using the EPP, where Week 24 was the baseline for safety assessments during the extension period, and the first IXE injection was the baseline for the AIESP from weeks 0–52.

RESULTS

Patient disposition. Of 417 patients randomized, 381 (91.4%) completed the double-blind period. All 381 completers entered the extension period, including 36 IR (27 PBO, 9 ADA) who were rerandomized to IXE at Week 16 (Supplementary Figure 1B, available with the online version of this article). While the study mandated discontinuation for patients who failed to demonstrate a certain level of efficacy during the extension period (based on predefined criteria), the majority of patients (n = 304, 80% EPP; 73% ITT) completed the extension period. Across the 6 treatment groups, these completed the extension period: 85% in IXEQ4W/IXEQ4W, 85% in IXEQ2W/IXEQ2W, 71% in PBO/IXEQ4W, 72% in PBO/IXEQ2W, 82% in ADA/IXEQ4W, and 73% ADA/IXEQ2W. Reasons for discontinuation were similar across the 6 treatment groups except for "lack of efficacy," which occurred at a higher frequency in the PBO/IXE and ADA/IXE groups (Supplementary Figure 1B).

Baseline characteristics. For patients who entered the extension period, baseline (Week 0) demographics and clinical characteristics are shown according to treatment group in Table 1. The mean age was 49.3 years, with the majority of patients being white (93.7%) and female (53.5%). Most patients were receiving conventional disease-modifying antirheumatic drugs (63.0%) and 58.3% had enthesitis, 36.7% had dactylitis, 70.1% had BSA ≥ 3%, and 70.1% had fingernail psoriasis.

Efficacy in 6 treatment groups (by assigned double-blind/extension period treatments). In the IXEQ4W/IXEQ4W and IXEQ2W/IXEQ2W groups, ACR20, ACR50, and ACR70 response rates persisted from week 0 to 52 in the ITT population (Figures 1b, 1d, 1f) and from Week 24 to 52 in the EPP (Figures 1a, 1c, 1e). At Week 52, patients rerandomized to IXE (i.e., PBO/IXE and ADA/IXE) also demonstrated relatively high ACR response rates (Table 2; EPP). Among ITT patients who met ACR20, ACR50, or ACR70 at Week 24, the majority maintained their respective response rates out to Week 52 (IXEQ4W/IXEQ4W: 80.6%, 81.4%, and 80.0%, respectively; IXEQ2W/IXEQ2W: 81.5%, 77.1%, and 80.0%, respectively).

At Week 52, physical function improved as demonstrated by reduction [MCB (SD)] in HAQ-DI of –0.53 (0.56) in the IXEQ4W/IXEQ4W and –0.55 (0.52) in the IXEQ2W/IXEQ2W group (Table 2; EPP). At Week 52, 57.1% of patients in the IXEQ4W/IXEQ4W and 57.1% in the IXEQ2W/IXEQ2W group achieved the MCID (in EPP patients who had a baseline score ≥ 0.35) in HAQ-DI. At Week 52, disease activity improved as demonstrated by reduction in DAS28-CRP of –2.3 (1.3) in the IXEQ4W/IXEQ4W and –2.4 (1.3) in the IXEQ2W/IXEQ2W group (Table 2; EPP). At Week 52, the percentage who met PsARC (EPP) was 67.0% in the IXEQ4W/IXEQ4W and 64.6% in the IXEQ2W/IXEQ2W group. For EPP patients with baseline LDI-B > 0 in the IXEQ4W/IXEQ4W and IXEQ2W/IXEQ2W groups, 85.7% and 87.5%, respectively, achieved resolution of dactylitis at Week 52. For EPP patients with baseline LEI > 0 in the IXEQ4W/IXEQ4W and IXEQ2W/IXEQ2W groups, 55.4% and 50.0%, respectively, achieved resolution of enthesitis at Week 52. Patients rerandomized to IXE (i.e., PBO/IXE and ADA/IXE) also demonstrated improvements on various additional efficacy measures at Week 52 (Table 2; EPP).

Over a 52-week period, minimal changes in mTSS were observed in all 6 groups of patients with PsA entering the extension period (Table 2; prespecified linear extrapolation, EPP). The mTSS change from baseline to Week 52 was numerically larger in the IXEQ4W/IXEQ4W [mean (SD), 0.54 (2.12)] than the IXEQ2W/IXEQ2W group [0.09 (0.95)]. The mean radiographic progression in the IXEQ4W/IXEQ4W group was driven, in part, by 1 patient whose mean mTSS change was 16 (Figure 2). A posthoc analysis of mTSS change from baseline to Week 52, which incorporated radiographic data collected after the planned visit, was comparable with the prespecified analysis, showing minimal radiographic progression over this period (Table 2). Cumulative probability plots of observed patient-level data of mTSS change from baseline at Week 52 are shown in Figure 2.

The percentages of patients without radiographic progression at Week 52, defined as a change from baseline ≤ 1.32 (SDC at Week 52), ≤ 0.5, and ≤ 0, were comparable between the IXEQ4W/IXEQ4W and IXEQ2W/IXEQ2W groups (Table 2; EPP). For patients rerandomized to IXE (i.e., PBO/IXE and ADA/IXE), the percentage without radiographic progression at Week 52 is also shown in Table 2.

For patients with baseline BSA ≥ 3% in the IXEQ4W/IXEQ4W and IXEQ2W/IXEQ2W groups, PASI 75, PASI 90, and PASI 100 response rates persisted from weeks 0 to 52 in the ITT population (Figures 3b, 3d, 3f) and from Week 24 to Week 52 in the EPP (Figures 3a, 3c, 3e). Among ITT patients who met PASI 75, PASI 90, or PASI 100 at Week 24, the majority maintained this response rate at Week 52 (IXEQ4W/IXEQ4W: 90.4%, 87.8%, and 80.6%,

Table 1. Baseline demographics and clinical characteristics (EPP at Week 0, prior to first study drug administration). Values are mean (SD), unless otherwise specified.

Characteristics	PBO/IXEQ4W, n = 45	ADA/IXEQ4W, n = 49	IXEQ4W/ IXEQ4W, n = 97	PBO/IXEQ2W, n = 46	ADA/ IXEQ2W, n = 48	IXEQ2W/ IXEQ2W, n = 96	Total IXEQ4W, n = 191	Total IXEQ2W, n = 190
Age, yrs	50.5 (13.2)	50.0 (12.6)	48.7 (10.2)	51.0 (11.3)	46.2 (12.1)	49.6 (12.8)	49.5 (11.6)	49.1 (12.3)
Male, n (%)	19 (42)	21 (43)	40 (41)	23 (50)	30 (63)	44 (46)	80 (42)	97 (51)
Weight, kg	85.3 (23.9)	89.0 (19.7)	86.1 (22.4)	84.5 (17.3)	90.1 (18.5)	81.3 (17.3)	86.6 (22.1)	84.1 (17.8)
BMI	30.3 (7.3)	30.5 (5.9)	30.5 (8.2)	29.0 (5.7)	30.6 (5.2)	28.4 (6.4)	30.5 (7.4)	29.0 (6.0)
Race, n (%)								
White	41 (91)	47 (96)	93 (96)	43 (93)	44 (92)	89 (93)	181 (95)	176 (93)
Asian	3 (7)	2 (4)	1 (1)	2 (4)	1 (2)	5 (5)	6 (3)	8 (4)
American Indian or Alaska Native	1 (2)	0	2 (2)	1 (2)	3 (6)	2 (2)	3 (2)	6 (3)
Other	0	0	1 (1)	0	0	0	1 (<1)	0
Time since PsA diagnosis, yrs	7.9 (7.6)	7.5 (7.8)	6.2 (6.5)	5.5 (6.5)	5.9 (5.6)	7.3 (8.3)	7.0 (7.1)	6.5 (7.3)
Time since psoriasis diagnosis, yrs	17.9 (15.7)	18.8 (14.5)	16.7 (13.6)	14.4 (12.2)	13.6 (10.1)	17.2 (14.1)	17.5 (14.3)	15.6 (12.8)
cDMARD experience, n (%)								
Naive	4 (9)	8 (16)	15 (15)	8 (17)	5 (10)	16 (17)	27 (14)	29 (15)
Past use	15 (33)	10 (20)	21 (22)	8 (17)	9 (19)	22 (23)	46 (24)	39 (21)
Current use	26 (58)	31 (63)	61 (63)	30 (65)	34 (71)	58 (60)	118 (62)	122 (64)
Patients with specific disease characteristics, n (%)								
Current psoriasis	45 (100)	46 (94)	91 (94)	44 (96)	47 (98)	88 (92)	182 (95)	179 (94)
Psoriasis BSA ≥ 3, n/Nx (%)	31/43 (72)	34/45 (76)	66/91 (73)	29/44 (66)	33/46 (72)	55/85 (65)	131/179 (73)	117/175 (67)
Current fingernail psoriasis[a]	31 (69)	33 (67)	64 (66)	35 (76)	35 (73)	69 (72)	128 (67)	139 (73)
Current dactylitis[a], n (%)	16 (36)	11 (22)	48 (49)	19 (41)	11 (23)	35 (36)	75 (39)	65 (34)
Current enthesitis[a]	22 (49)	28 (57)	67 (69)	26 (57)	25 (52)	54 (56)	117 (61)	105 (55)
Disease and QoL characteristics								
Tender joint count, 68 joints	18.5 (11.6)	18.8 (11.9)	20.8 (13.6)	19.2 (14.0)	18.8 (12.8)	21.3 (13.8)	19.7 (12.7)	20.2 (13.6)
Swollen joint count, 66 joints	9.6 (6.2)	10.1 (7.4)	11.0 (7.3)	10.7 (7.1)	9.6 (5.5)	12.2 (7.3)	10.4 (7.1)	11.2 (6.9)
Patient-reported pain VAS 0–100	53.8 (22.3)	58.0 (21.0)	59.4 (19.8)	60.7 (23.3)	58.6 (19.8)	58.1 (21.5)	57.7 (20.7)	58.8 (21.5)
PGA, mm	52.3 (17.9)	51.6 (20.4)	57.4 (19.4)	58.4 (20.1)	58.6 (16.5)	57.4 (19.1)	54.7 (19.4)	58.0 (18.6)
PtGA, mm	59.6 (22.5)	55.6 (20.8)	62.3 (19.1)	62.2 (23.2)	62.1 (17.9)	62.3 (20.1)	59.9 (20.5)	62.3 (20.3)
CRP, mg/l	15.4 (29.5)	12.5 (12.7)	13.1 (17.0)	16.9 (20.4)	14.4 (24.7)	15.5 (26.7)	13.5 (19.7)	15.6 (24.7)
HAQ-DI	1.1 (0.6)	1.1 (0.6)	1.3 (0.6)	1.2 (0.6)	1.1 (0.6)	1.2 (0.5)	1.2 (0.6)	1.2 (0.6)
DAS28-CRP	4.8 (0.9)	4.9 (0.9)	5.0 (1.0)	4.9 (1.2)	4.8 (1.0)	5.0 (1.1)	4.9 (0.9)	4.9 (1.1)
LEI	2.6 (1.5)	3.0 (1.5)	2.7 (1.6)	3.2 (1.9)	2.9 (1.7)	3.0 (1.7)	2.7 (1.5)	3.0 (1.7)
LDI-B	47.7 (62.6)	99.6 (125.2)	61.5 (102.1)	46.2 (75.4)	96.7 (104.6)	46.0 (57.2)	64.6 (99.1)	54.6 (73.6)
mTSS	11.5 (15.5)	15.6 (24.3)	19.6 (33.3)	24.5 (37.3)	15.4 (30.2)	15.2 (29.1)	16.6 (27.8)	17.5 (31.6)
PASI total score	6.3 (8.6)	5.7 (5.9)	7.0 (6.5)	6.3 (7.0)	5.3 (7.1)	6.0 (7.0)	6.5 (6.9)	5.9 (7.0)
NAPSI	19.1 (17.6)	26.7 (20.9)	21.1 (19.0)	19.9 (13.9)	15.6 (11.7)	26.1 (21.2)	22.1 (19.3)	22.0 (18.0)

[a] Patients with active disease at baseline (Week 0). ADA: adalimumab; BMI: body mass index; BSA: body surface area; cDMARD: conventional disease-modifying antirheumatic drugs; CRP: C-reactive protein; DAS28-CRP: 28-joint Disease Activity Score using CRP; EPP: extension period population; HAQ-DI: Health Assessment Questionnaire–Disability Index; IXEQ2W: 80 mg ixekizumab once every 2 weeks; IXEQ4W: 80 mg ixekizumab once every 4 weeks; LDI-B: Leeds Dactylitis Index–Basic; LEI: Leeds Enthesitis Index; mTSS: van der Heijde modified total Sharp score; NAPSI: Nail Psoriasis Severity Index; Nx: number of patients with non-missing values; PASI: Psoriasis Area and Severity Index; PBO: placebo; PsA: psoriatic arthritis; QoL: quality of life; VAS: visual analog scale; PGA: physician's global assessment; PtGA: patient's global assessment.

respectively; IXEQ2W/IXEQ2W: 91.5%, 92.5%, and 90.3%, respectively). Patients rerandomized to IXE (i.e., PBO/IXE and ADA/IXE) also showed improvements as reflected by PASI response rates at Week 52 (Table 2; EPP).

For EPP patients with baseline fingernail psoriasis (NAPSI > 0), NAPSI improvements [MCB (SD)] were –16.5 (18.5) in the IXEQ4W/IXEQ4W and –21.6 (20.6) in the IXEQ2W/IXEQ2W group at Week 52 (Table 2). Among

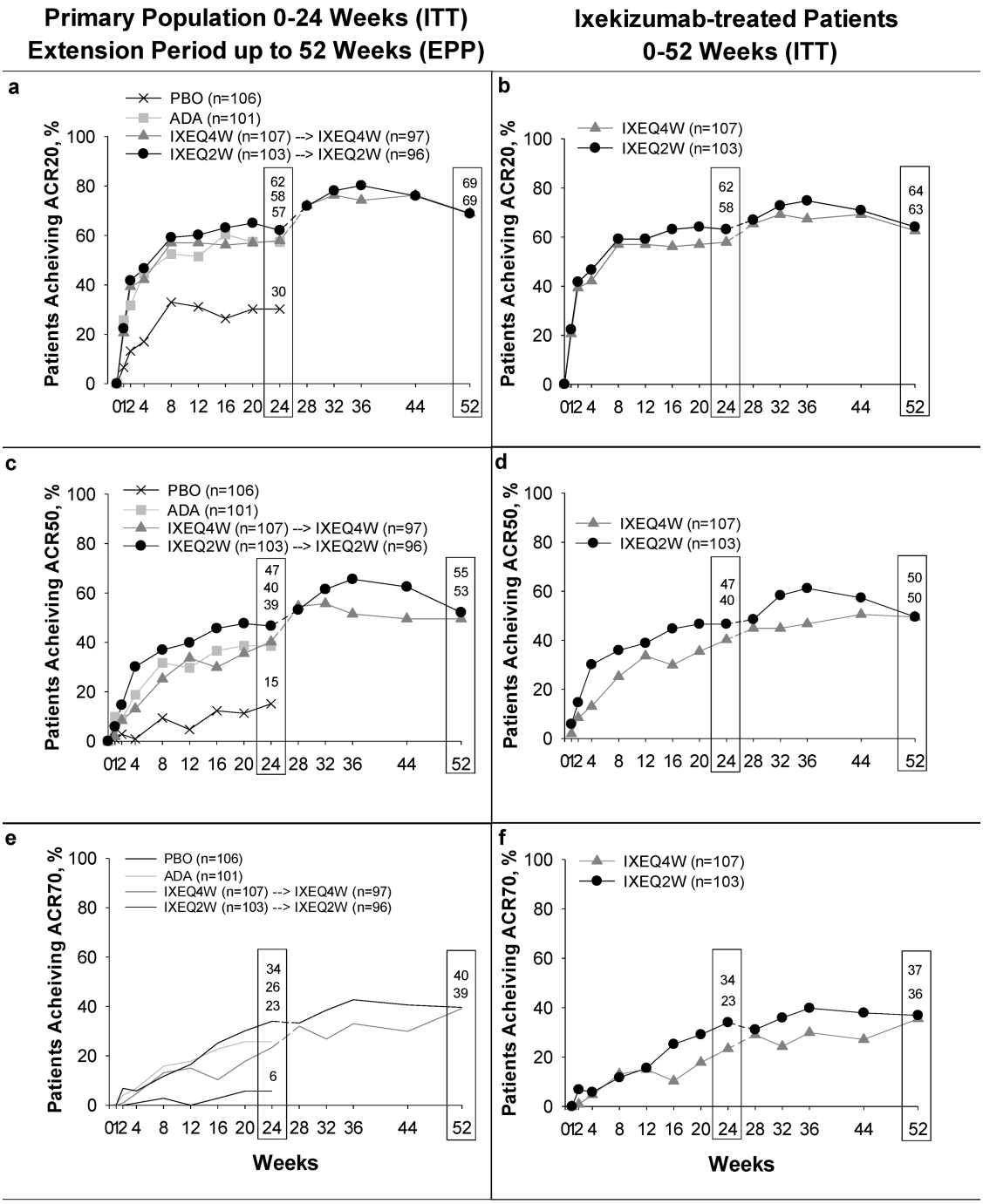

Figure 1. The percentage of patients in the ITT population who achieved (a) ACR 20, (c) ACR 50, and (e) ACR 70 during the 24-week double-blind period (weeks 0–24) and in the EPP during the extension period (weeks 28–52). The percentage of patients assigned to ixekizumab from the ITT population from Week 0 up to Week 52 who achieved (b) ACR20, (d) ACR50, and (f) ACR70. Missing data imputed by NRI. ACR: American College of Rheumatology; ADA: adalimumab; EPP: extension period population; ITT: intent to treat; IXEQ4W: ixekizumab every 4 weeks; IXEQ2W: ixekizumab every 2 weeks; NRI: nonresponder imputation; PBO: placebo.

these patients, 46.9% and 40.6% in the IXEQ4W/IXEQ4W and IXEQ2W/IXEQ2W groups, respectively, achieved complete resolution of fingernail psoriasis. At Week 52, patients with baseline fingernail psoriasis who were rerandomized to IXE (i.e., PBO/IXE and ADA/IXE) also showed mean NAPSI improvements, and > 32% achieved complete resolution of fingernail psoriasis.

Efficacy in 2 total IXE groups (by assigned extension period treatment). The percentage of patients who achieved ACR20, ACR50, and ACR70 at Week 52 in the Total IXEQ4W group

Table 2. Efficacy endpoints at Week 52 (EPP), including radiographic progression. Data are mean change from baseline (SD), unless otherwise specified.

Variables	PBO/IXEQ4W	ADA/IXEQ4W	IXEQ4W/ IXEQ4W	PBO/ IXEQ2W	ADA/ IXEQ2W	IXEQ2W/ IXEQ2W	Total IXEQ4W	Total IXEQ2W
ACR20*, n/N (%)	26/45 (57.8)	34/49 (69.4)	67/97 (69.1)	33/46 (71.7)	28/48 (58.3)	66/96 (68.8)	127/191 (66.5)	127/190 (66.8)
ACR50*, n/N (%)	19/45 (42.2)	29/49 (59.2)	53/97 (54.6)	21/46 (45.7)	21/48 (43.8)	51/96 (53.1)	101/191 (52.9)	93/190 (48.9)
ACR70*, n/N (%)	9/45 (20.0)	17/49 (34.7)	38/97 (39.2)	14/46 (30.4)	14/48 (29.2)	38/96 (39.6)	64/191 (33.5)	66/190 (34.7)
HAQ-DI, mBOCF	–0.38 (0.53)	–0.47 (0.48)	–0.53 (0.56)	–0.42 (0.60)	–0.42 (0.47)	–0.55 (0.52)	–0.48 (0.53)	–0.48 (0.53)
≥ 0.35 HAQ-DI improvement*, n/N (%)	16/37 (43.2)	26/43 (60.5)	52/91 (57.1)	16/40 (40.0)	20/42 (47.6)	48/84 (57.1)	94/171 (55.0)	84/166 (50.6)
DAS28-CRP, mBOCF	–1.9 (1.2)	–2.2 (1.3)	–2.3 (1.3)	–2.1 (1.1)	–2.1 (0.9)	–2.4 (1.3)	–2.2 (1.3)	–2.2 (1.2)
PsARC*, n/N (%)	26/45 (57.8)	34/49 (69.4)	65/97 (67.0)	34/46 (73.9)	30/48 (62.5)	62/96 (64.6)	125/191 (65.4)	126/190 (66.3)
LEI, mBOCF	–1.1 (2.2)	–2.0 (1.9)	–1.9 (1.7)	–1.7 (2.0)	–1.1 (2.3)	–1.8 (1.6)	–1.8 (1.8)	–1.6 (1.9)
LEI = 0*, n/N (%)	9/22 (40.9)	14/28 (50.0)	36/65 (55.4)	11/26 (42.3)	6/23 (26.1)	26/52 (50.0)	59/115 (51.3)	43/101 (42.6)
LDI-B, mBOCF	–47.7 (62.6)	–96.5 (125.5)	–57.9 (103.9)	–21.3 (21.7)	–93.1 (102.5)	–43.4 (55.5)	–61.9 (100.2)	–45.3 (63.0)
LDI-B = 0*, n/N (%)	7/10 (70.0)	6/8 (75.0)	30/35 (85.7)	8/14 (57.1)	7/10 (70.0)	21/24 (87.5)	43/53 (81.1)	36/48 (75.0)
Prespecified mTSS, linear extrapolation[a,c]								
Mx	31	36	80	37	34	80	147	151
Mean (SD)	0.27 (0.84)	0.32 (1.02)	0.54 (2.12)	0.41 (0.81)	–0.03 (0.39)	0.09 (0.95)	0.43 (1.69)	0.14 (0.83)
Posthoc mTSS, linear extrapolation[b,c]								
Mx	44	47	97	45	45	96	188	186
Mean (SD)	0.25 (0.79)	0.24 (0.90)	0.47 (1.94)	0.51 (1.10)	0.06 (0.54)	0.09 (0.88)	0.36 (1.51)	0.18 (0.89)
Posthoc mTSS ≤ 0, observed, n/Nx (%)[b]	29/34 (85.3)	35/40 (87.5)	68/81 (84.0)	22/35 (62.9)	29/35 (82.9)	70/83 (84.3)	132/155 (85.2)	121/153 (79.1)
Posthoc mTSS ≤ 0.5, observed, n/Nx (%)[b]	32/34 (94.1)	35/40 (87.5)	72/81 (88.9)	23/35 (65.7)	32/35 (91.4)	75/83 (90.4)	139/191 (89.7)	130/153 (85.0)
Posthoc mTSS ≤ 1.32, SDC, observed, n/Nx (%)[b]	33/34 (97.1)	36/40 (90.0)	75/81 (92.6)	30/35 (85.7)	34/35 (97.1)	77/83 (92.8)	144/155 (92.9)	141/153 (92.2)
PASI 75*, n/N (%)	19/31 (61.3)	22/34 (64.7)	52/66 (78.8)	19/29 (65.5)	22/33 (66.7)	45/55 (81.8)	93/131 (71.0)	86/117 (73.5)
PASI 90*, n/N (%)	16/31 (51.6)	17/34 (50.0)	44/66 (66.7)	18/29 (62.1)	17/33 (51.5)	43/55 (78.2)	77/131 (58.8)	78/117 (66.7)
PASI 100*, n/N (%)	15/31 (48.4)	12/34 (35.3)	37/66 (56.1)	13/29 (44.8)	15/33 (45.5)	37/55 (67.3)	64/131 (48.9)	65/117 (55.6)
NAPSI, mBOCF	–10.5 (13.5)	–16.8 (19.0)	–16.5 (18.5)	–12.8 (13.9)	–10.4 (11.3)	–21.6 (20.6)	–15.1 (17.6)	–16.6 (17.8)
NAPSI = 0*, n/N (%)	10/31 (32.3)	13/33 (39.4)	30/64 (46.9)	12/35 (34.3)	16/35 (45.7)	28/69 (40.6)	53/128 (41.4)	56/139 (40.3)

* Nonresponder imputation. [a] mTSS values were excluded from the summary if radiographs were not taken at the scheduled visit. [b] All available mTSS values were interpolated. [c] Any missing data were imputed using linear extrapolation. ADA: adalimumab; ACR: American College of Rheumatology; DAS28-CRP: 28-joint Disease Activity Score using C-reactive protein; EPP: extension period population; HAQ-DI: Health Assessment Questionnaire–Disability Index; IXEQ2W: 80 mg ixekizumab once every 2 weeks; IXEQ4W: 80 mg ixekizumab once every 4 weeks; LDI-B: Leeds Dactylitis Index–Basic; LEI: Leeds Enthesitis Index; mBOCF: modified baseline observation carried forward; mTSS: van der Heijde modified total Sharp score; Mx: no. patients with nonmissing or imputed data; NAPSI: Nail Psoriasis Severity Index; Nx: no. patients with nonmissing data; PASI: Psoriasis Area and Severity Index; PBO: placebo; PsARC: Psoriatic Arthritis Response Criteria; SDC: smallest detectable change.

was similar to the Total IXEQ2W group (Table 2). In general, the outcomes on other PsA measurements were similar in the Total IXEQ4W and Total IXEQ2W groups at Week 52. In EPP patients with baseline dactylitis, 81.1% in the Total IXEQ4W and 75.0% in the Total IXEQ2W group achieved complete resolution of dactylitis, and in EPP patients with baseline enthesitis, 51.3% in the Total IXEQ4W and 42.6% in the Total IXEQ2W group achieved complete resolution of enthesitis at Week 52.

At Week 52, radiographic progression (MCB in posthoc mTSS) was minimal in the Total IXEQ2W (0.18) and Total IXEQ4W group (0.36; Table 2).

For patients who started with PBO and were rerandomized to IXE, the MCB in posthoc mTSS was 0.25 in the PBO/IXEQ4W and 0.51 in the PBO/IXEQ2W group.

Safety. A total of 386 patients were exposed to either IXEQ4W [134.7 patient-years (PY)] or IXEQ2W (133.0 PY). For the 381 patients who entered the extension period, mean duration of exposure and total PY of exposure for each of the 6 treatment groups are shown in Table 3.

Safety in the extension period for weeks 24 to 52 (EPP). During the extension period, treatment-emergent AE (TEAE) frequency ranged from 40.8% to 62.2% across the 6 treatment groups (Table 3). The majority of TEAE were mild or moderate in severity; < 5% were rated severe. The most frequently reported TEAE (defined as ≥ 4% in any treatment group) were nasopharyngitis, injection site reaction, upper respiratory tract infection, back pain, injection site erythema, and pharyngitis. There were no deaths. No cases of uveitis were reported. Four patients discontinued as a result of an AE [leukopenia in 1 PBO/IXEQ4W patient, hepatitis B (transient positive serum HBV DNA below the level of quantification) in 1 IXEQ4W/IXEQ4W patient, upper respiratory tract infection in 1 ADA/IXEQ2W patient, and

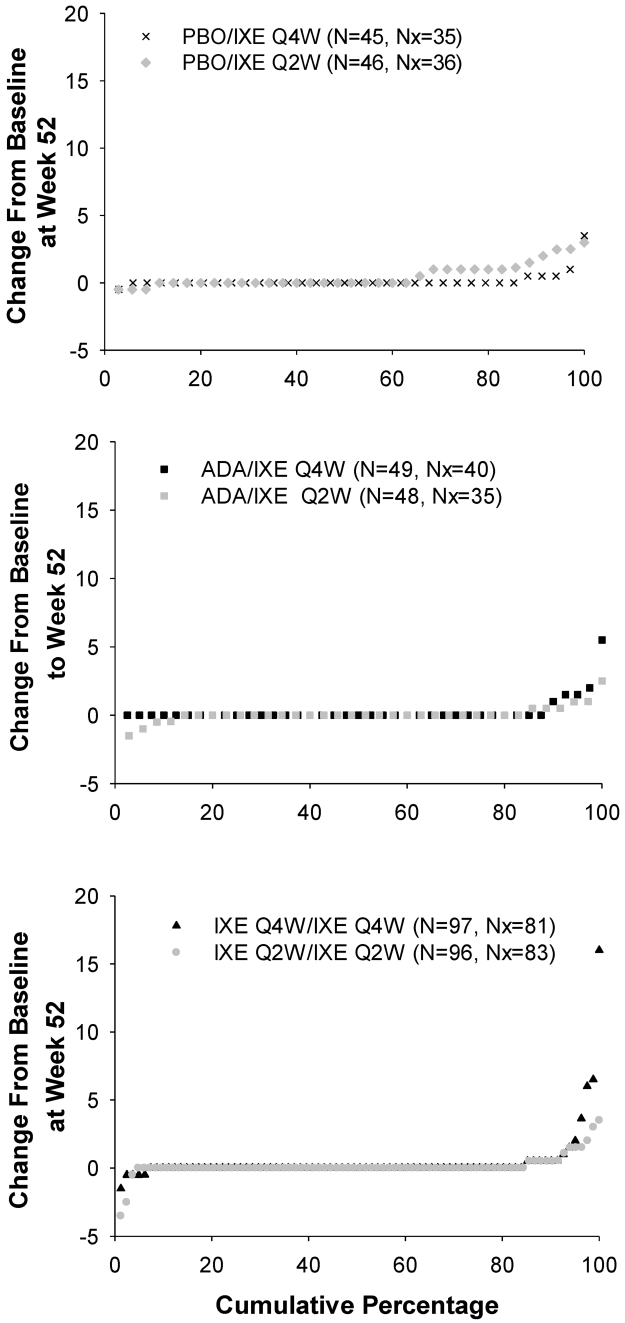

Figure 2. The mTSS individual-patient change from baseline to Week 52 cumulative probability plot (observed data). ADA: adalimumab; IXEQ4W: ixekizumab every 4 weeks; IXEQ2W: ixekizumab every 2 weeks; mTSS: Van der Heijde modified total Sharp score; N: total no. patients; Nx: no. patients with non-missing change from baseline data; PBO: placebo.

pregnancy in 1 PBO/IXEQ2W patient; the pregnancy was uncomplicated and resulted in the birth of a healthy infant]. The frequencies of serious adverse events (SAE) ranged from 0 in the IXEQ2W/IXEQ2W group to 10.2% (5 of 49 patients) in the smaller ADA/IXEQ4W group (Table 3). One SAE of infection (pneumonia) was reported during this period (IXEQ4W/IXEQ4W group).

There were no active tuberculosis and no invasive *Candida* or other invasive or endemic fungal infections reported during the extension period. Mucocutaneous candidiasis was reported in 7 patients: 5 with oral candidiasis and 1 each with skin or nail *Candida*. One patient in the PBO/IXEQ2W group had a TEAE of depression, rated as mild by the investigator, at Week 28 of the extension period. The patient discontinued owing to lack of efficacy and the depression later resolved. There were no reports of suicide or suicidal ideation. During the extension period, 3 patients experienced a confirmed cerebro-cardiovascular event (acute myocardial infarction, coronary artery occlusion, and anastomotic stenosis at the site of a peripheral arterial bypass in 1 patient each), all in the ADA/IXEQ4W group and all in patients with a medical history of cerebro-cardiovascular disease and/or events. All were SAE with an onset ranging from about 20 to 40 days after starting IXE; none led to study drug discontinuation. Hypersensitivity events were reported in 2.6% of patients in each of the Total IXEQ4W and Total IXEQ2W groups; all were nonanaphylactic, mild in severity, and nonserious (data not shown). Laboratory testing showed that among patients with normal baseline values, Grade 1 neutropenia occurred in 5.9% and 9.4%, and Grade 2 neutropenia occurred in 1.6% and 2.2% of patients in the Total IXEQ4W and Total IXEQ2W group, respectively. No patient had Grade 3 or 4 neutropenia postbaseline, regardless of baseline neutrophil concentration. No infections were reported within 14 days of the Grade 2 neutropenia.

A total of 36 patients developed treatment-emergent antidrug antibodies (TE-ADA) during the extension period (4 PBO/IXEQ4W, 3 PBO/IXEQ2W, 5 ADA/IXEQ4W, 4 ADA/IXEQ2W, 12 IXEQ4W/IXEQ4W, 8 IXEQ2W/IXEQ2W). None had confirmed neutralizing antibodies. Of the patients classified as TE-ADA–positive, 58.3% (7/12 patients) and 50.0% (4/8 patients) in the IXEQ4W/IXEQ4W and IXEQ2W/IXEQ2W groups, respectively, achieved ACR20 at Week 52. Of the patients classified as TE-ADA–negative, 76.6% (59/77 patients) and 72.1% (62/86 patients) in the IXEQ4W/IXEQ4W and IXEQ2W/IXEQ2W groups, respectively, achieved ACR20 at Week 52. The percentages of patients who had allergic reactions/hypersensitivity AE were similar between patients with and without antibodies to IXE. There was no apparent association between the development of antibodies to IXE and injection site reactions.

Double-blind and extension periods combined for weeks 0–52 (AIESP). In the AIESP over the entire 52-week treatment period, the TEAE frequencies were comparable between the Total IXEQ4W and Total IXEQ2W groups (Table 3). The distribution of TEAE severity was consistent with extension period findings. TEAE occurring in ≥ 4% of patients in either treatment group were the same as during

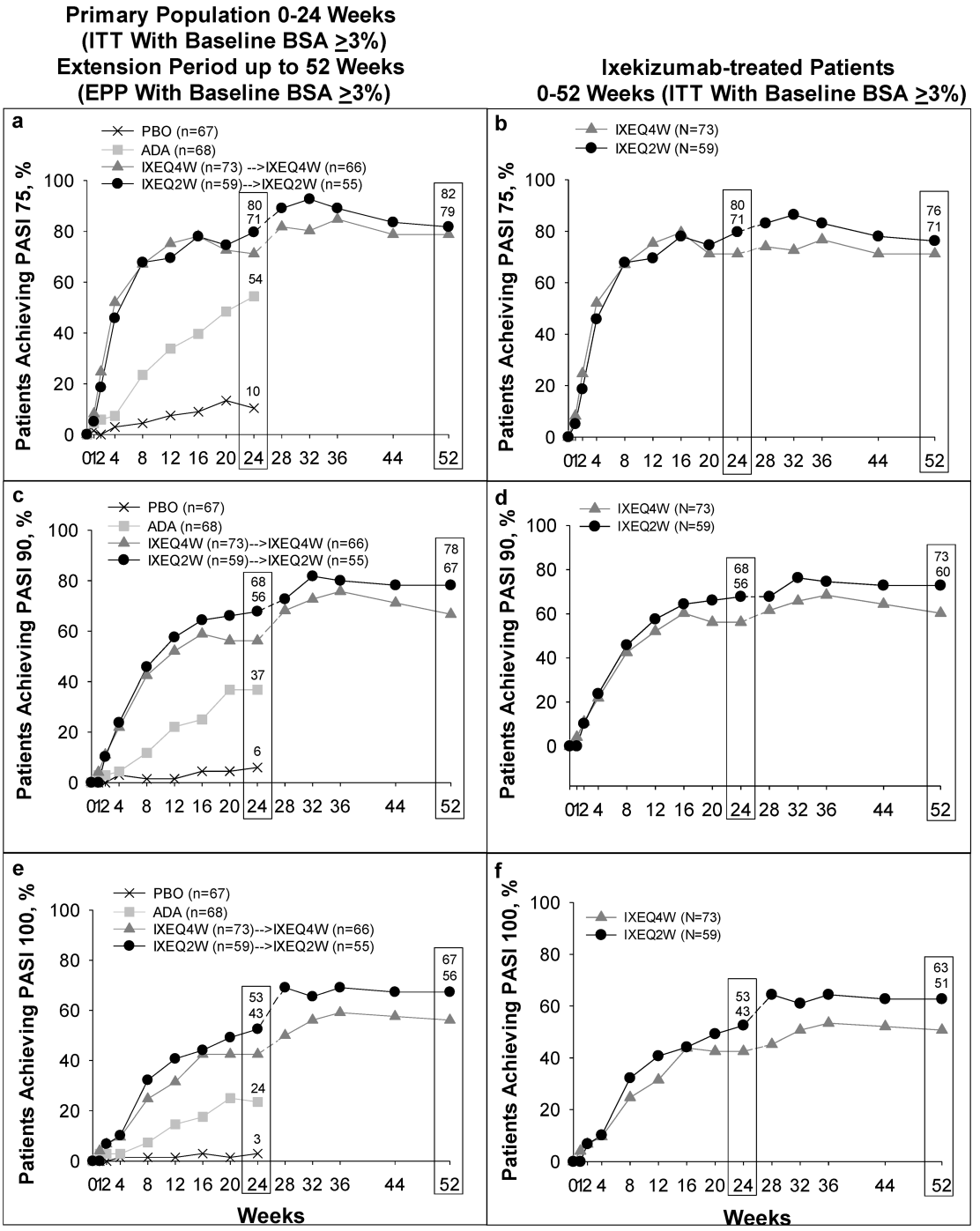

Figure 3. The percentage of patients with baseline BSA ≥ 3% in the ITT population who achieved (a) PASI 75, (c) PASI 90, and (e) PASI 100 during the 24-week double-blind period (weeks 0–24) and in the EPP during the extension period (weeks 28–52). The percentage of patients assigned to ixekizumab from the ITT population from Week 0 up to Week 52 who achieved (b) PASI 75, (d) PASI 90, and (f) PASI 100. Missing data imputed by NRI. ADA: adalimumab; BSA: body surface area; EPP: extension period population; ITT: intent to treat; IXEQ4W: ixekizumab every 4 weeks; IXEQ2W: ixekizumab every 2 weeks; NRI: nonresponder imputation; PASI: Psoriasis Area and Severity Index; PBO: placebo.

the extension period (Table 3). There were no deaths. Nine patients discontinued treatment as a result of an AE over the entire 52-week treatment period: 4 patients (2.0%) in the Total IXEQ4W group and 5 patients (2.6%) in the Total IXEQ2W group. Higher percentages of patients in the Total IXEQ4W (8.6%) and ADA/IXEQ4W (10.2%) groups during

Table 3. Adverse events reported during the extension period (EPP) by initial treatment assignment and exposure-adjusted incidence rates of AE reported between weeks 0 and 52 (all IXE exposure population). Values are n (%) unless otherwise specified.

Variables	EPP Dataset (Weeks 24–52)						AIESP Dataset (Weeks 0–52)	
	PBO/ IXEQ4W, n = 45	ADA/ IXEQ4W[a], n = 49	IXEQ4W/ IXEQ4W, n = 97	PBO/ IXEQ2W, n = 46	ADA/ IXEQ2W[a], n = 48	IXEQ2W/ IXEQ2W, n = 96	Total IXEQ4W, n = 197	Total IXEQ2W, n = 189
Exposure, PY	20.5	16.8	48.2	21.0	15.1	48.9	134.7	133.0
TEAE	28 (62.2)	20 (40.8)	54 (55.7)	27 (58.7)	21 (43.8)	54 (56.3)	130 (66.0)	131 (69.3)
TEAE severity								
Mild	12 (26.7)	13 (26.5)	30 (30.9)	16 (34.8)	15 (31.3)	31 (32.3)	64 (32.5)	73 (38.6)
Moderate	16 (35.6)	5 (10.2)	22 (22.7)	9 (19.6)	6 (12.5)	21 (21.9)	58 (29.4)	50 (26.5)
Severe	0	2 (4.1)	2 (2.1)	2 (4.3)	0	1 (1.0)	8 (4.1)	8 (4.2)
Most frequent TEAE (≥ 4% of patients per treatment group)								
Injection site reaction	2 (4.4)	3 (6.1)	6 (6.2)	2 (4.3)	3 (6.3)	7 (7.3)	21 (10.7)	25 (13.2)
Injection site erythema	2 (4.4)	1 (2.0)	0	2 (4.3)	2 (4.2)	1 (1.0)	21 (10.7)	18 (9.5)
Nasopharyngitis	4 (8.9)	2 (4.1)	7 (7.2)	2 (4.3)	1 (2.1)	10 (10.4)	18 (9.1)	16 (8.5)
Upper respiratory tract infection	1 (2.2)	4 (8.2)	5 (5.2)	1 (2.2)	0	4 (4.2)	14 (7.1)	10 (5.3)
Back pain	1 (2.2)	1 (2.0)	5 (5.2)	2 (4.3)	0	1 (1.0)	8 (4.1)	6 (3.2)
Headache	0	1 (2.0)	1 (1.0)	0	1 (2.1)	2 (2.1)	7 (3.6)	7 (3.7)
Psoriatic arthropathy	0	0	3 (3.1)	0	0	1 (1.0)	7 (3.6)	3 (1.6)
Urinary tract infection	1 (2.2)	1 (2.0)	2 (2.1)	0	1 (2.1)	2 (2.1)	7 (3.6)	3 (1.6)
Pharyngitis	0	0	1 (1.0)	0	2 (4.2)	4 (4.2)	2 (1.0)	6 (3.2)
SAE[b]	1 (2.2)[c]	5 (10.2)[d]	4 (4.1)[e]	1 (2.2)[f]	1 (2.1)[g]	0	17 (8.6)[c,d,e,h]	5 (2.6)[f,g,i]
Deaths	0	0	0	0	0	0	0	0
Discontinued due to AE	1 (2.2)	0	1 (1.0)	1 (2.2)	0	0	4 (2.0)	5 (2.6)
AE of special interest								
Infections[j]	14 (31.1)	8 (16.3)	31 (32.0)	9 (19.6)	12 (25.0)	32 (33.3)	68 (34.5)	67 (35.4)
Oral candidiasis	1 (2.2)	0	0	0	1 (2.1)	3 (3.1)	2 (1.0)	4 (2.1)
Esophageal candidiasis	0	0	0	0	0	0	0	1 (0.5)
Nail *Candida*	1 (2.2)	0	0	0	0	0	1 (0.5)	0
Skin *Candida*	0	0	1 (1.0)	0	0	0	1 (0.5)	0
Serious infections	0	0	1 (1.0)	0	0	0	4 (2.0)	2 (1.1)
Injection site reactions[k]	6 (13.3)	5 (10.2)	9 (9.3)	8 (17.4)	4 (8.3)	9 (9.4)	39 (19.8)	44 (23.3)
Hepatic event	1 (2.2)	0	1 (1.0)	2 (4.3)	1 (2.1)	4 (4.2)	8 (4.1)	12 (6.3)
Allergic reaction/ hypersensitivity	3 (6.7)	0	2 (2.1)	1 (2.2)	0	4 (4.2)	7 (3.6)	9 (4.8)
Neutropenia	4 (8.9)	1 (2.0)	12 (12.4)	11 (23.9)	2 (4.2)	12 (12.5)	3 (1.5)	2 (1.1)
Leukopenia	4 (8.9)	1 (2.0)	12 (12.4)	11 (23.9)	4 (8.3)	10 (10.4)	2 (1.0)	4 (2.1)
Thrombocytopenia	1 (2.2)	2 (4.1)	4 (4.1)	2 (4.3)	1 (2.1)	2 (2.1)	0	2 (1.1)
Adjudicated cerebro-cardiovascular events	0	3 (6.1)	0	0	0	0	3 (1.5)	0
Depression	0	0	0	1 (2.2)	0	0	2 (1.0)	3 (1.6)
ATTC	0	1 (2.0)	0	0	0	0	1 (0.5)	0
Inflammatory bowel disease[l]	0	0	0	0	0	0	0	0
Malignancy	0	0	1 (1.0)[m]	0	0	0	0	0

[a]The ADA 40 mg Q2W treatment arm served as active reference for comparison with placebo. The study was not powered to test equivalence or noninferiority of IXE versus ADA. [b]More than 1 event could be reported in the same patient. [c]Gastrointestinal inflammation. [d]Acute cholecystitis, acute myocardial infarction, anastomotic stenosis, coronary artery occlusion, and osteoarthritis. [e]Clavicle fracture, large intestine benign neoplasm, paternal exposure, and pneumonia. [f]Intervertebral disc protrusion. [g]Ligament injury. [h]Carotid artery occlusion and cholecystolithiasis (1 patient), fibula fracture, gastroenteritis, lumbar spinal stenosis, pancreatitis, posttraumatic headache, and uterine polyp. [i]Acquired phimosis; cervical myelopathy, esophageal candidiasis, and worsening gastroparesis (1 patient); and herpes zoster. [j]*Candida* infections were limited to mucocutaneous infections. [k]Includes all terms for reactions at the injection site, including injection site reaction, and the following conditions at the injection site: erythema, pain, papule, bruising, pruritus, rash, and mass. [l]Crohn disease and ulcerative colitis. [m]The event was not a malignancy, but rather a benign neoplasm that was more accurately recoded by the investigator as a gallbladder adenoma after Week 52; the event was not considered serious and did not lead to study drug discontinuation. ADA: adalimumab; AE: adverse event; AIESP: all ixekizumab exposure safety population, regardless of treatment period; ATTC: Antithrombotic Trialists' Collaboration; EPP: extension period population; IXEQ2W: 80 mg ixekizumab once every 2 weeks; IXEQ4W: 80 mg ixekizumab once every 4 weeks; PBO: placebo; PY: patient years; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

the extension period had an SAE than in the Total IXEQ2W group (2.6%).

DISCUSSION

In our report, treatment with IXE, an IL-17A antagonist, resulted in sustained improvements in joint and skin manifestations, physical function, and quality of life over 52 weeks in patients with active PsA who had previously been naive to bDMARD. Additionally, the ACR and PASI responses obtained at Week 24 were largely maintained at 52 weeks with IXE treatment. Notably, patients rerandomized from PBO or ADA to IXE treatment demonstrated improvements at Week 52 that were comparable to the efficacy achieved by the IXE/IXE groups at Week 52.

Over 52 weeks, radiographic progression of structural joint damage, as measured by mTSS, was minimal in all 6 groups. Additionally, the vast majority of patients had radiographic progression below the smallest detectable change in mTSS (SDC = 1.32). The data reported here suggest that for patients who remained on IXE from Week 0 through the extension period, inhibition of radiographic progression was sustained through Week 52.

The safety profile observed for IXE-treated patients during the extension period remained consistent with the safety profile observed during the double-blind placebo-controlled period except for injection-site reactions, which were reported in fewer patients during the extension period[10]. This finding was expected and is in alignment with longer-term IXE studies in patients with plaque psoriasis[27]. The AIESP safety analysis, including safety data from all 52 weeks of this study, demonstrated safety and tolerability consistent with the known safety profile of IXE.

The 52-week efficacy and safety findings of IXE from this trial of patients with active PsA are generally consistent with the mechanism of IL-17A antagonism[28,29].

Some study limitations should be considered. First, there was no placebo group during the extension period of this study. Also, this study evaluated a population of only bDMARD-naive patients. The efficacy of IXE in tumor necrosis factor–inadequate responders is currently being investigated.

During the extension period of our study of patients with active PsA, treatment with IXEQ4W or IXEQ2W demonstrated sustained efficacy in key clinical PsA domains over 52 weeks with a safety profile that was consistent with other studies investigating IXE. Overall, these findings support IL-17A antagonism with IXE in bDMARD-naive patients with PsA.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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Correction

Efficacy and Safety of Ixekizumab in Patients with Active Psoriatic Arthritis: 52-week Results from a Phase III Study (SPIRIT-P1)

Van der Heijde D, Gladman DD, Kishimoto M, Okada M, Rathmann SS, Moriarty SR, Shuler CL, Carlier H, Benichou O, Mease PJ. Efficacy and safety of ixekizumab in patients with active psoriatic arthritis: 52-week results from a phase III study (SPIRIT-P1). J Rheumatol 2018; doi:10.3899/jrheum.170429. Numbers originally reported on page 373 of this article, column 2, second full paragaph, were incorrect. They should read as follows: "A total of 38 patients developed treatment-emergent antidrug antibodies (TE-ADA) during the extension period (4 PBO/IXEQ4W, 3 PBO/IXEQ2W, 6 ADA/IXEQ4W, 5 ADA/IXEQ2W, 12 IXE/IXEQ4W, 8 IXE/IXEQ2W). Twenty had confirmed neutralizing antibodies."

The efficacy and safety conclusions reported in the article were not affected by these corrections and remain unchanged.

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