

## Clinically meaningful improvement in work productivity loss in active psoriatic arthritis: post-hoc analysis of SPIRIT-P1 and SPIRIT-P2 trials

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employees and shareholder of Eli Lilly  
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### ABSTRACT

**Objective.** To determine the proportion of patients in Phase 3 studies (SPIRIT-P1 and SPIRIT-P2) who achieved minimal clinically important difference (MCID) for work productivity loss and activity impairment domains of Work Productivity and Activity Impairment Specific Health Problem (WPAI-SHP) questionnaire.

**Methods.** In the SPIRIT-P1 study, comprising a 24-week double-blind treatment period, biologic-naïve patients with active psoriatic arthritis (PsA) were randomised to ixekizumab 80 mg every 4 weeks (IXEQ4W) or every 2 weeks (IXEQ2W) (starting dose of 160 mg), adalimumab 40 mg every 2 weeks (ADAQ2W), or placebo. SPIRIT-P2 enrolled tumour necrosis factor inhibitor (TNFi)-experienced patients who were randomised to receive IXEQ4W, IXEQ2W or placebo for 24 weeks of double-blind treatment. In this post-hoc analysis, we investigated the proportion of patients in SPIRIT-P1 and P2 studies who achieved 15% improvement in work productivity loss and 20% improvement in activity impairment domains of WPAI-SHP during double-blind treatment period.

**Results.** In SPIRIT-P1, at Week 24, 57.1% and 55.8% of biologic-naïve patients on IXEQ4W and ADAQ2W respectively, achieved MCID estimates for work productivity loss compared to 25.6% of patients treated with placebo. The proportion of ixekizumab- and adalimumab-treated patients achieving MCIDs for activity impairment were significantly higher (IXEQ4W:  $p < 0.001$ ; ADAQ2W:  $p = 0.001$ ) compared to placebo-treated patients at Week 24. In SPIRIT-P2, significantly more TNFi-experienced patients on IXEQ4W ( $p < 0.001$ ) achieved MCIDs compared to placebo at Week 24.

**Conclusion.** Treatment with ixekizumab was associated with clinically meaningful improvements in WPAI-SHP domains in biologic-naïve and TNFi-experienced patients with active PsA.

### Introduction

Psoriatic arthritis (PsA) is an inflammatory articular disease of joint, spine or entheses in patients with current or

history of psoriasis (1). Psoriatic arthritis can result in irreversible joint damage leading to substantial negative impact on physical function, quality of life and ability to work (2).

The population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis survey reported significant negative impact of PsA on work productivity and employment status (3). In this survey, nearly one-third of patients reported difficulty in working full time or missed work within the past 12 months (3). It is associated with high levels of unemployment up to 50% and work disability up to 39% and patients begin to experience work disability very early in the course of the disease prior to diagnosis (4, 5).

The Work Productivity and Activity Impairment Specific Health Problem (WPAI-SHP) questionnaire assesses the impact of disease on work productivity and activities outside of work (6). Ixekizumab is a high-affinity monoclonal antibody that selectively targets IL-17A. In two Phase 3 studies of ixekizumab, significant improvements were reported in three of four WPAI-SHP domains in patients treated with ixekizumab and adalimumab (SPIRIT-P1) and patients treated with ixekizumab (SPIRIT-P2) as compared to placebo. These improvements were maintained in ixekizumab-treated patients until Week 52 (7, 8).

Minimal clinically important difference (MCID) is the minimal difference that patients perceive as beneficial and is a standard approach to assess clinical importance across studies for changes in patient-reported outcomes (PROs) (9). Studies reporting improvements in WPAI-SHP did not assess clinical meaningfulness of these improvements, as MCID estimates were not yet available for patients with active PsA (7, 8). Tillett and colleagues estimated the MCIDs for work productivity loss and activity impairment domains as 15% and 20% improvement from baseline, respectively, among biologic-naïve and tumour necrosis factor inhibitor (TNFi)-experienced patients with PsA (10). This study assessed the proportion of patients in SPIRIT-P1 and SPIRIT-P2 studies achieving MCID for improvements in work productivity

**Table I.** Baseline employment status and WPAI-SHP domain scores in SPIRIT-P1 and SPIRIT-P2 studies (7, 8, 10).

Baseline characteristics	SPIRIT-P1 (Biologic-naïve)				SPIRIT-P2 (TNFi-experienced)		
	PBO (n=106)	ADAQ2W (n=101)	IXEQ4W (n=107)	IXEQ2W (n=103)	PBO (n=118)	IXEQ4W (n=122)	IXEQ2W (n=123)
Employment, n (%)							
Work for pay (full time)	48 (45.3)	47 (46.5)	62 (57.9)	54 (52.4)	53 (44.9)	52 (42.6)	57 (46.3)
Work for pay (part time)	13 (12.3)	15 (14.9)	11 (10.3)	8 (7.8)	12 (10.2)	12 (9.8)	13 (10.6)
Unable to work due to PsA	9 (8.5)	11 (10.9)	13 (12.1)	8 (7.8)	18 (15.3)	12 (9.8)	20 (16.3)
Unable to work due to non-PsA reasons	6 (5.7)	6 (5.9)	4 (3.7)	9 (8.7)	7 (5.9)	9 (7.4)	8 (6.5)
Other	30 (28.3)	22 (21.8)	17 (15.9)	24 (23.3)	28 (23.7)	37 (30.3)	25 (20.3)
Volunteer	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	-	-	-
House keeping	6 (5.7)	4 (4.0)	7 (6.5)	5 (4.9)	13 (11.0)	10 (8.2)	6 (4.9)
Retired	21 (19.8)	17 (16.8)	10 (9.3)	19 (18.4)	15 (12.7)	27 (22.1)	18 (14.6)
Student	2 (1.9)	1 (1.0)	0 (0.0)	0 (0.0)	-	-	-
Missing	-	-	-	-	0 (0.0)	0 (0.0)	1 (0.8)
WPAI-SHP domains, mean (SD)							
% Absenteeism	8.9 (24.5)	8.7 (21.4)	9.2 (21.0)	7.7 (23.0)	11.9 (28.1)	11.6 (26.6)	8.8 (23.2)
% Presenteeism	32.4 (21.2)	37.3 (24.5)	40.0 (26.7)	35.8 (21.6)	40.4 (28.8)	45.0 (25.7)	36.9 (25.0)
% Overall work productivity	34.6 (23.4)	40.6 (25.2)	42.3 (28.5)	37.4 (21.6)	41.5 (29.6)	46.9 (26.7)	38.8 (26.6)
% Activity impairment	46.1 (24.7)	46.9 (26.0)	47.9 (26.3)	47.1 (23.4)	54.0 (25.8)	53.9 (24.9)	49.3 (26.5)

ADAQ2W: adalimumab 40 mg every 2 weeks; IXEQ2W: ixekizumab 80 mg every 2 weeks; IXEQ4W: ixekizumab 80 mg once every 4 weeks; PBO: placebo; PsA: psoriatic arthritis; SD: standard deviation; TNFi: tumour necrosis factor inhibitor; WPAI-SHP: Work Productivity and Activity Impairment: Specific Health Problem questionnaire.

loss and activity impairment domains of WPAI-SHP questionnaire.

**Materials and methods**

*Study design and patients*

SPIRIT-P1 (NCT01695239) and SPIRIT-P2 (NCT02349295) were randomised, double-blind, Phase 3 studies of ixekizumab in biologic-naïve and TNFi-experienced patients with active PsA, respectively. Details regarding the 24-week double-blind treatment period have been reported previously (11, 12). Briefly, in SPIRIT-P1, patients were randomised to ixekizumab 80 mg every 4 weeks (IXEQ4W), ixekizumab 80 mg every 2 weeks (IXEQ2W), an active reference arm (adalimumab 40 mg every 2 weeks [ADAQ2W]) or placebo for 24 weeks. In SPIRIT-P2, patients were randomised to IXEQ4W, IXEQ2W or placebo for 24 weeks. Patients assigned to ixekizumab arms received 160-mg starting dose in both studies.

Common key inclusion criteria in the two studies were: patients aged ≥18 years with PsA for ≥6 months; need to meet Classification for Psoriatic Arthritis criteria (1); presence of active PsA defined as ≥3 of 68 tender joint count (TJC) and ≥3 of 66 swollen joint counts (SJC) and; presence of active psoriatic skin lesion or history of plaque psoriasis. In SPIRIT-P1, patients also had

to have ≥1 joint erosion as seen on hand/foot x-rays or C-reactive protein >6mg/L. In SPIRIT-P2, treatment with ≥1 conventional disease-modifying anti-rheumatic drugs (cDMARDs) and treatment with 1-2 TNFi were other key inclusion criteria. The study protocols were approved by respective institutional review board or ethics committee at each study site. All participants provided written informed consent. Both studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with local laws and regulations (11, 12).

*Assessment*

In both studies, WPAI-SHP questionnaire (version 2.0) was completed by patients at baseline, and during the double-blind treatment period (Weeks 0–24) (6, 10). The questionnaire consisted of six questions that assessed the following: i) employment status (working for full pay), ii) hours missed from work due to PsA, iii) hours missed from work due to other reasons, iv) actual hours worked, v) the impact of PsA on work productivity, and vi) the impact of PsA on activities outside of work. Patients who were not currently employed could skip questions 2 to 5 and proceed to question 6. Based on the responses, percentages of absenteeism, presentee-

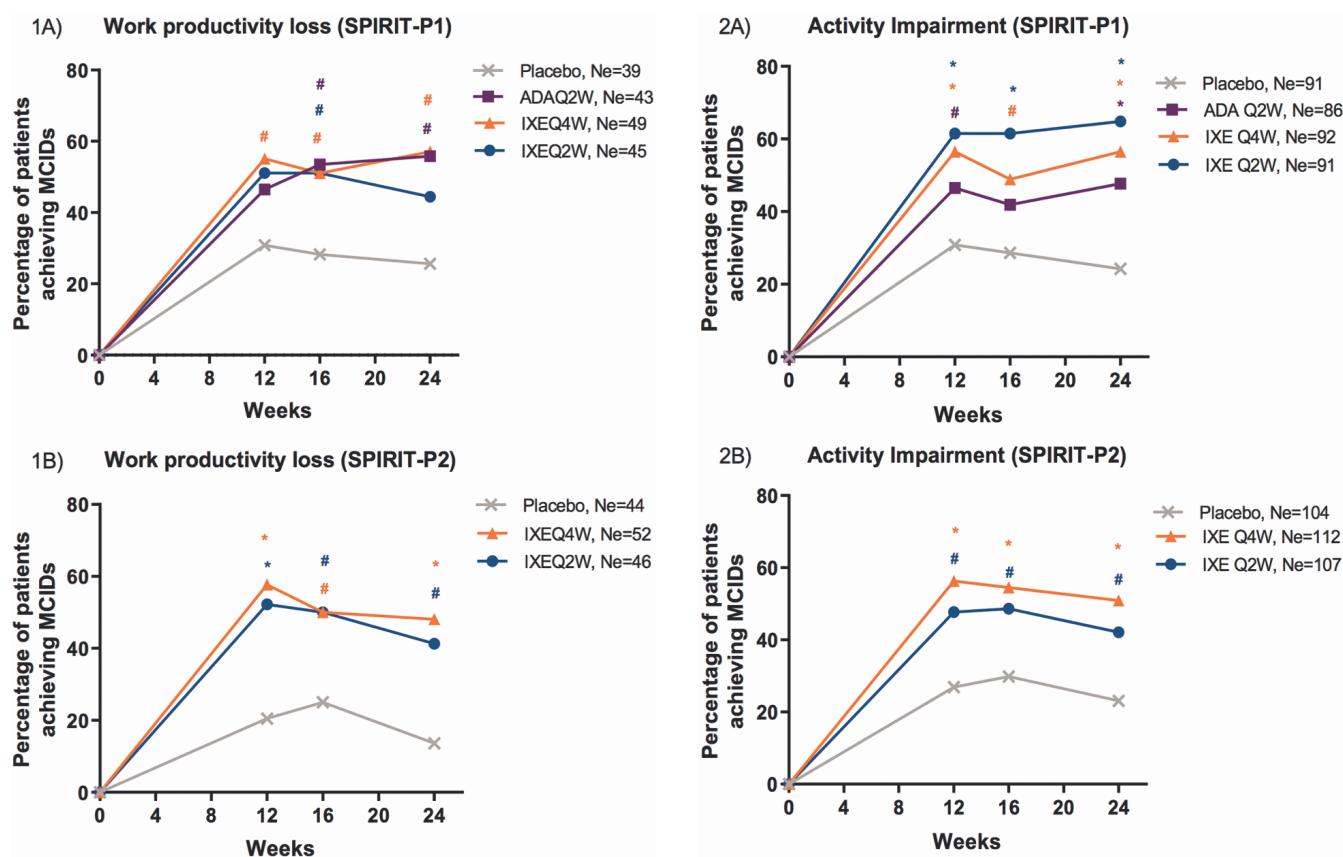
ism, work productivity loss (incorporates absenteeism and presenteeism), and activity impairment outside of work were calculated. With increases in scores, degree of impairment was greater (6, 10).

The proportions of biologic-naïve and TNFi-experienced patients achieving MCID estimates at each post-baseline visit were compared across the treatment groups. MCIDs were defined as 15% improvement in work productivity loss domain and a 20% improvement in activity impairment domain scores from baseline (10).

Based on baseline Composite Psoriatic Disease Activity Index (CPDAI) scores, patients were classified as non-severe and severe (peripheral arthritis domain score ≥3 and total score ≥8) subgroups (13, 14). Proportion of patients achieving MCIDs at Week 24 in these subgroups were also assessed using integrated analysis of SPIRIT-P1 and -P2 studies to adequately power the analysis.

*Statistical analysis*

Patients with baseline WPAI-SHP domain scores greater than the MCID estimates were included in the analyses. Proportion of intent-to-treat patients achieving the MCIDs at Weeks 12, 16 and 24 were assessed. Treatment comparisons between active treat-



**Fig. 1.** Proportion of patients achieving a meaningful improvement for work productivity loss (NRI) up to Week 24 in (A) Biologic-naive population (SPIRIT-P1) and (B) TNFi-experienced population (SPIRIT-P2). \* $p < 0.001$ , # $p < 0.05$  vs. placebo. ADAQ2W: adalimumab 40 mg every 2 weeks; IXEQ4W: ixekizumab 80 mg once every 4 weeks; IXEQ2W: ixekizumab 80 mg every 2 weeks; MCID: minimal clinically important difference; Ne: number of eligible patients; NRI: non-responder imputation; TNFi: tumour necrosis factor inhibitor.

**Fig. 2.** Proportion of patients achieving a meaningful improvement for activity impairment (NRI) up to Week 24 in (A) Biologic-naive population (SPIRIT-P1) and (B) TNFi-experienced population (SPIRIT-P2). \* $p < 0.001$ , # $p < 0.05$  vs. placebo. ADAQ2W: adalimumab 40 mg every 2 weeks; IXEQ2W: ixekizumab 80 mg every 2 weeks; IXEQ4W: ixekizumab 80 mg once every 4 weeks; MCID: minimal clinically important difference; Ne: number of eligible patients; NRI: non-responder imputation; TNFi: tumour necrosis factor inhibitor.

ment and placebo were done using a logistic regression model adjusting for randomisation factors. Randomisation factors included geographic region, and cDMARD experience at baseline/TNFi experience in SPIRIT-P1 and-P2 respectively. In these studies, patients who did not meet pre-specified improvement ( $\geq 20\%$ ) in TJC and SJC at Week 16 received rescue therapy and were classified as inadequate responders. Data from these patients at Week 24 were excluded. Missing values were imputed by non-responder imputation. Two-sided  $p$ -values  $< 0.05$  were considered statistically significant. Treatment comparisons within CPDAI subgroups were done using Fisher's test.

## Results

Demographics and baseline disease characteristics of patient population in SPIRIT-P1 ( $n=417$ ) and SPIRIT-P2

( $n=363$ ) have been reported previously; these were balanced between treatment groups (11, 12). In SPIRIT-P1 and SPIRIT-P2, 211 (50.6%) and 162 (44.6%) patients were employed full time, and 47 (11.3%) and 37 (10.2%) patients were employed part time, respectively (Table I) (10). The baseline scores for WPAI-SHP domains for both patient populations are presented in Table I (7, 8). Proportion of patients achieving MCIDs for work productivity loss and activity impairment were higher among those with severe disease compared to non-severe disease, defined by baseline CPDAI scores (Supplementary file).

### SPIRIT-P1: Biologic-naive patients

At Weeks 12, 16 and 24, significantly higher proportions of patients treated with IXEQ4W (Week 12: 55.1%,  $p=0.021$ ; Week 16: 51.0%,  $p=0.025$ ;

Week 24: 57.1%,  $p=0.003$ ) achieved the MCID for work productivity loss compared to placebo (Fig. 1A). At Weeks 16 and 24, the proportions of adalimumab-treated patients achieving MCID for work productivity loss were significantly higher (Week 16: 53.5%,  $p=0.020$ ; Week 24: 55.8%,  $p=0.008$ ) compared to placebo (Fig. 1A).

Proportions of patients treated with IXEQ4W who achieved MCIDs for activity impairment were significantly higher compared to placebo at Weeks 12 (56.5%,  $p < 0.001$ ), 16 (48.9%,  $p=0.006$ ) and 24 (56.5%,  $p < 0.001$ ) (Fig. 2A). A similar trend was also observed with IXEQ2W at these time points. The proportions of patients treated with ADAQ2W who achieved MCIDs for activity impairment were significantly higher compared to placebo at Weeks 12 (46.5%,  $p=0.030$ ) and 24 (47.7%,  $p=0.001$ ) (Fig. 2A).

**SPiRiT-P2:***TNF $\alpha$ -experienced patients*

At Weeks 12, 16 and 24, significantly higher proportions of patients treated with IXEQ4W (Week 12: 57.7%,  $p < 0.001$ ; Week 16: 50.0%,  $p = 0.010$ ; Week 24: 48.1%,  $p < 0.001$ ) achieved the MCID for work productivity loss compared to placebo (Fig. 1B). Similarly, significantly more patients achieved the MCIDs for activity impairment with IXEQ4W treatment (Week 12: 56.3%; Week 16: 54.5%; Week 24: 50.9%,  $p < 0.001$  for all) compared to placebo (Fig. 2B). A similar trend was observed in patients treated with IXEQ2W for both work productivity loss and activity impairment domains.

**Discussion**

Here we report that over half of biologic-naïve patients (56%) and nearly half of TNF $\alpha$ -experienced patients (48%) treated with ixekizumab achieved clinically meaningful improvements in work productivity loss and activity impairment domains at Week 24. Proportions of patients achieving MCID were significantly higher among those treated with IXEQ4W compared to placebo at Weeks 12, 16 and 24. These results indicate that irrespective of the type of prior drug exposure, patients with active disease would be able to attain clinically meaningful improvement in work disability. Changes in PRO measures from baseline, though statistically significant, may not be clinically meaningful. Use of responder definitions or MCIDs helps to interpret changes in PROs reported in clinical trials (15).

A major strength of this study is the use of MCIDs that were estimated using established methodologies namely, anchor-based method supplemented by the distribution-based method (10). The study assessed the MCID achievements in two different populations: biologic-naïve and TNF $\alpha$ -experienced patient populations. A limitation is that the analysis of MCID estimates for work productivity loss included only patients who were categorised under

employment status as “work for pay” (full time/part time).

In conclusion, results from Phase 3 studies suggest that treatment with ixekizumab is associated with clinically meaningful improvements in work productivity loss and activity impairment domains of WPAI-SHP among biologic-naïve and TNF $\alpha$ -experienced patient populations.

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**Data sharing statement**

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

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