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Ixekizumab treatment and the impact on SF-36: results from three pivotal phase III randomised controlled trials in patients with moderate-to-severe plaque psoriasis

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Abstract

Purpose To assess improvements in health-related quality of life (HRQoL) with ixekizumab treatment in patients with moderate-to-severe psoriasis.

Methods Adults with plaque psoriasis were enrolled in phase III, double-blind, randomised, controlled trials (UNCOVER-1, UNCOVER-2, or UNCOVER-3). All 3 protocols included a 12-week, placebo-controlled induction period; UNCOVER-2 and UNCOVER-3 also had an active-control group (50 mg etanercept) during induction. After induction, patients in UNCOVER-1 and UNCOVER-2 entered a 48-week withdrawal (maintenance) period (Weeks 12–60), during which Week-12 sPGA (0,1) responders were rerandomized to receive placebo, or 80 mg ixekizumab every 4 weeks (Q4W) or 12 weeks. As a secondary objective, HRQoL was measured by the generic Medical Outcomes Survey Short Form-36 (SF-36) at baseline and Weeks 12 and 60. Changes in mean SF-36 Physical and Mental Component Summary (PCS and MCS) and domain scores and proportions of patients reporting improvements ≥ minimal important differences in SF-36 scores were compared between groups.

Results At Week 12, ixekizumab-treated patients (both dose groups in UNCOVER-1, -2, and -3) reported statistically significantly greater improvements in mean SF-36 PCS and MCS and all 8 SF-36 domain scores versus placebo. Further, more ixekizumab-treated patients than placebo-treated patients reported at least minimal treatment responses in SF-36 PCS and MCS scores and domain scores. Overall improvements in SF-36 PCS and MCS scores were maintained through Week 60.

Conclusions Ixekizumab-treated patients reported statistically significant improvements in HRQoL at 12 weeks that persisted through 1 year.

Keywords Ixekizumab · Psoriasis · SF-36 · Quality of life

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Introduction

Moderate-to-severe psoriasis causes scaling, erythema, pruritus, and pain—signs and symptoms that can profoundly impact patients' psychosocial well-being [1–4]. Patients with psoriasis report shame, anger, depression, anxiety, social stigmatisation, physical limitations, sexual dysfunction, and employment issues that are not assessed by clinician-rated measures of disease severity [5–9]. Impairment in mental and physical functioning is comparable to or worse than that of other chronic medical conditions such as heart disease and arthritis [10]. Psoriasis can profoundly affect health-related quality of life (HRQoL) with cumulative effects that may cause some patients to not achieve their full-life potential [1–4, 10, 11].

Biologic agents are important therapies in the treatment of moderate-to-severe psoriasis [12–14], offering better safety and efficacy than other systemic psoriasis treatments, and greatly improving patients' HRQoL [12–19]. Although a 75% improvement in Psoriasis Area Severity Index (PASI 75) is the accepted threshold for assessing efficacy in randomised controlled trials (RCTs), residual skin lesions and associated symptoms, such as pain and pruritus, can still negatively impact HRQoL [20]. Consequently, treatment goals for psoriasis are shifting to a patient-centred approach, with clinical trials using both physician-measured scales and patient-reported outcomes to determine therapy success in the treatment of patients with moderate-to-severe psoriasis [21]. One such patient-reported measure is the generic 36-item Medical Outcomes Survey Short Form (SF-36), which is a simple multi-item scale that assesses 8 different health concepts intended to detect medically and socially relevant differences in health status and changes in health over time [22].

Interleukin (IL)-17A is a key cytokine in the pathogenesis of psoriasis [23]. Ixekizumab is a high-affinity monoclonal antibody that selectively targets IL-17A [24–26] and has been studied in numerous controlled trials, including 3 multicentre, phase III, double-blind, placebo-controlled RCTs: UNCOVER-1, UNCOVER-2, and UNCOVER-3 (NCT01474512, NCT01597245, and NCT01646177, respectively) [27, 28]. In all of these RCTs, the Week-12 coprimary efficacy objectives were met as both ixekizumab treatment groups were superior to placebo in UNCOVER-1, UNCOVER-2, and UNCOVER-3 [27, 28] and superior to etanercept in UNCOVER-2 and UNCOVER-3 [27] in the proportion of patients achieving PASI 75 and the proportion achieving a static Physician's Global Assessment (sPGA) score of 0 or 1 (with at least a 2-point improvement from baseline). In support of the previously reported clinician-rated efficacy, here we present patient-reported outcomes from the SF-36 for patients enrolled in the UNCOVER trials. This is the first report of SF-36 results following ixekizumab treatment for psoriasis in phase III RCTs and is intended to improve the understanding of the psoriasis disease burden and the impact of ixekizumab treatment in this population.

Methods

Study design and patients

Patients aged ≥ 18 years with confirmed diagnoses of chronic plaque psoriasis at least 6 months before randomisation were eligible for UNCOVER-1, UNCOVER-2, and UNCOVER-3. The 3 trials had similar key enrolment criteria [27, 28], which included ≥ 10% body surface area involvement and both an sPGA score ≥ 3 and a PASI score ≥ 12 at screening and baseline visits. Additional details of the UNCOVER trials, including randomisation, blinding, and inclusion/exclusion criteria, have been presented elsewhere [27, 28].

Study design and treatment

In UNCOVER-1, patients were randomised 1:1:1 to receive subcutaneous ixekizumab 80 mg every 2 weeks (Q2W), ixekizumab 80 mg every 4 weeks (Q4W) (each with a starting dose of 160 mg), or placebo [28]. The 12-week induction period was followed by a 48-week randomised withdrawal (maintenance) period (Weeks 12–60) during which ixekizumab Week-12 responders (patients with sPGA [0,1]) were rerandomised in a 1:1:1 ratio to receive subcutaneous placebo, 80 mg ixekizumab Q4W, or 80 mg ixekizumab every 12 weeks (Q12W). Patients in any group who achieved an sPGA score of ≥ 3 (relapse) during the maintenance period were readministered 80 mg ixekizumab Q4W. In UNCOVER-2 and UNCOVER-3, patients were randomised 2:2:2:1 to receive subcutaneous ixekizumab Q2W, ixekizumab Q4W (each with a starting dose of 160 mg), etanercept 50 mg twice weekly, or placebo [27]. The 12-week induction period of UNCOVER-2 was followed by a randomised withdrawal (maintenance) period (Weeks 12–60) during which ixekizumab Week-12 responders (patients with sPGA [0,1]) were rerandomised in a 1:1:1 ratio to receive subcutaneous placebo, 80 mg ixekizumab Q4W, or 80 mg ixekizumab every 12 weeks (Q12W). Patients in any group whose sPGA score increased to ≥ 3 (relapse) during the maintenance period were readministered 80 mg ixekizumab Q4W [28]. UNCOVER-3 did not have a maintenance period; thus, each patient completing the 12-week induction period could proceed to an open-label long-term extension period if the investigator concluded that the patient maintained his or her efficacy response with adequate overall safety. A long-term extension period followed the randomised withdrawal

period for UNCOVER-1 and UNCOVER-2. Upon entering the extension period of the UNCOVER trials, all patients were assigned to ixekizumab Q4W and were evaluated for up to a total of 5 years.

Data from the primary efficacy and safety analyses have been reported elsewhere [27, 28].

SF-36

The SF-36 (v2 acute), which has a 1-week recall period, assesses patients' general health status [22, 29]. The SF-36 has eight domains: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH), and two overarching component summaries, physical component summary (PCS), and mental component summary (MCS) scores [29]. Z-transformed and norm-based domain and component summaries were scored using 2009 USA general population normative data, derived using QualityMetric Health Outcomes Scoring Software version 4.5 [29]. A protocol-specified secondary objective was to compare changes from baseline in PCS and MCS scores in ixekizumab-treated patients with patients receiving placebo (and etanercept in UNCOVER-2 and UNCOVER-3), with the hypothesis that treatment with ixekizumab would yield greater improvements. In this analysis, the SF-36 (v2) minimal important difference (MID) treatment response definitions were applied to the component summary scores, defined as a >3.8-point change from baseline in PCS and >4.6 in MCS [29]. For the eight domains, the MID definitions were changes from baseline in PF: ≥ 4.3, RP: ≥ 4.0, BP: ≥ 5.5, GH: ≥ 7.0, VT: ≥ 6.7, SF: ≥ 6.2, RE: ≥ 4.6, and MH: ≥ 6.7 [29].

Statistical analyses

This analysis included comparing mean changes in SF-36 scores at Weeks 12 (UNCOVER-1, UNCOVER-2, and UNCOVER-3) and 60 (UNCOVER-1 and UNCOVER-2), percentages of patients reporting scores $\geq$ norms (50) at Week 12 (UNCOVER-2 and UNCOVER-3; post hoc), and percentages with improvements $\geq$ MID SF-36 domain and component scores at Week 12 (UNCOVER-1, UNCOVER-2, UNCOVER-3; post hoc).

The analysis population for the first 12 weeks was the intent-to-treat population, defined as all randomised patients (whether or not they received study drug). In UNCOVER-1, an additional 48-week data analysis was conducted based on the maintenance primary population, defined as patients who were initially randomised to ixekizumab and were Week-12 responders (patients with sPGA [0,1]). In UNCOVER-1, randomisation was stratified by geographic regions (North America or Other), previous nonbiologic systemic therapy (inadequate response to, intolerance to, or contraindication to <3 or ≥ 3 conventional systemic therapies), and weight (<100 kg or ≥ 100 kg) [28]. For categorical outcomes, treatment comparison was made by logistic model, controlled for randomization factors for the first 12 weeks. For continuous outcomes, treatment comparisons used an analysis of covariance (ANCOVA) model, including baseline SF-36 score and randomization factors during the 12-week induction period, whereas a mixed model for repeated measures (MMRM) analysis was used for treatment comparisons during the maintenance period. The MMRM model included baseline SF-36 score, rerandomised treatment group, baseline weight category, visit, and treatment-by-visit interaction as factors. In UNCOVER-2 and UNCOVER-3, patients were randomised by centre [27]. For continuous outcomes, treatment comparisons used ANCOVA with treatment, pooled centre, and baseline outcome value in the model in the first 12 weeks; pooled centre was dropped for the additional 48 weeks of UNCOVER-2. Randomised patients without at least 1 postbaseline observation were not included for evaluation. For categorical outcomes, treatment comparisons used the Cochran–Mantel–Haenszel test stratified by pooled centre. For all 12-week analyses of UNCOVER-1, UNCOVER-2, and UNCOVER-3 data, missing continuous variables were imputed by the last observation carried forward (LOCF), and missing categorical data were imputed using the nonresponder imputation (NRI). For 60-week analyses of UNCOVER-1 and UNCOVER-2 data, the MMRM approach was used to estimate the most likely treatment effect in the presence of missing continuous outcomes for patients who continued on ixekizumab Q4W through 60 weeks.

Results

A total of 1296 patients entered treatment in UNCOVER-1, 1224 entered UNCOVER-2, and 1346 entered UNCOVER-3. In UNCOVER-1, patient mean ages were 45 to 46 years, 30% to 33% were female, and 92% to 93% were white. Mean baseline SF-36 PCS scores were 46.6 to 47.2, and SF-36 MCS scores were 47.4 to 48.8 (Table 1). Across the individual SF-36 domains, patients reported the most impairment at baseline in RE, SF, and BP domains (Table 1). The baseline characteristics were similar across treatment arms in UNCOVER-1 (Table 1). Similar to UNCOVER-1, patient mean ages were 45 to 46 years, 29% to 37% were female, and 89% to 94% were white across treatment groups in UNCOVER-2 and -3 (Table 2). Mean baseline SF-36 PCS scores were 47.1 to 48.7 (UNCOVER-2 and UNCOVER-3), and SF-36 MCS scores were 47.0 to 49.0 (UNCOVER-2 and UNCOVER-3) (Table 2). In the individual SF-36 domains, patients reported the most impairment at baseline in the SF,

Table 1 Baseline demographics in UNCOVER-1 (ITT population)

	PBO $N=431$	IXE Q4W $N=432$	IXE Q2W $N=433$
Age (years), mean (SD)	46.4 (13.4)	45.6 (13.0)	45.1 (12.4)
Female, *n* (%)	128 (29.7)	143 (33.1)	142 (32.8)
Race, *n* (%)			
Asian	21 (4.9)	23 (5.3)	18 (4.2)
Black/African American	8 (1.9)	10 (2.3)	8 (1.8)
White	401 (93.0)	397 (91.9)	401 (92.6)
Other/mixed	1 (0.2)	2 (0.4)	6 (1.4)
Geographic region, *n* (%)			
Australia	19 (4.4)	15 (3.5)	8 (1.8)
Asia	13 (3.0)	12 (2.8)	8 (1.8)
Europe	176 (40.8)	180 (41.7)	192 (44.3)
North America	223 (51.7)	225 (52.1)	225 (52.0)
Weight (kg), mean (SD)	91.8 (25.0)	92.5 (23.9)	92.4 (22.7)
Duration of psoriasis symptoms from onset (years), mean (SD)	19.5 (11.7)	19.5 (11.9)	19.9 (11.9)
Percentage of BSA involved, mean (SD)	27.4 (17.8)	27.4 (16.2)	28.2 (17.8)
Psoriatic arthritis, *n* (%)	115 (26.7)	107 (24.8)	119 (27.5)
DLQI, mean (SD)	12.8 (7.1)	13.2 (7.0)	13.4 (7.0)
SF-36, mean (SD)			
PCS	46.9 (9.8)	47.2 (9.3)	46.6 (9.1)
MCS	48.8 (11.2)	47.4 (11.6)	48.0 (11.5)
Physical functioning	48.5 (10.5)	49.1 (9.4)	48.2 (9.7)
Role-physical	48.1 (10.4)	47.2 (10.3)	46.9 (10.6)
Bodily pain	44.7 (11.5)	44.7 (11.2)	44.4 (10.9)
General health	46.2 (10.0)	46.3 (10.0)	46.6 (9.9)
Vitality	51.3 (10.7)	50.2 (10.3)	50.4 (10.2)
Social functioning	46.2 (11.7)	45.8 (11.3)	45.5 (11.6)
Mental health	48.1 (11.1)	47.0 (11.2)	48.2 (10.9)
Role-emotional	48.3 (11.2)	47.3 (11.3)	46.6 (12.1)

Some data from Gordon et al. [28]

BSA body surface area, *DLQI* Dermatology Life Quality Index, *ITT* intent-to-treat, *IXE* ixekizumab, *MCS* mental component summary, *N* population size, *n* number in group, *PBO* placebo, *PCS* physical component summary, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SD* standard deviation, *SF-36* Medical Outcomes Survey Short Form-36

BP, RE, and GH domains (Table 2). Baseline characteristics were similar across treatment arms in UNCOVER-2 and UNCOVER-3 (Table 2). Patient disposition for each group, including losses and exclusions after randomization, together with reasons, was previously reported [27, 28].

Discontinuations were low in all 3 trials through Week 12. In UNCOVER-1, 97%, 98%, and 99% of patients in the PBO, IXEQ4W, and IXEQ2W groups had nonmissing data at Week 12; in UNCOVER-2, 95%, 94%, 96%, and 98% of patients in the PBO, ETN, IXEQ4W, and IXEQ2W groups had nonmissing data at Week 12; and in UNCOVER-3, 95%, 98%, 97%, and 96% of patients in the PBO, ETN, IXEQ4W, and IXEQ2W groups had nonmissing data by Week 12. The amount of missing data at Week 60 was more substantial, mostly due to relapse in patients rerandomized to placebo or IXEQ12W in the maintenance period: in UNCOVER-1, 12%, 53%, and 79% of patients in the IXE/PBO, IXE/IXEQ12W, and IXE/IXEQ4W groups had nonmissing data by Week 60, and in UNCOVER-2, 11%, 52%, and 82% of patients in the IXE/PBO, IXE/IXEQ12W, and IXE/IXEQ4W groups had nonmissing data by Week 60 (Tables 3, 4).

Patients reported statistically significantly greater improvements in mean SF-36 PCS and MCS scores after treatment with ixekizumab Q2W or Q4W than placebo at 12 weeks in UNCOVER-1 (Table 3), UNCOVER-2 (Table 4), and UNCOVER-3 (Table 4). In UNCOVER-2 and UNCOVER-3, which included an active comparator, statistically significantly greater improvements in mean SF-36 PCS and MCS scores were also reported with ixekizumab Q2W or Q4W relative to etanercept at 12 weeks with a few exceptions: in UNCOVER-2, ixekizumab Q4W was not statistically significantly different from etanercept in mean MCS

Table 2 Baseline demographics in UNCOVER-2 and UNCOVER-3 (ITT population)

	UNCOVER-2				UNCOVER-3			
	PBO (*N* = 168)	ETN (*N* = 358)	IXE Q4W (*N* = 347)	IXE Q2W (*N* = 351)	PBO (*N* = 193)	ETN (*N* = 382)	IXE Q4W (*N* = 386)	IXE Q2W (*N* = 385)
Age (years), mean (SD)	45.3 (12.1)	45.3 (12.8)	45.0 (13.5)	44.5 (13.3)	46.4 (12.1)	45.8 (13.8)	45.6 (13.1)	45.6 (13.1)
Female, *n* (%)	48 (28.6)	122 (34.1)	103 (29.7)	130 (37.0)	56 (29.0)	113 (29.6)	128 (33.2)	131 (34.0)
Race, *n* (%)								
Asian	6 (3.6)	8 (2.3)	11 (3.2)	12 (3.4)	7 (3.6)	11 (2.9)	11 (2.8)	12 (3.1)
Black/African American	10 (6.0)	13 (3.7)	11 (3.2)	5 (1.4)	8 (4.1)	10 (2.6)	9 (2.3)	5 (1.3)
White	149 (88.7)	331 (93.5)	315 (91.8)	330 (94.3)	176 (91.2)	351 (91.9)	360 (93.3)	361 (93.8)
Other/mixed	3 (1.8)	2 (0.6)	6 (1.8)	3 (0.9)	2 (1.0)	10 (2.6)	6 (1.8)	7 (1.7)
Geographic region, *n* (%)								
Australia	7 (4.2)	13 (3.6)	15 (4.3)	16 (4.6)	0	0	0	0
Central/South America	0	0	0	0	14 (7.3)	30 (7.9)	29 (7.5)	58 (7.5)
Europe	72 (42.9)	152 (42.5)	145 (41.8)	147 (41.9)	88 (45.6)	162 (42.4)	166 (43.0)	173 (44.9)
North America	89 (53.0)	193 (53.9)	187 (53.9)	188 (53.6)	91 (47.2)	190 (49.7)	191 (49.5)	183 (47.5)
Weight (kg), mean (SD)	91.8 (21.9)	92.9 (22.4)	92.5 (22.5)	89.2 (21.6)	91.0 (21.5)	92.2 (24.3)	91.2 (23.9)	90.4 (23.4)
Duration of psoriasis symptoms from onset (years), mean (SD)	19.1 (12.7)	18.9 (12.5)	18.5 (12.7)	18.3 (12.1)	18.2 (12.5)	18.1 (11.8)	18.5 (12.4)	17.8 (12.2)
Percentage of BSA involved, mean (SD)	27.2 (18.1)	25.3 (15.5)	27.0 (17.2)	25.1 (15.8)	28.6 (17.5)	28.3 (17.4)	28.4 (16.5)	28.0 (17.3)
Psoriatic arthritis, *n* (%)	47 (28.0)	79 (22.1)	75 (21.6)	87 (24.8)	42 (21.8)	72 (18.8)	83 (21.5)	77 (20.0)
DLQI, mean (SD)	12.8 (7.2)	12.7 (7.0)	11.6 (6.7)	12.4 (6.9)	12.7 (7.0)	11.5 (6.8)	11.9 (7.0)	12.4 (6.9)
SF-36, mean (SD)								
PCS	47.7 (9.5)	47.5 (9.2)	47.6 (9.0)	47.7 (9.0)	47.1 (9.5)	48.7 (8.5)	47.6 (9.5)	47.8 (8.8)
MCS	47.8 (10.6)	48.6 (10.7)	49.0 (10.9)	47.7 (11.7)	47.0 (11.6)	48.3 (11.7)	48.6 (11.3)	48.2 (11.4)
Physical functioning	49.2 (10.1)	48.0 (10.7)	49.3 (8.9)	48.7 (9.8)	47.8 (10.2)	50.0 (8.7)	48.8 (10.2)	49.0 (9.3)
Role-physical	48.1 (10.0)	48.4 (9.8)	48.3 (9.6)	48.1 (10.3)	47.9 (9.8)	48.8 (9.2)	48.1 (10.2)	48.1 (9.7)
Bodily pain	45.0 (11.7)	45.8 (11.4)	45.7 (11.2)	45.6 (11.0)	44.9 (11.2)	47.1 (11.0)	46.0 (11.0)	46.0 (11.4)
General health	47.0 (10.0)	47.6 (9.9)	46.9 (9.7)	47.0 (10.1)	45.9 (10.4)	46.6 (9.2)	46.9 (9.5)	46.6 (9.0)
Vitality	50.9 (10.3)	50.9 (9.8)	51.2 (10.0)	50.8 (10.4)	50.3 (10.3)	51.6 (10.2)	51.5 (9.4)	51.3 (9.3)
Social functioning	45.6 (11.8)	46.3 (11.1)	47.1 (11.1)	45.5 (11.9)	45.0 (11.1)	47.3 (11.0)	46.8 (10.9)	46.3 (11.5)
Mental health	47.5 (10.4)	48.2 (10.9)	48.7 (10.2)	47.9 (11.0)	46.5 (11.4)	48.2 (11.0)	48.3 (11.0)	48.3 (10.6)
Role-emotional	47.6 (10.5)	48.2 (10.9)	48.3 (10.8)	47.1 (11.7)	46.9 (11.0)	47.9 (10.9)	47.6 (11.3)	47.4 (11.0)

Some data from Griffiths et al. [27] and Gordon et al. [28]

BSA body surface area, *DLQI* Dermatology Life Quality Index, *ETN* etanercept, *ITT* intent-to-treat, *IXE* ixekizumab, *MCS* mental component summary, *N* population size, *n* number in group, *PBO* placebo, *PCS* physical component summary, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SD* standard deviation, *SF-36* Medical Outcomes Survey Short Form-36

scores, and in UNCOVER-3, ixekizumab Q2W was not statistically significantly different from etanercept in mean PCS scores (Table 4).

In UNCOVER-1, -2, and -3, ixekizumab-treated patients at Week 12 reported statistically significantly greater improvements than placebo across all 8 SF-36 domains (Table 5, 6; Supplemental Fig. 1).

Week-60 UNCOVER-1 and -2 data revealed that SF-36 PCS and MCS score improvements were consistent in

Table 3 SF-36 physical and mental component summary scores at week 12 and week 60 in UNCOVER-1

	Induction period (LOCF)		
	PBO $N=431$	IXE Q4W $N=432$	IXE Q2W $N=433$
PCS[a]			
n	420	422	429
Week 12, mean (SD)	47.0 (9.5)	51.7 (7.9)	51.4 (7.9)
Change from baseline, LS mean (SE)	−0.1 (0.4)	4.3 (0.4)[†]	4.4 (0.4)[†]
MCS[a]			
n	420	422	429
Week 12, mean (SD)	49.5 (11.2)	51.6 (9.3)	52.4 (8.6)
Change from baseline, LS mean (SE)	0.9 (0.5)	3.8 (0.5)[†]	4.2 (0.4)[†]
			Maintenance period (MMRM)
			IXE/IXE Q4W $N=229$
PCS[b]			
n			181
Week 60, mean (SD)			52.9 (7.5)
Change from baseline, LS mean (SE)			4.3 (0.5)
MCS[b]			
n			181
Week 60, mean (SD)			53.7 (8.3)
Change from baseline, LS mean (SE)			5.6 (0.5)

ANCOVA analysis of covariance, *IXE* ixekizumab, *LOCF* last observation carried forward, *LS* least squares, *MCS* mental component summary, *MMRM* mixed model for repeated measures, *N* population size, *n* number in group, *PBO* placebo, *PCS* physical component summary, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q12W* every 12 weeks, *SD* standard deviation, *SE* standard error, *SF-36* Medical Outcomes Survey Short Form-36

[†]$P<0.001$ treatment versus PBO comparison using an ANCOVA model that included treatment, geographic region, previous nonbiologic systemic therapy, baseline weight category, and baseline SF-36 value

[a]By Week 12, 97%, 98%, and 99% of patients in the PBO, IXEQ4W, and IXEQ2W groups had nonmissing data

[b]By Week 60, 12%, 53%, and 79% of patients in the IXE/PBO, IXE/IXEQ12W, and IXE/IXEQ4W groups had nonmissing data

responders who continued on ixekizumab Q4W through 60 weeks (Tables 3, 4).

At Week 12 in UNCOVER-1, statistically significantly greater proportions of ixekizumab Q2W and Q4W patients reported improvements ≥ MID in PCS and MCS relative to placebo (Fig. 1). Similarly, statistically significantly more ixekizumab Q2W and Q4W patients reported changes ≥ MID in PCS relative to placebo in UNCOVER-2 and UNCOVER-3; however, only ixekizumab Q2W was statistically significantly greater than placebo in MCS in UNCOVER-2 (Fig. 2a, b). In UNCOVER-2 only, statistically significantly more ixekizumab Q4W patients reported scores ≥ MID in PCS relative to etanercept (Fig. 2a). Conversely, statistically significantly more Q2W patients reported changes ≥ MID in MCS relative to etanercept (Fig. 2a).

At Week 12, a statistically significantly greater proportion of ixekizumab Q2W and Q4W patients reported scores ≥ population norms (scores ≥ 50) in PCS and MCS relative to placebo, with the exception of Q4W patients in UNCOVER-2 (UNCOVER-1, UNCOVER-2, and UNCOVER-3; Supplemental Fig. 2a–c). Statistically significantly more ixekizumab Q2W and Q4W patients reported scores that met or exceeded the PCS and MCS norms relative to etanercept in UNCOVER-2 (Supplemental Fig. 2b). A cumulative probability plot was created to examine the robustness of the superiority of ixekizumab in the proportions of patients reporting values ≥ MID. Across all component and domain scores, the superiority of ixekizumab treatment was consistently observed (Supplemental Figs. 3, 4).

Discussion

Consistent with observations that psoriasis substantially reduces HRQoL [1–4, 10], patients enrolled in UNCOVER-1, UNCOVER-2, and UNCOVER-3 reported diminished HRQoL at baseline assessed by the generic SF-36. In UNCOVER-1, patients treated with the approved ixekizumab dosage in the USA and Europe (Q2W induction; Q4W maintenance) [30] reported statistically significantly greater improvements in SF-36 than placebo at Week 12. Likewise, patients in UNCOVER-2 and UNCOVER-3 also

Table 4 SF-36 Physical and Mental Component Summary Scores at week 12 and week 60 in UNCOVER-2 and UNCOVER-3

	UNCOVER-2 Induction period[a] (LOCF)				UNCOVER-3 Induction period[b] (LOCF)			
	PBO $N=168$	ETN $N=358$	IXE Q4W $N=347$	IXE Q2W $N=351$	PBO $N=193$	ETN $N=382$	IXE Q4W $N=386$	IXE Q2W $N=385$
PCS								
n	159	336	334	343	183	376	374	371
Week 12, mean (SD)	47.2 (9.4)	50.2 (8.7)	52.2 (8.1)	51.4 (8.5)	47.3 (9.8)	51.4 (8.2)	51.9 (8.4)	51.9 (8.3)
Change from baseline, LS mean (SE)	−0.5 (0.5)	2.6 (0.4)†	4.6 (0.4)†¥	3.8 (0.4)†¥	−0.2 (0.5)	3.1 (0.4)†	4.2 (0.4)†¥	4.0 (0.4)†
MCS								
n	159	336	334	343	183	376	375	371
Week 12, mean (SD)	47.7 (11.0)	51.0 (9.8)¶	51.7 (8.9)	52.5 (8.4)	48.8 (10.6)	50.9 (10.0)	52.1 (8.7)	52.5 (7.7)
Change from baseline, LS mean (SE)	−0.1 (0.6)	2.3 (0.4)†	2.8 (0.4)†	4.5 (0.4)†¥	1.1 (0.6)	2.6 (0.4)¶	3.8 (0.4)†¥	4.3 (0.4)†¥

	Maintenance period[c] (MMRM) IXE/IXEQ4W $N=187$
PCS	
n	154
Week 60, mean (SD)	4.1 (8.7)
Change from baseline, LS mean (SE)	3.9 (0.6)
MCS	
n	154
Week 60, mean (SD)	5.9 (10.0)
Change from baseline, LS mean (SE)	5.9 (0.6)**

ANCOVA analysis of covariance, *LS* least squares, *ETN* etanercept, *IXE* ixekizumab, *LOCF* last observation carried forward, *LS* least squares, *MCS* Mental Component Summary, *N* population size, *n* number in group, *PBO* placebo, *PCS* Physical Component Summary, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q12W* every 12 weeks, *SD* standard deviation, *SE* standard error, *SF-36* Medical Outcomes Survey Short Form-36

†$P<0.001$ treatment versus placebo comparison using an ANCOVA model including treatment, pooled centre, and baseline SF-36 value for UNCOVER-2 and UNCOVER-3

¶$P<0.05$ treatment versus placebo comparison using an ANCOVA model including treatment, pooled centre, and baseline SF-36 value for UNCOVER-2 and UNCOVER-3

¥$P\leq0.05$ treatment versus etanercept comparison using an ANCOVA model including treatment, pooled centre, and baseline SF-36 value for UNCOVER-2 and UNCOVER-3

**$P\leq0.05$ treatment versus placebo comparison using an MMRM model including baseline, treatment, visit, and treatment-by-visit interaction as fixed effects with variance–covariance structure set to unstructured

[a]By Week 12, 95%, 94%, 96%, and 98% of patients in the PBO, ETN, IXEQ4W, and IXEQ2W groups had nonmissing data

[b]By Week 12, 95%, 98%, 97%, and 96% of patients in the PBO, ETN, IXEQ4W, and IXEQ2W groups had nonmissing data

[c]By Week 60, 11%, 52%, and 82% of patients in the IXE/PBO, IXE/IXEQ12W, and IXE/IXEQ4W group had nonmissing data

reported that the approved ixekizumab dosage provided statistically significantly greater improvements in SF-36 than etanercept (a tumour necrosis factor inhibitor) and placebo.

The SF-36 is a generic measure of HRQoL. Results reported here are augmented by data obtained for the skin-related DLQI. In both UNCOVER-2 and UNCOVER-3, ixekizumab-treated patients reported improved mean changes from baseline in the DLQI beginning at Week 2 with greater proportions of patients treated with ixekizumab Q2W or ixekizumab Q4W having DLQI 0/1 compared with placebo or etanercept ($P<0.0001$, for both ixekizumab doses versus placebo or etanercept); these statistically significant differences persisted through Week 12 [27]. Moreover, in UNCOVER-2 and UNCOVER-3, clearer skin was associated

Table 5 SF-36 domain scores at Week 12 in UNCOVER-1

	Induction period (LOCF)		
	PBO $N=431$	IXE Q4W $N=432$	IXE Q2W $N=433$
Physical functioning			
Week 12, mean (SD)	48.9 (10.1)	52.0 (7.8)	51.8 (7.7)
Change from baseline, LS mean (SE)	0.04 (0.4)	2.8 (0.4)†	3.1 (0.4)†
Role-physical			
Week 12, mean (SD)	48.7 (10.3)	51.8 (7.6)	51.6 (8.0)
Change from baseline, LS mean (SE)	0.7 (0.5)	4.2 (0.5)†	4.2 (0.4)†
Bodily pain			
Week 12, mean (SD)	45.0 (11.6)	52.6 (9.6)	52.7 (9.6)
Change from baseline, LS mean (SE)	-0.2 (0.6)	7.4 (0.6)†	7.6 (0.5)†
General health			
Week 12, mean (SD)	46.2 (9.7)	49.2 (8.9)	49.5 (9.2)
Change from baseline, LS mean (SE)	-0.3 (0.4)	2.8 (0.4)†	2.8 (0.4)†
Vitality			
Week 12, mean (SD)	51.4 (10.5)	53.8 (9.1)	54.0 (9.3)
Change from baseline, LS mean (SE)	0.2 (0.4)	3.3 (0.4)†	3.3 (0.4)†
Social functioning			
Week 12, mean (SD)	47.1 (11.7)	51.8 (8.3)	52.1 (7.5)
Change from baseline, LS mean (SE)	0.7 (0.5)	5.6 (0.5)†	6.0 (0.5)†
Mental health			
Week 12, mean (SD)	49.1 (11.1)	51.0 (9.6)	52.1 (9.0)
Change from baseline, LS mean (SE)	1.1 (0.5)	3.6 (0.5)†	4.0 (0.4)†
Role-emotional			
Week 12, mean (SD)	48.7 (11.2)	51.6 (8.7)	51.7 (7.7)
Change from baseline, LS mean (SE)	0.3 (0.5)	3.8 (0.5)†	4.1 (0.5)†

ANCOVA analysis of covariance, *IXE* ixekizumab, *LOCF* last observation carried forward, *LS* least squares, *N* population size, *n* number in group, *PBO* placebo, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q12W* every 12 weeks, *SD* standard deviation, *SE* standard error, *SF-36* Medical Outcomes Survey Short Form-36

†$P<0.001$ treatment versus placebo comparison using an ANCOVA model including treatment, geographic region, previous nonbiologic systemic therapy, baseline weight category, and baseline SF-36 value

with progressive improvements in DLQI, whereby more patients reported a DLQI 0/1 score among patients achieving 100% PASI improvement or a 90–99% PASI improvement compared with patients achieving 75–89% PASI improvement [27]. Other phase III RCTs with anti–IL-17A psoriasis treatment have reported statistically significantly greater improvements in DLQI compared to etanercept and placebo [15], which shows that IL-17A inhibition can provide greater improvement in skin-related quality of life.

Patients treated with ixekizumab Q2W and Q4W reported statistically significantly greater improvements than placebo in HRQoL in SF-36 PCS and/or MCS scores as well all eight domain scores (UNCOVER-1, UNCOVER-2, and UNCOVER-3). Additionally, greater improvements compared with etanercept in SF-36 PCS (UNCOVER-2, UNCOVER -3 [Q4W only]) and MCS scores (UNCOVER-2 [Q2W only], UNCOVER-3) were observed. In UNCOVER-1 and UNCOVER-2, improvements in PCS and MCS scores were sustained when ixekizumab treatment continued through Week 60 rather than being switched to placebo or Q12W (not an approved dose). The SF-36 is a generic instrument that is suitable for many diseases, and thus may lack the precision of other disease-specific measures. For this reason, we may expect some variation in statistically significant findings across domains. As noted above, SF-36 data are a useful supplementation to the DLQI findings previously reported as the SF-36 addresses a broader range of HRQoL concepts, and data may be compared across different disease populations.

The amount of missing data during the induction period (Week 12) in the UNCOVER-1 and UNCOVER-2 studies was minimal; thus, the LOCF imputation method was sufficiently robust. A greater amount of missing data, particularly for IXE/PBO and IXE/IXEQ12W, was apparent at Week 60 in the UNCOVER-1 and UNCOVER-2 studies. With the exception of patients who were rerandomized to Q4W at Week 12, patients who met relapse criteria (sPGA ≥ 3) at any time were switched to IXEQ4W [28],

Table 6 SF-36 domain scores at week 12 in UNCOVER-2 and UNCOVER-3

	UNCOVER-2 (LOCF)				UNCOVER-3 (LOCF)			
	PBO $N=168$	ETN $N=358$	IXE Q4W $N=347$	IXE Q2W $N=351$	PBO $N=193$	ETN $N=382$	IXE Q4W $N=386$	IXE Q2W $N=385$
Physical functioning								
Week 12, mean (SD)	48.8 (10.5)	50.2 (9.8)	52.2 (7.8)	51.4 (8.9)	48.6 (9.6)	51.5 (8.7)	51.6 (9.0)	51.4 (8.9)
Change from baseline, LS mean (SE)	−0.2 (0.5)	1.8 (0.4)[¶]	3.2 (0.4)[†¥]	2.7 (0.4)[†]	0.2 (0.5)	2.0 (0.4)[¶]	2.8 (0.4)[†]	2.4 (0.4)[†]
Role-physical								
Week 12, mean (SD)	47.4 (10.2)	50.6 (9.0)	52.1 (7.8)	51.9 (8.0)	48.1 (9.6)	51.2 (8.0)	51.9 (7.9)	52.1 (7.6)
Change from baseline, LS mean (SE)	−0.7 (0.5)	2.2 (0.4)[†]	3.8 (0.4)[†¥]	3.7 (0.4)[†¥]	−0.0 (0.5)	2.7 (0.4)[†]	3.6 (0.4)[†]	3.9 (0.4)[†¥]
Bodily pain								
Week 12, mean (SD)	44.7 (11.6)	50.5 (10.1)	53.0 (10.1)	53.0 (9.5)	46.3 (11.4)	52.2 (9.7)	53.1 (9.6)	53.2 (9.8)
Change from baseline, LS mean (SE)	−0.5 (0.7)	4.6 (0.5)[†]	7.2 (0.5)[†¥]	7.3 (0.5)[†¥]	0.5 (0.7)	5.8 (0.5)[†]	7.1 (0.5)[†]	7.1 (0.5)[†¥]
General health								
Week 12, mean (SD)	46.7 (9.6)	49.3 (9.3)	50.3 (9.3)	49.9 (8.7)	46.1 (10.0)	49.0 (9.1)	50.5 (8.5)	49.9 (8.3)
Change from baseline, LS mean (SE)	−0.3 (0.5)	1.7 (0.4)[¶]	3.2 (0.4)[†¥]	2.8 (0.4)[†¥]	0.0 (0.5)	2.6 (0.4)[†]	3.9 (0.3)[†¥]	3.4 (0.3)[†]
Vitality								
Week 12, mean (SD)	50.3 (9.9)	53.3 (10.6)	53.8 (9.7)	53.9 (9.2)	51.3 (10.0)	53.9 (9.8)	54.9 (8.6)	55.3 (8.3)
Change from baseline, LS mean (SE)	−0.4 (0.6)	2.2 (0.4)[†]	2.7 (0.4)[†]	3.2 (0.4)[†]	0.6 (0.6)	2.4 (0.4)[¶]	3.5 (0.4)[†¥]	3.9 (0.4)[†¥]
Social functioning								
Week 12, mean (SD)	46.2 (11.3)	49.9 (9.5)	51.9 (8.3)	51.9 (7.8)	45.8 (11.4)	50.9 (8.6)	51.9 (8.0)	52.3 (7.2)
Change from baseline, LS mean (SE)	0.3 (0.6)	3.5 (0.4)[†]	5.1 (0.4)[†¥]	6.0 (0.4)[†¥]	−0.1 (0.6)	4.2 (0.4)[†]	5.3 (0.4)[†]	5.8 (0.4)[†¥]
Mental health								
Week 12, mean (SD)	47.3 (10.9)	50.4 (10.6)	51.6 (9.7)	52.1 (9.0)	48.6 (9.9)	50.5 (10.1)	51.7 (9.1)	51.6 (8.7)
Change from baseline, LS mean (SE)	−0.2 (0.6)	2.1 (0.4)[¶]	3.0 (0.4)[†]	4.0 (0.4)[†¥]	1.4 (0.6)	2.4 (0.4)	3.5 (0.4)[¶¥]	3.5 (0.4)[¶¥]
Role-emotional								
Week 12, mean (SD)	47.3 (12.2)	50.3 (9.6)	51.4 (8.2)	52.1 (7.6)	48.4 (10.1)	50.5 (9.2)	51.2 (8.5)	51.5 (8.3)
Change from baseline, LS mean (SE)	−0.3 (0.6)	2.2 (0.4)[†]	3.2 (0.4)[†]	4.5 (0.4)[†¥]	0.9 (0.6)	2.8 (0.4)[¶]	3.7 (0.4)[†]	4.0 (0.4)[†¥]

ANCOVA analysis of covariance, *ETN* etanercept, *IXE* ixekizumab, *LOCF* last observation carried forward, *LS* least squares, *N* population size, *n* number in group, *PBO* placebo, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q12W* every 12 weeks, *SD* standard deviation, *SE* standard error, *SF-36* Medical Outcomes Survey Short Form-36

[†] $P<0.001$ treatment versus placebo comparison at each visit using an ANCOVA model including treatment, pooled centre, and baseline SF-36 value in UNCOVER-2 and UNCOVER-3

[¶] $P<0.05$ treatment versus placebo comparison at each visit using an ANCOVA model including treatment, pooled centre, and baseline SF-36 value in UNCOVER-2 and UNCOVER-3

[¥] $P<0.05$ treatment versus etanercept comparison at each visit using an ANCOVA model including treatment, pooled centre, and baseline SF-36 value in UNCOVER-2 and UNCOVER-3

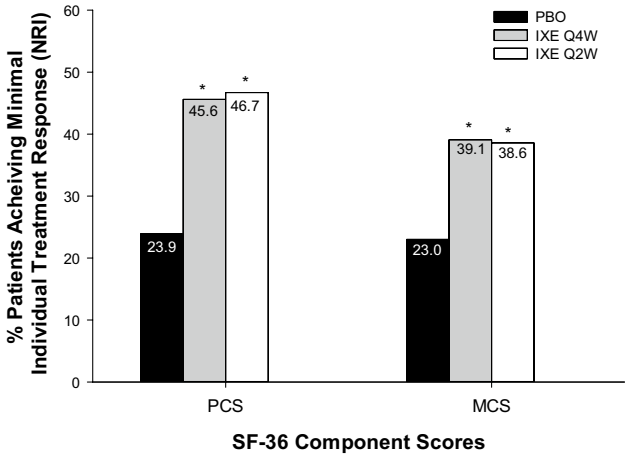

Fig. 1 Patients reporting improvements greater than the minimal important difference in individual treatment response on the medical outcomes survey short form-36 (SF-36) Component Summary Scores in UNCOVER-1 at Week 12. All patients are shown. Minimal important difference definitions were a ≥ 3.8-point change from baseline for PCS and a ≥ 4.6-point change from baseline for MCS [29]. *$P < 0.001$ versus placebo (PBO). *P* value is based on a logistic model including baseline treatment, geographic region, previous nonbiologic systemic therapy, and baseline weight category for induction period. *IXE* ixekizumab, *PBO* placebo, *PCS* Physical Component Summary, *MCS* Mental Component Summary, *NRI* nonresponder imputation, *SF-36* Medical Outcomes Survey Short Form-36, *Q2W* every 2 weeks, *Q4W* every 4 weeks

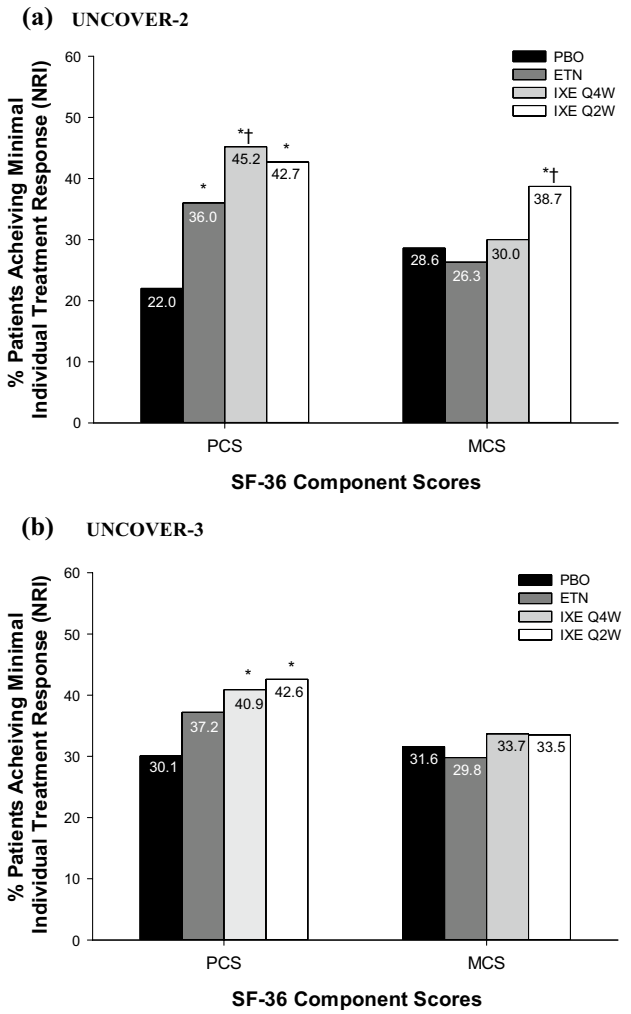

Fig. 2 Patients reporting improvements greater than the minimal important difference in individual treatment response on the Medical Outcomes Survey Short Form-36 (SF-36) Component Summary Scores in UNCOVER-2 and UNCOVER-3 at Week 12. All patients are shown. Minimal individual treatment response definitions Minimal important difference were a ≥ 3.8-point change from baseline for PCS and a ≥ 4.6-point change from baseline for MCS [29]. *$P < 0.05$ versus placebo (PBO). †$P < 0.05$ versus etanercept (ETN). *P* value is based on Cochran–Mantel–Haenszel (CMH) test stratified by pooled centre for induction period. *IXE* ixekizumab, *PBO* placebo, *PCS* Physical Component Summary, *MCS* Mental Component Summary, *NRI* nonresponder imputation, *SF-36* Medical Outcomes Survey Short Form-36, *Q2W* every 2 weeks, *Q4W* every 4 weeks

and data collected post re-treatment in those patients could no longer be used to support a maintenance effect and were not included in the analyses. Due to the substantial amount of missing data at Week 60, we used a MMRM approach for analyses because improvements observed at Week 12 were expected to diminish after treatment withdrawal. Instead of explicitly imputing missing data as in the LOCF method, the MMRM approach leverages all available data across multiple time points to estimate the most likely treatment effect as if patients had remained in the trial [31].

In this analysis, the SF-36 (v2) minimal individual treatment response definitions, in terms of T-score points, were applied to the summary components and the eight domains. Consistent with PCS, MCS, and domain score findings noted above, the proportions of patients reporting SF-36 scores ≥ MID were also generally statistically significantly higher among ixekizumab-treated than placebo patients. These criteria are described as sharing some likeness to the reliable change index, but with differences that assume a small correlation between baseline and subsequent scores as well as weighing the risk of falsely identifying someone as having an MID treatment response versus that of overlooking a true response to treatment [29]. Sensitivity analyses (shown in probability plots) were also conducted and support the robustness of the ixekizumab treatment response regardless of the individual response definition across PCS, MCS, and domain scores.

Results should be interpreted in light of a few additional limitations. These studies enrolled patients in RCT settings, and even though inclusion criteria may largely reflect patients affected with moderate-to-severe plaque psoriasis, generalisability might be limited by the exclusion criteria. Generalisability may be further limited by demographics consisting of relatively young men who were predominantly

white and the higher treatment compliance rates traditionally observed in clinical trial populations than in the general population. Finally, the long-term results were analysed in the population of clinical responders to ixekizumab treatment at Week 12, which is a population more likely to continue to benefit from ixekizumab treatment.

Among moderate-to-severe psoriasis patients with diminished HRQoL, statistically significant improvements in HRQoL were reported with ixekizumab relative to placebo and an active comparator at 12 weeks. Improvements in HRQoL persisted through 1 year of treatment.

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Compliance with ethical standards

Conflict of interest Ms Nikaï and Edson-Heredia, and Drs Zhu, Goldblum, Carlier, Burge, Lin, and Hollister are employees of Eli Lilly and Company and own stock. Professor Langley is a consultant for AbbVie, Amgen, Celgene, Pfizer, Janssen, Boehringer Ingleheim, LEO Pharma, and Valeant. He has received grants/has pending grants, has received honoraria, has received payment for development of educational programs including speaker bureau service, and received expenses covered or reimbursed for travel from AbbVie, Amgen, Celgene, Pfizer, Janssen, Boehringer Ingleheim, and LEO Pharma. Professor Reich has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim Pharma, Celgene, Centocor, Covagen, Forward Pharma, Fresenius Medical Care, Galapagos, GlaxoSmith-Kline, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Eli Lilly and Company, Medac, Merck Sharp & Dohme Corp., Novartis, Miltenyi Biotec, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, Valeant, and XenoPort. Dr Feldman reports that a third party that was supported by Eli Lilly and Company assisted with manuscript preparation. He is a consultant for Eli Lilly and Company, Novartis, Janssen, and Celgene. He received Honoria from Eli Lilly and Company, AbbVie, Celgene, Janssen, and Novartis. He reports grant support or pending grant support from Eli Lilly and Company, Novartis, Janssen, AbbVie, and Celgene (support paid to institution). Dr. Strand reports consulting fees from Eli Lilly and Company, AbbVie, Amgen, Anthera, AstraZeneca, BMS, Boehringer Ingelheim, Celltrion, EMD Serono, Genentech/Roche, GSK, Janssen, Novartis, Pfizer, Regeneron, Sanofi, UCB, outside the submitted work. Dr Paul has received grant support from ADERMI. He reports honoria and reimbursed travel expenses from AbbVie, Boerhinger, Celgene, Eli Lilly and Company, Janssen Cilag, Almirall, Regeneron, Sanofi, Novartis, Pfizer, LEO Pharma, and Pierre Fabre. Dr Gordon received research support from AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Novartis, and Jannsen. He has received consulting fees or honoraria from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dermira, Novartis, Janssen, and Eli Lilly and Company. Dr Richard Warren has actively consulted for AbbVie, Almiral, Amgen, Boehringer Ingelheim, Celgene, Pfizer, Novartis, Janssen, LEO Pharma, XenPort, Eli Lilly and Company, and UCB. Dr Warren's institution has grants/grants pending from LEO Pharma, AbbVie, Novartis, and Eli Lilly and Company. Dr Warren has received an honorarium from AbbVie, Almiral, Amgen, Boehringer Ingelheim, Celgene, Pfizer, Novartis, Janssen, LEO Pharma, XenPort, Eli Lilly and Company, and UCB. Dr Toth has served as an investigator or speaker for Abbvie, Amgen, BMS, Boehringer Ingelheim, Celgene, Elli Lilly and Company, Incyte, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron, Sanofi-Genzyme, and UCB. M. Augustin has served as a consultant and/or paid speaker for and/or has received research grants and/or honoraries for consulting and/or scientific lectures for and/or received travel expense reimbursement and/or participated in clinical trials sponsored by companies that manufacture drugs used for treatment of psoriasis including AbbVie, Almirall, Amgen, Biogen (Biogen Idec), Boehringer Ingelheim, Celgene, Centocor, Eli Lilly and Company, Janssen-Cilag, LEO Pharma, Medac, MSD (formerly Essex, Schering-Plough), Mundipharma, Novartis, Pfizer, (formerly Wyeth), Pohl Boskamp, Sandoz, and XenoPort.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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