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 ORIGINAL ARTICLE

Effect of Ixekizumab on Patient Reported Outcomes and Quality of Life in Patients With Moderate-to-Severe Plaque Psoriasis: 5-Year Results from the UNCOVER-1 and -2 Studies

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ABSTRACT

Objective: We describe patient-reported outcomes and quality of life through 5 years of treatment in patients with moderate-to-severe plaque psoriasis in the UNCOVER-1 and -2 studies.

Methods: This analysis included patients who were randomized to ixekizumab every 2 weeks then received ixekizumab every 4 weeks during the maintenance period, and who achieved static physician global assessment (0,1) at week 12, completed week 60, and entered the long-term extension period (weeks 60–264). Outcomes measures included responses in itch numeric rating scale (NRS), skin pain visual analog scale (VAS), and dermatology life quality index (DLQI) (0,1), and mean change from baseline in short form health survey (SF-36) mental (MCS) and physical component summaries (PCS), psoriasis skin appearance bothersomeness (PSAB), and work productivity activity impairment (WPAI).

Results: At week 264 in UNCOVER-1 and -2, the observed itch NRS ≥4 responses were 82.4% and 93.1%, respectively, the itch NRS=0 responses were 51.7% and 58.5%, respectively, the skin pain VAS=0 responses were 59.3% and 63.1%, respectively, and the DLQI (0,1) responses were 75.0% and 88.1%, respectively. The observed mean changes from baseline at week 264 in UNCOVER-1 and UNCOVER-2 were 3.4 and 6.5, respectively, for SF-36 MCS, 4.4 and 4.8, respectively, for SF-36 PCS, and -21.3 and -22.0, respectively, for PSAB. WPAI psoriasis item scores improved from baseline in both UNCOVER-1 and -2.

Conclusion: Ixekizumab provided clinically meaningful and sustained improvements in itch, skin pain, DLQI, PSAB, SF-36 PCS, SF-36 MCS, and WPAI through 5 years of treatment in patients with moderate-to-severe plaque psoriasis.

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INTRODUCTION

Psoriasis is a chronic, systemic, immune-mediated disease recognized by its cutaneous manifestation of well-demarcated, erythematous, scaly plaques. These skin lesions, often associated with significant pruritus, stinging, and burning, cause substantial psychosocial impairment and overall decreased quality of life (QoL).[1]

Patient-reported outcome (PRO) measures provide patients and clinicians with a tool to assess physical and psychological functioning, facilitate treatment decision making, and identify coping strategies. When used effectively, individual and aggregated PRO data can inform and evaluate treatment, aid the holistic management of patients, and improve communication between patients and clinicians.[2,3] The motivation to completely

clear psoriasis plaques from the skin of patients has grown in response to accumulating evidence that residual skin disease can affect patients' health-related QoL.[4,5]

In one study, clinicians reported that itch, flaking, and pain were the primary symptoms of psoriasis.[6] In the same study, patients rated itch as the most important, most severe, and most troublesome psoriasis symptom.[6] Furthermore, patients reported that itch negatively impacted their daily activities, concentration, sleep, and absenteeism and presenteeism, as well as emotions such as anxiety and embarrassment.[6] It is particularly important for studies to assess the impact of psoriasis treatments on absenteeism and presenteeism because work productivity loss increases progressively with increasing dermatology life quality index (DLQI) scores and body surface area affected, and its associated costs contribute to the economic burden of psoriasis.[7]

Ixekizumab is a high-affinity monoclonal antibody that selectively targets interleukin-17A (IL-17A). IL-17A is a member of the family of proinflammatory IL-17 cytokines and plays an important role in the pathogenesis of psoriasis and other immune-related diseases.[8] Two randomized, double-blinded, multicenter, phase 3 clinical studies of ixekizumab (UNCOVER-1 and UNCOVER-2) have shown greater efficacy than placebo and etanercept through 60 weeks of treatment in patients with moderate-to-severe plaque psoriasis.[9,10] As psoriasis is a chronic disease with a cumulative burden if not treated, treatment should be efficacious and well tolerated long-term, particularly as drug exposure increases over time. The objective of this analysis was to report PROs for UNCOVER-1 and UNCOVER-2 in patients with moderate-to-severe plaque psoriasis through 5 years of treatment with ixekizumab.

MATERIALS AND METHODS

Study Design

The present report includes side-by-side data from the UNCOVER-1 (NCT01474512) and UNCOVER-2 (NCT01597245) studies.The study designs for these studies have been described previously.[9,10] An active drug control (etanercept) was also included in UNCOVER-2. Both the studies included a blinded induction period from weeks 0–12. Patients in UNCOVER-1 (N=1296) were randomized in a 1:1:1 ratio to receive ixekizumab 80 mg every 2 weeks (Q2W), ixekizumab 80 mg every 4 weeks (Q4W), or placebo. In UNCOVER-2, patients (N=1224) were randomly assigned in a 2:2:2:1 ratio to receive ixekizumab Q2W, ixekizumab Q4W, etanercept 50 mg twice weekly, or placebo. In both studies, patients treated with ixekizumab received an initial loading dose of 160 mg. During the maintenance period (weeks 12–60) in both studies, static physician global assessment (sPGA) <2 responders were re-randomized in the same ratio to receive any study treatment, and non-responders were assigned to ixekizumab Q4W in both UNCOVER-1 and -2. Here, we report the efficacy results for patients who responded at week 12 (sPGA 0,1), were initially randomized to ixekizumab Q2W, who received ixekizumab Q4W during the maintenance period, completed week 60, and continued into the long-term extension periods (weeks 60–264) of UNCOVER-1 and -2. UNCOVER-1 was conducted in Australia, Canada, Denmark, Germany, Hungary, Italy, Japan, Poland, Romania, the United Kingdom, and the United States. UNCOVER-2 was conducted in Australia, Austria, Canada, the Czech Republic, France, Germany, the Netherlands, Poland, Romania, Spain, the United Kingdom, and the United States.

Both studies included in this analysis were compliant with ethical guidelines including the Declaration of Helsinki and other relevant laws and regulations. Each site's ethical review committee or institutional review board approved the study protocols and all patients provided written informed consent.

Study Population

Detailed eligibility criteria have been published.[9,11] Briefly, eligible patients were aged 18 years or older and had a diagnosis of chronic plaque psoriasis at least 6 months before baseline (randomization), involvement of 10% or greater body surface area at both screening and baseline visits, at least a moderate clinical severity as measured by sPGA ≥3, a psoriasis area and severity index (PASI) score of ≥12, and were candidates for phototherapy, systemic therapy, or both. Prior therapy with biologics was permitted except for prior use of etanercept, which was an exclusion criterion in UNCOVER-2.

Assessments

Efficacy outcome measurements included the proportion of patients achieving improvement in itch numeric rating scale ≥4-point improvement from baseline (itch NRS ≥4), itch NRS 0 for patients with baseline itch NRS >0, skin pain visual analog (VAS) scale 0, DLQI 0,1, and mean change from baseline in the psoriasis skin appearance bothersomeness (PSAB) measure. The PSAB measure asks patients to indicate how bothered they are by the 3 dimensions of skin appearance (redness or discoloration, areas or thickness, and scaling or flakiness) due to psoriasis skin plaques included in the physician-assessed PASI.[12] Each dimension is rated on an 11-point NRS ranging from 0 (not bothered at all) to 10 (extremely bothered). The 3-item scores were summed for a total score ranging from 0 to 30, with higher scores indicating more bothersomeness due to skin appearance. Additionally, mean change from baseline in the short form health survey (SF-36) physical (PCS) or mental component summaries (MCS) along with individual domains were measured, as well as work productivity activity impairment (WPAI) psoriasis item scores. The clinical meaningfulness of improvements in WPAI psoriasis item scores for work productivity loss and work activity impairment was assessed by determining the minimal clinically importance difference (MCID), using a cutoff of 20% as previously described.[13]

Statistical Methods

Change from baseline analyses for the continuous variables SF-36 MCS, SF-36 PCS, PSAB, WPAI, and MCID were conducted using a modified baseline observation carried forward (mBOCF) method. Change from baseline analyses for the categorical variables itch NRS, skin pain VAS, and DLQI were conducted using a modified non-responder imputation (mNRI) method. Missing data were imputed using a mBOCF method for continuous variables and a mNRI method for categorical measures.

RESULTS

Patients

An overview of patient demographics and baseline disease characteristics for the long-term extension populations in UNCOVER-1 and UNCOVER-2 are presented in Table 1. The mean age of patients was 44.9 years and 41.9 years in UNCOVER-1 and UNCOVER-2, respectively. In both studies, approximately two thirds of the patients were male. The mean itch scores were 6.7 and 6.6, the mean skin pain VAS scores were 42.1 and 45.9, and the mean DLQI total scores were 12.2 and 12.1 in UNCOVER-1 and UNCOVER-2, respectively.

The proportion of patients that discontinued treatment over the long-term extension portion of the studies (weeks 60–264) was 20% in UNCOVER-1 and 13% in UNCOVER-2. The proportion who discontinued due to a lack of efficacy was 3% and 0% in UNCOVER-1 and UNCOVER-2, respectively. The proportion who discontinued due to an adverse event (AE) was 4% and 3% in UNCOVER-1 and UNCOVER-2, respectively. No discontinuations due to adverse events were related to study drug in either UNCOVER-1 or UNCOVER-2. There were no deaths during the long term extension portion of either study.

TABLE 1.

Baseline Demographics and Disease Characteristics		
	UNCOVER-1	UNCOVER-2
	IXE Q2W/ IXE Q4W (N=110)	IXE Q2W/ IXE Q4W (N=96)
Age, years (SD)	44.9 (13.0)	41.9 (12.9)
Male	75 (68.2)	65 (67.7)
Weight, kg (SD)	94.1 (23.0)	87.9 (18.5)
Age of patient at psoriasis onset, years (SD)	25.8 (12.3)	24.9 (12.7)
Itch NRS score	6.7 (2.4)	6.6 (2.6)
PASI score	19.6 (7.6)	19.1 (5.9)
Percentage body surface area affected	29.2 (18.5)	24.8 (12.6)
Skin pain VAS score	42.1 (30.9)	45.9 (30.0)
DLQI total score	12.2 (6.9)	12.1 (6.9)
PSAB score	23.5 (7.1)	23.6 (6.8)
SF-36 MCS	48.9 (11.4)	48.0 (11.0)
SF-36 PCS	47.5 (8.6)	48.9 (8.9)

Data are mean (SD) unless otherwise stated.
Abbreviations: DLQI, dermatology life quality index; IXE Q2W, ixekizumab every 2 weeks; IXE Q4W, ixekizumab every 4 weeks; MCS, mental component summary; NRS, numeric rating scale; PASI, psoriasis area and severity index; PCS, physical component summary; PSAB, psoriasis skin appearance bothersomeness; SD, standard deviation; SF-36, medical outcomes survey short form-36; VAS, visual analog scale.

Patient-Reported Outcomes at 264 Weeks of Treatment

In patients with baseline itch NRS ≥4 in UNCOVER-1 and -2, the proportion with observed itch NRS ≥4 responses at 60 weeks (87.4% and 91.4%, respectively) was sustained through 264 weeks (82.4% and 93.1%, respectively) (Figure 1A and 1B). In patients with baseline itch NRS >0 in UNCOVER-1 and -2, the proportion with observed itch NRS=0 responses at 60 weeks (56.0% and 55.9%, respectively) was sustained through 264 weeks (51.7% and 58.5%, respectively) (Figure 1C and 1D). In patients with baseline skin pain VAS >0 in UNCOVER-1 and -2, the proportion with observed skin pain VAS=0 responses at 60 weeks (64.2% and 53.7%, respectively) were sustained through 264 weeks (59.3% and 63.1%, respectively) (Figure 2A and 1B). The proportion of patients in UNCOVER-1 and -2 with DLQI (0,1) responses at 60 weeks (80.0% and 83.3%, respectively) was sustained through 264 weeks (75.0% and 88.1%, respectively) (Figure 3A and 3B). For itch, skin pain and DLQI, the observed responses were similar to those determined by mNRI analyses (Figures 1, 2, and 3).

In UNCOVER-1 and -2, the observed mean changes from baseline in SF-36 MCS at 60 weeks (4.4 and 6.5, respectively) were sustained through 264 weeks (3.4 and 6.5, respectively) (Figure 4A and 4B). Likewise, the observed mean changes in SF-36 PCS in UNCOVER-1 and -2 at 60 weeks (4.5 and 4.0, respectively) were sustained through 264 weeks (4.4 and 4.8, respectively) (Figures 4C and 4D). The observed mean changes in PSAB in UNCOVER-1 and -2 at 60 weeks (-21.5 and -22.1, respectively) were also sustained through 264 weeks (-21.3 and -22.0, respectively) (Figure 5A and 5B). The observed changes from baseline in SF-36, SF-PCS, and PSAB were consistent with those determined by mBOCF analyses (Figures 4 and 5).

The baseline and mean changes from baseline in WPAI questionnaire psoriasis item scores at week 264 in UNCOVER-1 and UNCOVER-2 are presented in Table 2. The changes from baseline in scores for work absenteeism, presenteeism, productivity loss, and activity impairment were similar for UNCOVER-1 and UNCOVER-2 based on mBOCF analyses (Table 2). The proportion of patients who achieved MCID of 20% for work productivity loss and work activity impairment at week 264 were also similar in UNCOVER-1 and UNCOVER-2 (Table 2).

FIGURE 1. Proportion of patients with itch responses with ixekizumab through 264 weeks of treatment in UNCOVER-1 (A and C) and UNCOVER-2 (B and D). Patients with itch NRS >0 at baseline were assessed for itch NRS=0, and patients with itch NRS ≥4 at baseline were assessed for itch NRS ≥4-point reduction. Ns for the observed data are listed beneath each graph. Abbreviations: mNRI, modified non-responder imputation; NRS, numeric rating scale.

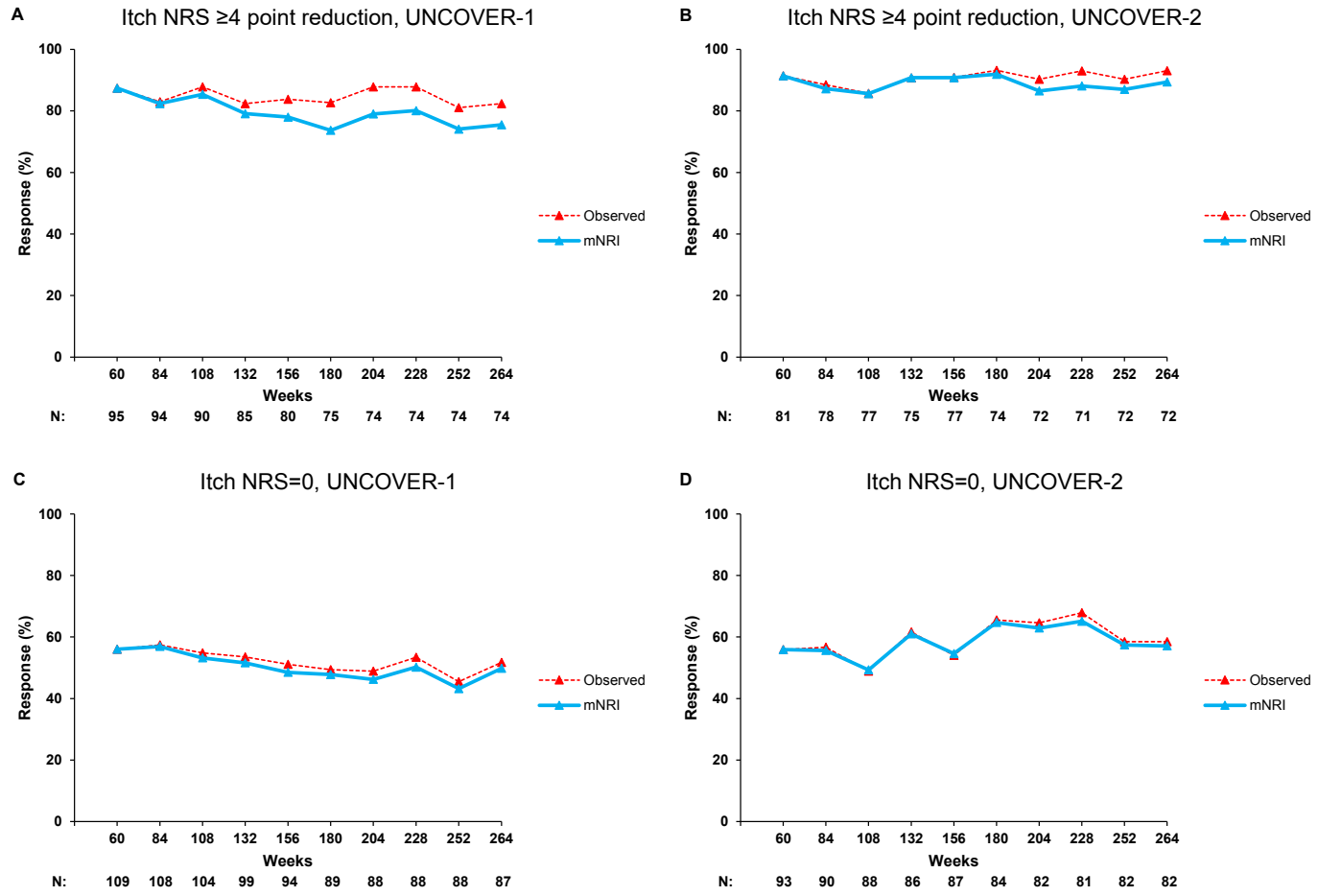

FIGURE 2. Proportion of patients with skin pain responses with ixekizumab through 264 weeks of treatment in UNCOVER-1 (A) and UNCOVER-2 (B). Patients with skin pain VAS >0 at baseline were assessed for skin pain VAS=0. Ns for the observed data are listed beneath each graph. Abbreviations: mNRI, modified non-responder imputation; VAS, visual analog scale.

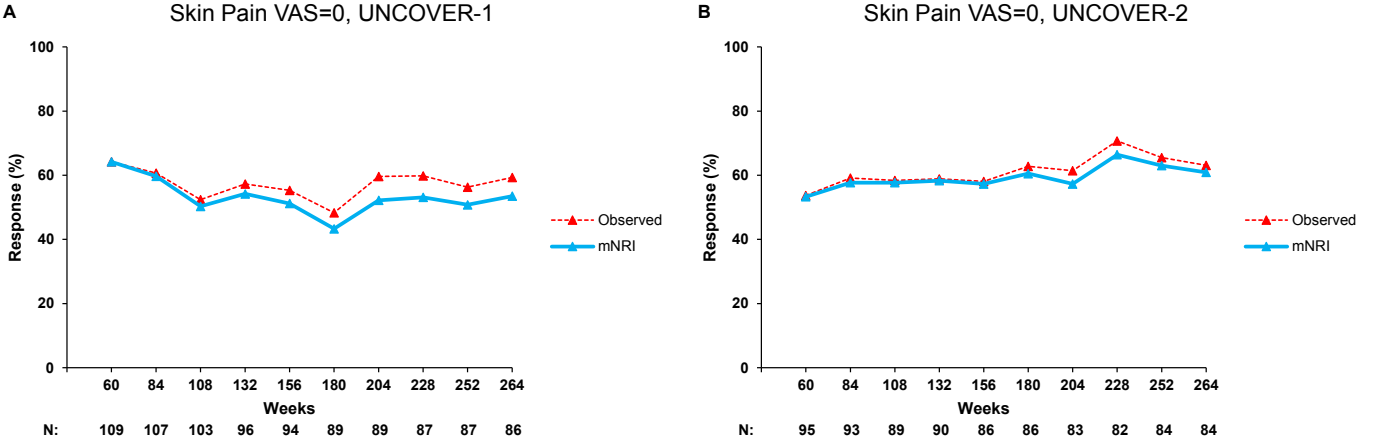

FIGURE 3. Proportion of patients with DLQI responses with ixekizumab through 264 weeks of treatment in UNCOVER-1 (A) and UNCOVER-2 (B). Ns for the observed data are listed beneath each graph. Abbreviations: DLQI, dermatology life quality index; mNRI, modified non-responder imputation.

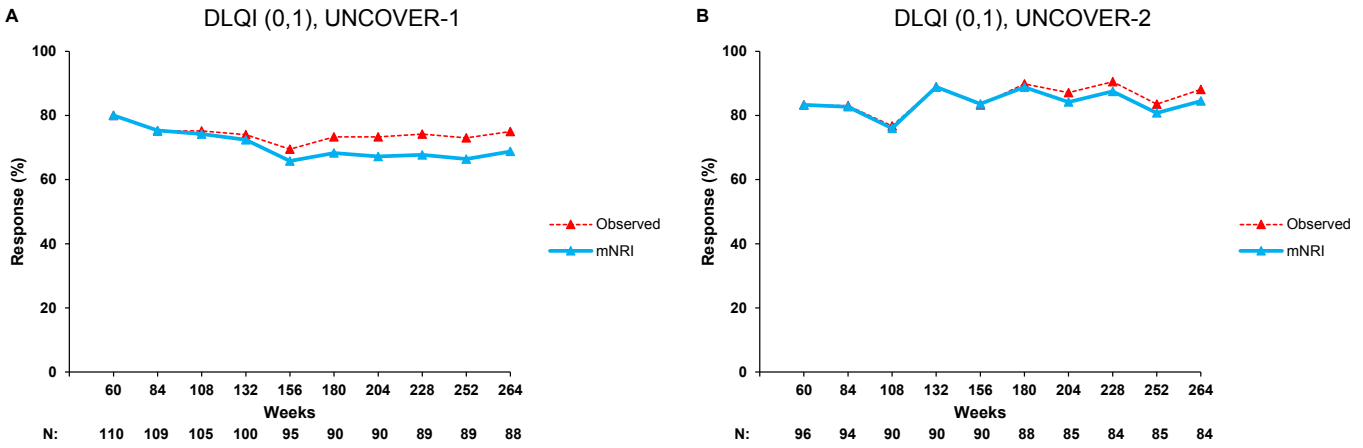

FIGURE 4. Proportion of patients with SF-36 MCS and PCS responses with ixekizumab through 264 weeks of treatment in UNCOVER-1 (A and C) and UNCOVER-2 (B and D). Ns for the observed data are listed beneath each graph. Abbreviations: mBOCF, modified baseline observation carried forward; MCS, mental component summary; PCS, physical component summary; SF-36, medical outcomes survey short form-36.

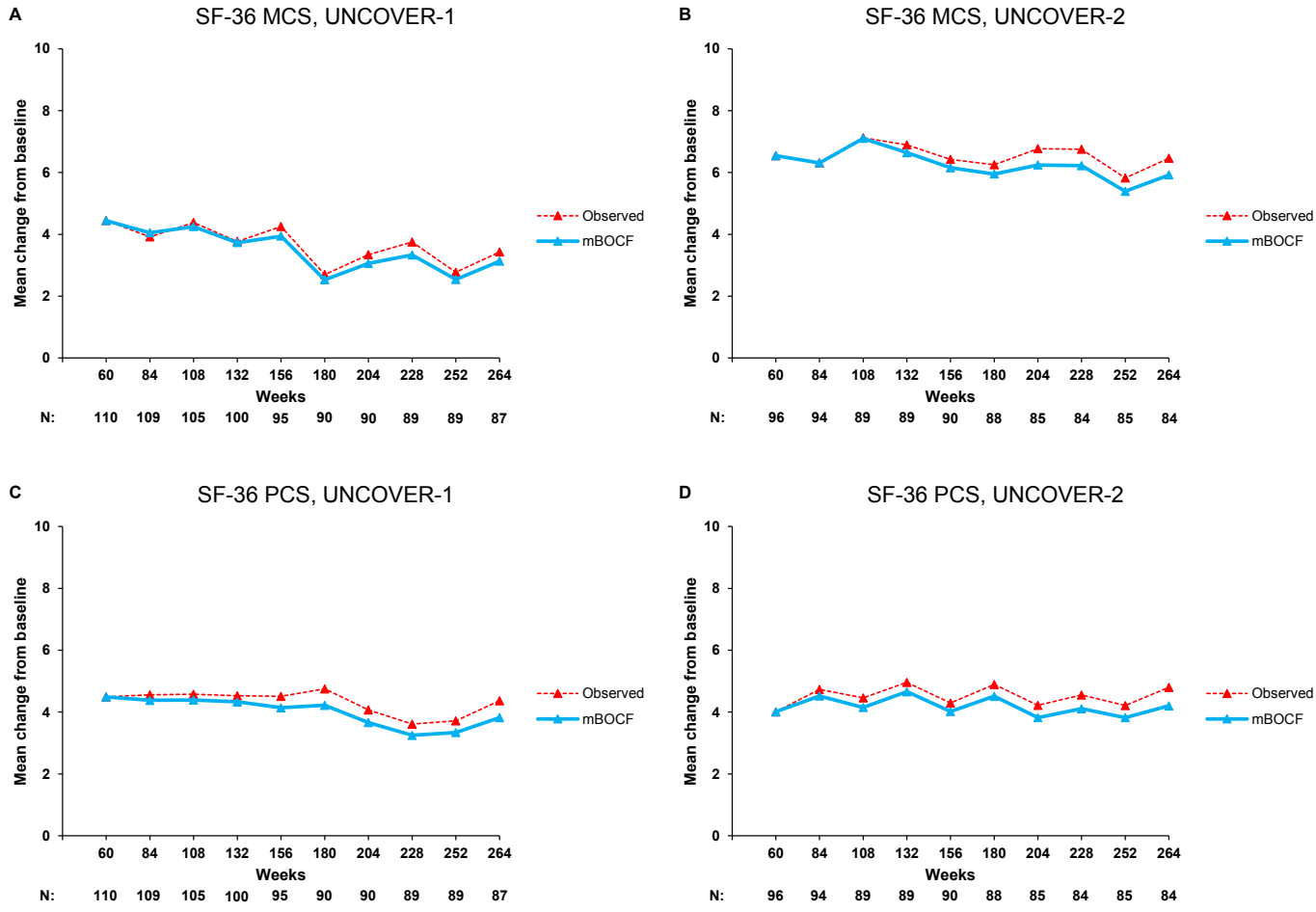

FIGURE 5. Proportion of patients with PSAB responses with ixekizumab through 264 weeks of treatment in UNCOVER-1 (A) and UNCOVER-2 (B). Ns for the observed data are listed beneath each graph. Abbreviations: mBOCF, modified baseline observation carried forward; PSAB, psoriasis skin appearance bothersomeness.

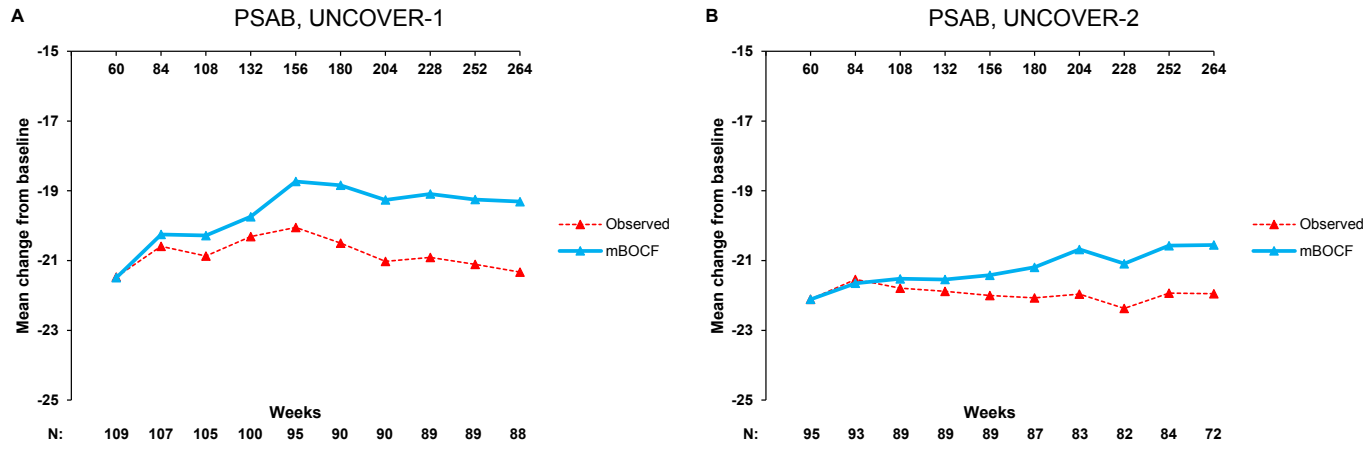

FIGURE 6. Mean change from baseline in WPAI questionnaire psoriasis item scores with ixekizumab through 264 weeks of treatment in UNCOVER-1 (A) and UNCOVER-2 (B). Abbreviations: mBOCF, modified baseline observation carried forward; WPAI, work productivity activity impairment.

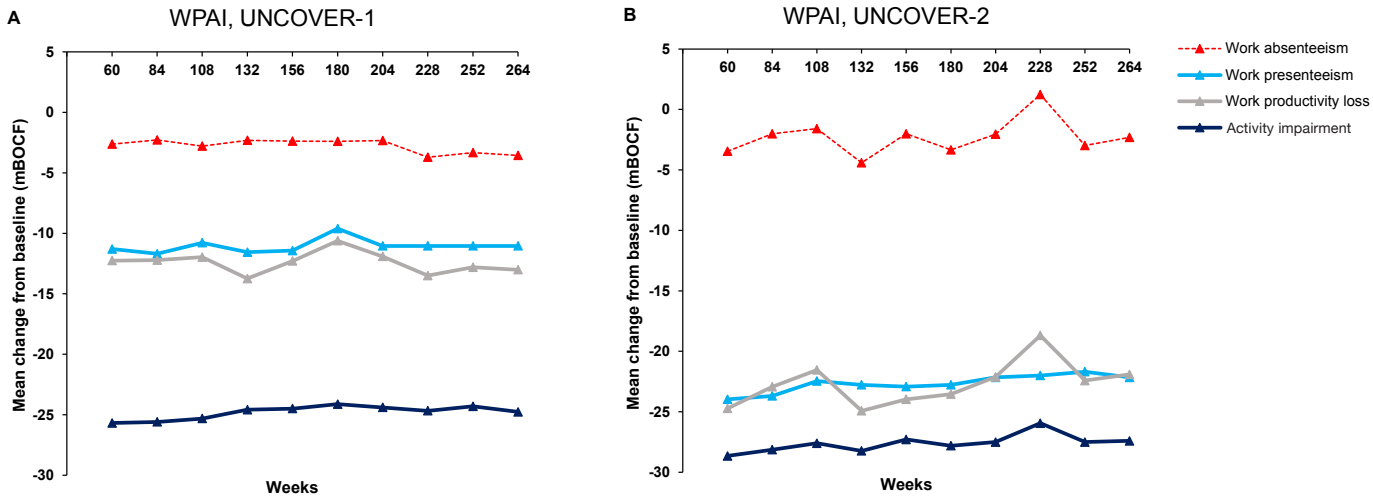

TABLE 2.

Work Productivity and Activity Impairment With Ixekizumab Through 264 Weeks of Treatment

	Baseline Mean (SD)		Change from Baseline to Week 264 Mean (SD)		Proportion of Patients Achieving MCID of 20% at Week 264 Mean % (95% CI)	
	UNCOVER-1	UNCOVER-2	UNCOVER-1	UNCOVER-2	UNCOVER-1	UNCOVER-2
	IXE Q2W/ IXE Q4W (N=110)	IXE Q2W/ IXE Q4W (N=96)	IXE Q2W/ IXE Q4W (N=110)	IXE Q2W/ IXE Q4W (N=96)	IXE Q2W/ IXE Q4W (N=110)	IXE Q2W/ IXE Q4W (N=96)
Work absenteeism	4.6 (18.2)	4.4 (14.1)	-3.6 (19.4)	-2.3 (12.8)	NA	NA
Work presenteeism	15.2 (20.2)	24.3 (24.6)	-11.0 (19.4)	-22.2 (24.1)	NA	NA
Work productivity loss	18.1 (23.0)	26.2 (26.8)	-13.0 (24.0)	-21.9 (24.3)	71% (58%–84%)	68% (54%–82%)
Activity impairment	30.0 (28.4)	30.0 (29.0)	-24.8 (27.7)	-27.4 (28.7)	77% (68%–86%)	88% (81%–96%)

Data were analyzed by modified baseline observation carried forward method.
Abbreviations: CI, confidence intervals; IXE Q2W, ixekizumab every 2 weeks; IXE Q4W, ixekizumab every 4 weeks; MCID, minimal clinically important difference; NA, not applicable.

DISCUSSION

This study shows that ixekizumab treatment resulted in improvements in the PROs of itch and skin pain, health-related QoL, bothersomeness of skin disease, and work productivity in patients with moderate-to-severe plaque psoriasis that were sustained from 60 to 264 weeks of treatment in the UNCOVER-1 and -2 studies. Although these studies were not designed to compare the ixekizumab study arms across the 2 studies, they appeared to result in similar health outcome results at week 264. The baseline characteristics and disease characteristics of the long-term extension population were similar to that of overall population previously reported.[9,11] The patient baseline mean PASI score and skin pain VAS were indicative of high disease severity at study enrollment, and the SF-36 MCS and SF-36 PCS suggested psoriasis was having a moderate impact on patients' health-related QoL.

Ixekizumab treatment also resulted in improved DLQI and SF-36 measures at 264 weeks in both the UNCOVER-1 and -2 studies. Improvement related to skin symptoms was demonstrated by PROs as measured by the itch NRS and DLQI scores. Ixekizumab treatment resulted in improved DLQI scores, with over three quarters of patients reporting that their psoriasis-associated skin symptoms had no effect on their lives (DLQI 0,1). These findings have substantial implications for patients with moderate-to-severe psoriasis since improvements in the severity of skin disease have been shown to be associated with enhanced health-related QoL.[14-16]

The personal and economic burden of psoriasis is considerable. Impaired physical function and work difficulties are associated with psoriatic skin disease, whereas severity of the skin disease is associated with poor mental functioning.[17] A nationwide, cross sectional study of patients in the US with moderate to-severe psoriasis showed that biologic therapy was associated with significantly greater increases in measures of physical and mental functioning compared with oral therapy.[18] In the UNCOVER-1, -2, and -3 studies, patients treated with ixekizumab reported statistically significant improvements in mean SF-36 PCS and SF-36 at 12 weeks that persisted through week 60.[19] Here, we build on these findings and show that patients treated with ixekizumab reported improvements in skin disease, with improvements in health-related QoL measured by the DLQI and SF-36 as well as the individual domain scores, that were maintained through 264 weeks of treatment.

There are also indirect costs for people with psoriasis, including disability (short- and long-term) and lost productivity through an inability to undertake paid and unpaid work.[17] In our study, patients treated with ixekizumab reported sustained work productivity measured by reduced presenteeism (reduced/impaired effectiveness at work), work productivity loss (overall work impairment associated with absenteeism and presenteeism), and activity impairment (activities performed outside of work) at week 264.

The main limitation of this study was that the active comparator, etanercept, was only evaluated up to 12 weeks and the long-term treatment period was open-label. The strength of this study is that the inclusion criteria reflect most patients affected with moderate-to-severe plaque psoriasis, making the results generalizable to a large population. In addition, the efficacy results were validated through replication in 2 independent studies.

CONCLUSION

Ixekizumab provided clinically meaningful and sustained improvements in itch, skin pain, QoL, PSAB, SF-36 MCS, and SF-36 PCS through 5 years of continuous treatment in patients with moderate-to-severe plaque psoriasis.

DISCLOSURES

Melinda Gooderham has been an investigator, speaker, and/or advisor for AbbVie, Amgen, Akros, Arcutis, Boehringer Ingelheim, BMS, Celgene, Dermira, Dermvant, Eli Lilly and Company, Galderma, GlaxoSmithKline, Incyte, Janssen, Kyowa Kirin, LEO Pharma, MedImmune, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Sun Pharma, UCB, and Bausch/Valeant. Boni Elewski served as a consultant receiving honoraria for Arcutis, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene Corporation, Eli Lilly and Company, LEO Pharma, Menlo, Novartis, Pfizer, Sun Pharma, UCB, Valeant, and Verrica, and received clinical research support funding to her university from AbbVie, AnaptysBio, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, Incyte, LEO Pharma, Menlo Therapeutics, Merck, Novartis, Pfizer, Regeneron, Sun Pharma, Valeant, and Vanda. Matthias Augustin has served as a consultant or paid speaker for AbbVie, Almirall, Amgen, Beiersdorf, Biogen, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly and Company, Galderma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Medac, Merck, Merck Sharp & Dohme, Novartis, Pierre-Fabre, Pfizer, Sanofi, Trevi, UCB, and XenoPort. Lars Iversen has been an investigator, paid speaker, consultant, and advisory board member for AbbVie, Eli Lilly and Company, Janssen-Cilag, LEO Pharma, Merck Sharp & Dohme, Novartis, and Pfizer; has been a paid speaker, consultant, and advisory board member for Almirall; has been an investigator for Amgen; has been an advisory board member for UCB; and has received research and educational grants from AbbVie, LEO Pharma, Merck Sharp & Dohme, Novartis, and Pfizer. Hideshi Torii has received consulting fees or honoraria from AbbVie, Celgene, Eli Lilly and Company, Janssen, Kyowa Hakko Kirin, Mitsubishi Tanabe Pharma, and Novartis. Russel Burge, Kyoungah See, Gaia Gallo, and William J Eastman are full time employees of, and own stock in, Eli Lilly and Company. Missy McKean-Matthews is a full time employee of Syneos Health.

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