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 ORIGINAL ARTICLE

Sustained High Efficacy and Favorable Safety Over Five Years in Patients With Burdensome Psoriasis (UNCOVER-1/UNCOVER-2)

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ABSTRACT

Background: Long-term efficacy, safety, and quality of life with ixekizumab (IXE) through 5 years in UNCOVER-1 and UNCOVER-2 patients with baseline scalp, nail, or palmoplantar psoriasis were assessed.

Methods: Patients included in this intent-to-treat subanalysis had baseline involvement in at least one of the three anatomic areas (scalp, fingernail, or palmoplantar locations) and 1) received IXE through week 60, with a 160-mg starting dose 80 mg Q2W through week 12 and Q4W thereafter, 2) achieved a static Physician's Global Assessment score of 0 or 1 at week 12, and 3) completed week 60 and continued treatment with IXE Q4W or were escalated to Q2W during the long-term extension. Efficacy outcomes (e.g., percent improvement in Psoriasis Scalp Severity Index [PSSI], Nail Psoriasis Severity Index [NAPSI], Palmoplantar Psoriasis Area and Severity [PPASI], and Dermatology Life Quality Index [DLQI]) were summarized by descriptive statistics through week 264.

Results: Patients rapidly achieved and sustained improvements in scalp, nail, and palmoplantar psoriasis for up to 5 years with IXE. Patients achieved complete clearance at year 5: observed (scalp, 82%; nail, 73%; palmoplantar, 96%) and mNRI (scalp, 77%; nail, 67%; palmoplantar, 85%). Up to 80% of patients reported DLQI 0,1 responses at week 12, which were sustained through week 264. No increases in the number of annual treatment-emergent adverse events were observed from years 1–5.

Conclusion: Patients receiving IXE for 5 years sustained high rates of improvement in scalp, nail, and palmoplantar psoriasis, with a long-term quality of life benefit with no unexpected safety signals.

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INTRODUCTION

Scalp, nail, and palmoplantar psoriasis are highly prevalent among psoriasis patients and often lead to greater impairment of patients' quality of life (QoL).[1] Up to half of patients with psoriasis have burdensome psoriasis affecting the scalp (50%), nail (50%), and palmoplantar areas (17%).[2-4] With non-biologic treatment options, complete clearance is infrequent, efficacy decreases with time, and systemic side effects limit their use.[5] Currently, the joint American Academy of Dermatology (AAD)-National Psoriasis Foundation (NPF) guidelines recommend prescribing anti-psoriatic biologic therapies for adults with scalp, nail, and palmoplantar psoriasis.[6]

Interleukin (IL)-17A inhibitors have demonstrated significant improvements in patients with burdensome psoriasis up to 60 weeks and up to 80 weeks for ixekizumab (IXE)[3,7,8] and secukinumab,[9-12] respectively. While longer-term sustained response through 5 years in UNCOVER-3 has been reported,[13] here we present longer-term data from UNCOVER-1 and UNCOVER-2. Additionally, improvements in health-related QoL up to 12 weeks have been reported with IXE in patients with burdensome psoriasis.[14] In this integrated analysis, the long-term efficacy and safety, as well as the impact of IXE on QoL, through 5 years in patients with baseline scalp, nail, or palmoplantar psoriasis were assessed.

MATERIALS AND METHODS

Study Design

Data from patients with baseline burdensome psoriasis from UNCOVER-1 (NCT01474512, N=1296) and UNCOVER-2 (NCT01597245, N=1224) trials were assessed. The study designs for these trials have been reported previously).[15]

Patients/Treatment

Patients who completed week 60 were eligible to enter the long-term extension period if the investigator concluded that the patient had maintained efficacy response with adequate overall safety. Patients could escalate to every 2-week (Q2W) dosing per investigator opinion. Patients included in this intent-to-treat subanalysis had baseline involvement in at least one of the three anatomic areas (scalp, fingernail, or palmoplantar locations) and 1) received IXE through week 60, with a 160-mg starting dose 80 mg Q2W through week 12 and every 4 weeks (Q4W) thereafter, 2) achieved a static Physician's Global Assessment score of 0 or 1 at week 12, and 3) completed week 60 and continued treatment with IXE Q4W or were escalated to Q2W during the long-term extension.[15]

Outcomes/Evaluation Methods

Efficacy outcomes in UNCOVER-1 and UNCOVER-2 were represented as percent improvement for the following: 1) 90%/100% improvement in Psoriasis Scalp and Severity Index (PSSI 90/100), 2) Nail Psoriasis Severity Index of zero (NAPSI 0), and 3) 90%/100% improvement in Palmoplantar Psoriasis Area and Severity Index (PPASI 90/100). Improvement in Dermatology Life Quality Index (DLQI) was measured from weeks 60 through 264.

Statistical Methods

Combined long-term data regarding efficacy, health outcomes, and safety through 5 years were analyzed with SAS Version 9.4 (SAS Institute Inc., Cary, NC). Data were recorded at baseline, weeks 1, 2, 4, Q4W through week 60, and every 12 weeks, thereafter, through week 264. The continuous efficacy analyses (PSSI, NAPSI total score, and PPASI) were performed based on patients with the corresponding baseline involvement (e.g. PSSI, PPASI, or NAPSI for patients with baseline scalp, palmoplantar, or fingernail involvement, respectively) and were summarized as the change and percent improvement from baseline using descriptive statistics for observed data and last observation carried forward (LOCF) for missing data. Response rates for the categorical measures (PSSI 90/100, NAPSI 0, PPASI 90/100) were summarized as the percentages of responders at each time point for both observed data and modified non-responder imputation (mNRI) for missing data. Percentages of patients with DLQI total scores of (0,1) who had baseline involvement in each of the three areas (observed and mNRI) were calculated. Categorical safety measures were summarized as percentage rates for each year, from year 1 through year 5, for patients in each of the three burdensome areas.

RESULTS

Demographics

Patient demographics and clinical characteristics in each of the subcategories are listed in Table 1. In all categories, there were more males than females. A high percentage of patients with nail psoriasis also had concomitant scalp psoriasis (93.5%) and palmoplantar (40.7%) psoriasis. About 87.7% of patients with palmoplantar psoriasis also had nail psoriasis. Otherwise, the baseline demographics and clinical characteristics were similar between subcategories.

TABLE 1.

Demographics and Clinical Characteristics in Patients with Scalp, Nail, and Palmoplantar Psoriasis at Baseline (UNCOVER-1 and UNCOVER-2)

Parameter	Scalp (N=189)	Nail (N=123)	Palmoplantar (N=57)
Age, years, mean (SD)	43.4 (12.8)	44.8 (12.2)	48.2 (11.4)
Gender, n (%)			
Male	126 (66.7)	90 (73.2)	46 (80.7)
BMI, kg/m^2, mean (SD)	30.5 (7.1)	31.1 (7.0)	31.2 (7.1)
Duration of psoriasis symptoms, years, mean (SD)	18.4 (12.1)	19.3 (11.8)	21.6 (12.0)
PASI score, mean (SD)	19.5 (7.0)	20.0 (7.9)	22.0 (9.2)
Prior biologic use, n (%)	63 (33.3)	46 (37.4)	24 (42.1)
Scalp psoriasis, n (%)	189 (100)	115 (93.5)	55 (96.5)
PSSI score, mean (SD)	20.7 (14.3)	20.4 (15.0)	20.0 (15.3)
Palmoplantar psoriasis, n (%)	55 (29.1)	50 (40.7)	57 (100)
PPASI score, mean (SD)	5.5 (7.4)	5.1 (5.9)	5.4 (7.3)
Nail psoriasis, n (%)	115 (60.8)	123 (100)	50 (87.7)
NAPSI score, mean (SD)	22.4 (16.2)	22.1 (16.1)	24.4 (16.8)
PsA, n (%)	45 (23.8)	34 (27.6)	20 (35.1)
DLQI score, mean (SD)	12.6 (6.8)	12.2 (7.0)	12.5 (5.6)

Abbreviations: BMI=body mass index; DLQI=Dermatology Life Quality Index; N=number of patients; n=number of patients in a subgroup; NAPSI= Nail Psoriasis Severity Index; PPASI=Palmoplantar Psoriasis Area and Severity Index; PsA=psoriatic arthritis; PSSI=Psoriasis Scalp Severity Index; SD=standard deviation.

TABLE 2.

Overview of Adverse Events in Patients with Scalp, Nail, and Palmoplantar Psoriasis by Year (UNCOVER-1 UNCOVER-2).

	n (IR) [95% CI][a]					
Treatment-Emergent AEs	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**LTE Period**
Scalp psoriasis (n=189)	188.2 PY	179.2 PY	151.3 PY	125.3 PY	108.5 PY	552.9 PY
Any TEAE(s)	166 (88.2) [75.8, 102.7]	129 (72.0) [60.6, 85.5]	121 (80.0) [66.9, 95.6]	106 (84.6) [70.0, 102.4]	95 (87.5) [71.6, 107.0]	174 (31.5) [27.1, 36.5]
SAEs	5 (2.7) [1.1, 6.4]	17 (9.5) [5.9, 15.3]	12 (7.9) [4.5, 14.0]	11 (8.8) [4.9, 15.9]	11 (10.1) [5.6, 18.3]	38 (6.9) [5.0, 9.4]
TEAEs severity						
Mild	72 (38.3) [30.4, 48.2]	58 (32.4) [25.0, 41.9]	51 (33.7) [25.6, 44.3]	43 (34.3) [25.5, 46.3]	36 (33.2) [23.9, 46.0]	44 (8.0) [5.9, 10.7]
Moderate	81 (43.0) [34.6, 53.5]	58 (32.4) [25.0, 41.9]	57 (37.7) [29.1, 48.8]	53 (42.3) [32.3, 55.4]	43 (39.6) [29.4, 53.4]	92 (16.6) [13.6, 20.4]
Severe	13 (6.9) [4.0, 11.9]	13 (7.3) [4.2, 12.5]	13 (8.6) [5.0, 14.8]	10 (8.0) [4.3, 14.8]	16 (14.7) [9.0, 24.1]	38 (6.9) [5.0, 9.4]
Nail psoriasis (n=123)	122.4 PY	116.4 PY	99.2 PY	78.2 PY	65.5 PY	353.5 PY
Any TEAE(s)	115 (93.9) [78.3, 112.8]	87 (74.7) [60.6, 92.2]	85 (85.7) [69.3, 105.9]	74 (94.6) [75.4, 118.9]	69 (105.3) [83.2, 133.3]	114 (32.2) [26.8, 38.7]
SAEs	4 (3.3) [1.2, 8.7]	13 (11.2) [6.5, 19.2]	9 (9.1) [4.7, 17.4]	8 (10.2) [5.1, 20.5]	5 (7.6) [3.2, 18.3]	26 (7.4) [5.0, 10.8]
TEAEs severity						
Mild	44 (35.9) [26.7, 48.3]	37 (31.8) [23.0, 43.9]	30 (30.2) [21.1, 43.2]	28 (35.8) [24.7, 51.9]	28 (42.7) [29.5, 61.9]	27 (7.6) [5.2, 11.1]
Moderate	61 (49.8) [38.8, 64.0]	41 (35.2) [25.9, 47.8]	46 (46.4) [34.7, 61.9]	38 (48.6) [35.4, 66.8]	33 (50.4) [35.8, 70.8]	62 (17.5) [13.7, 22.5]
Severe	10 (8.2) [4.4, 15.2]	9 (7.7) [4.0, 14.9]	9 (9.1) [4.7, 17.4]	8 (10.2) [5.1, 20.5]	8 (12.2) [6.1, 24.4]	25 (7.1) [4.8, 10.5]
Palmoplantar psoriasis (n=57)	56.6 PY	51.9 PY	41.2 PY	30.3 PY	24.4 PY	145.6 PY
Any TEAE(s)	55 (97.1) [74.6, 126.5]	36 (69.4) [50.1, 96.2]	40 (97.1) [71.3, 132.4]	31 (102.3) [72.0, 145.5]	29 (119.1) [82.7, 171.3]	49 (33.7) [25.4, 44.5]
SAEs	2 (3.5) [0.9, 14.1]	4 (7.7) [2.9, 20.5]	2 (4.9) [1.2, 19.4]	1 (3.3) [0.5, 23.4]	4 (16.4) [6.2, 43.8]	9 (6.2) [3.2, 11.9]
TEAEs severity						
Mild	21 (37.1) [24.2, 56.9]	15 (28.9) [17.4, 48.0]	11 (26.7) [14.8, 48.2]	11 (36.3) [20.1, 65.6]	12 (49.3) [28.0, 86.8]	10 (6.9) [3.7, 12.8]
Moderate	30 (53.0) [37.0, 75.8]	16 (30.8) [18.9, 50.3]	25 (60.7) [41.0, 89.9]	18 (59.4) [37.4, 94.3]	12 (49.3) [28.0, 86.8]	29 (19.9) [13.8, 28.7]
Severe	4 (7.1) [2.7, 18.8]	5 (9.6) [4.0, 23.2]	4 (9.7) [3.6, 25.9]	2 (6.6) [1.7, 26.4]	5 (20.5) [8.5, 49.3]	10 (6.9) [3.7, 12.8]

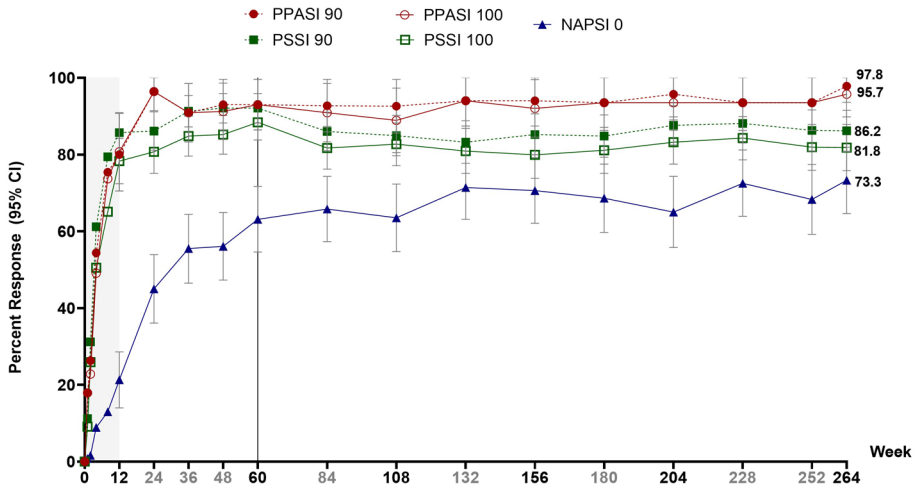
Abbreviations: AE=adverse events; CI=confidence interval; IR=incidence rate per 100 patient years; PY=patient years; SAEs=serious adverse events; TEAE=treatment-emergent adverse events; LTE=long term extension.
[a]Confidence intervals of incidence rate are from likelihood ratio test of treatment effect from the Poisson regression.
*Some patients had psoriasis in more than one region, so the same events may be listed for more than one subpopulation.

Efficacy

IXE-treated patients rapidly achieved and sustained improvements in scalp, nail, and palmoplantar psoriasis for up to 5 years (Figure 1, Figure 2). A large percentage of patients achieved complete clearance at year 5: observed (scalp, 82%; nail, 73%; palmoplantar, 96%) and mNRI (scalp, 77%; nail, 67%; palmoplantar, 85%) (Figure 1). The mean change from baseline (observed and LOCF) was maintained from week 12 through week 264 for patients with scalp and palmoplantar psoriasis and weeks 36 through 264 for patients with nail psoriasis (Figure 2). High percentages of patients (observed or LOCF) with baseline scalp (94%, 95%), nail (73%, 72%), and palmoplantar (98%, 98%) psoriasis showed improvement at week 24, as measured by the

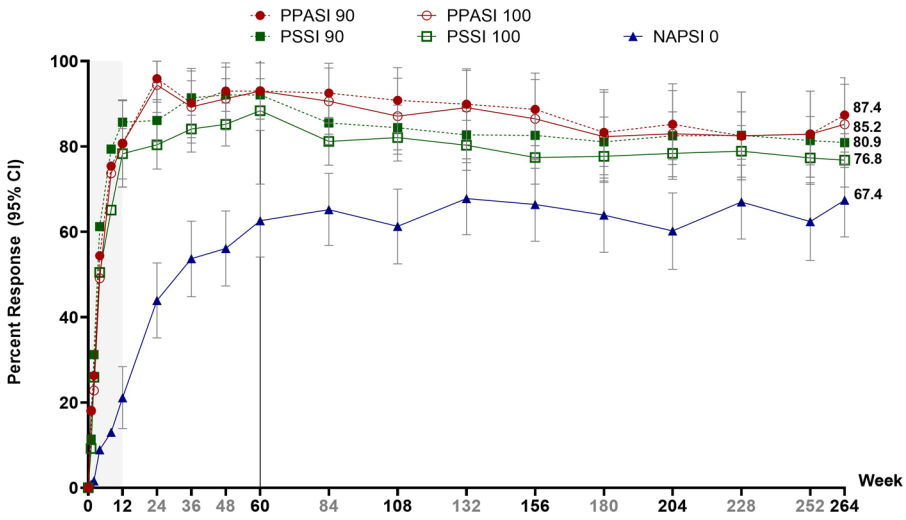
FIGURE 1. Ixekizumab-treated patients in UNCOVER-1 and UNCOVER-2 rapidly achieved and sustained improvements in scalp, nail, and palmoplantar psoriasis for up to 5 years (Observed and mNRI). Improvement measured as the percentages of responders to achieve PSSI, PPASI and NAPSI standards at each time point and represented with both (A) observed data and (B) modified non-responder imputation (mNRI) for missing data. The shaded area indicates the treatment induction period (0–12 weeks) and the solid line at week 60 indicates the beginning of the long-term extension period. NAPSI (0) = clear; PPASI 90/100 = at least 90%/100% improvement in PPASI score from baseline; PSSI 90/100 = at least 90%/100% improvement in PSSI score from baseline.

A) Observed



Nx	W0	W12	W60	W108	W156	W204	W264
PPASI (N=57)	57	57	57	54	50	46	46
PSSI (N=189)	189	189	189	179	169	161	159
NAPSI (N=123)	123	122	122	115	109	103	101

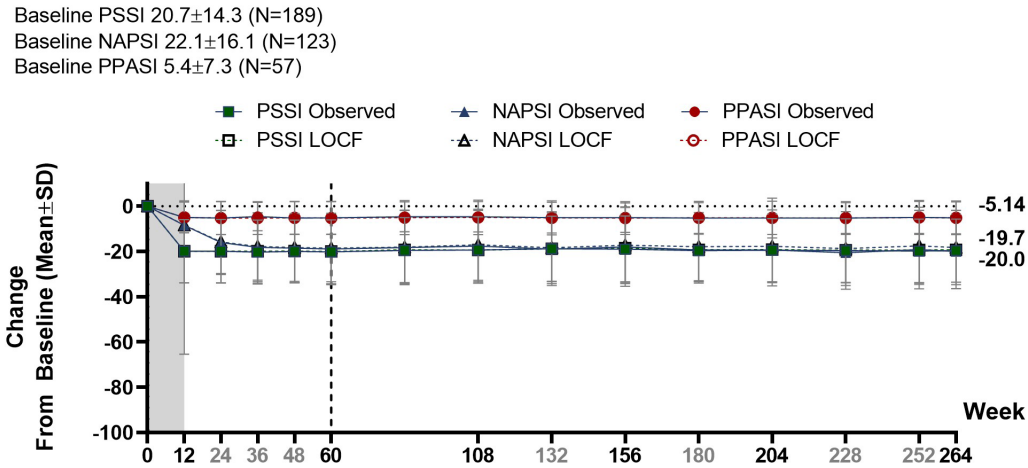
B) mNRI



PPASI (N=57) **PSSI (N=189)** **NAPSI (N=123)**

Abbreviations: CI=confidence interval; mNRI=modified non-responder imputation; NAPSI=Nail Psoriasis Severity Index; Nx=number of patients at a particular timepoint; PPASI=Palmoplantar Psoriasis Area and Severity Index; PSSI=Psoriasis Scalp Severity Index; W=week.

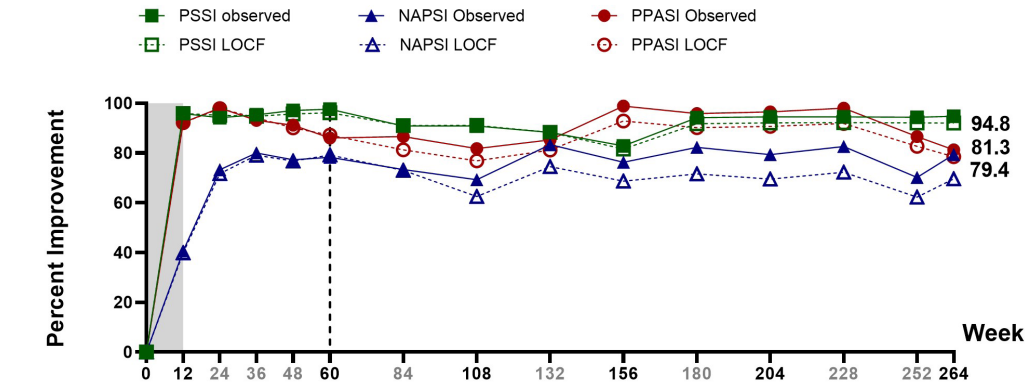
FIGURE 2. Ixekizumab-treated patients in UNCOVER-1 and UNCOVER-2 rapidly achieved and sustained improvements in scalp, nail, and palmoplantar psoriasis for up to 5 years—Mean change from baseline (Observed and LOCF). The shaded area indicates the treatment induction period (0–12 weeks) and the solid line at week 60 indicates the beginning of the long-term extension period. The values represented on the graph at week 264 are observed values.



Nx		W0	W12	W60	W108	W156	W204	W264
PSSI	Obs	189	189	189	179	169	161	159
	LOCF	189	189	189	189	189	189	189
PPASI	Obs	57	57	57	54	50	46	46
	LOCF	57	57	57	57	57	57	57
NAPSI	Obs	123	122	122	115	109	103	101
	LOCF	123	123	123	123	123	123	123

Abbreviations: LOCF=last observation carried forward; NAPSI=Nail Psoriasis Severity Index; Nx=number of patients at a particular timepoint; Obs=observed; PPASI=Palmoplantar Psoriasis Area and Severity Index; PSSI=Psoriasis Scalp Severity Index; SD=standard deviation; W=week.

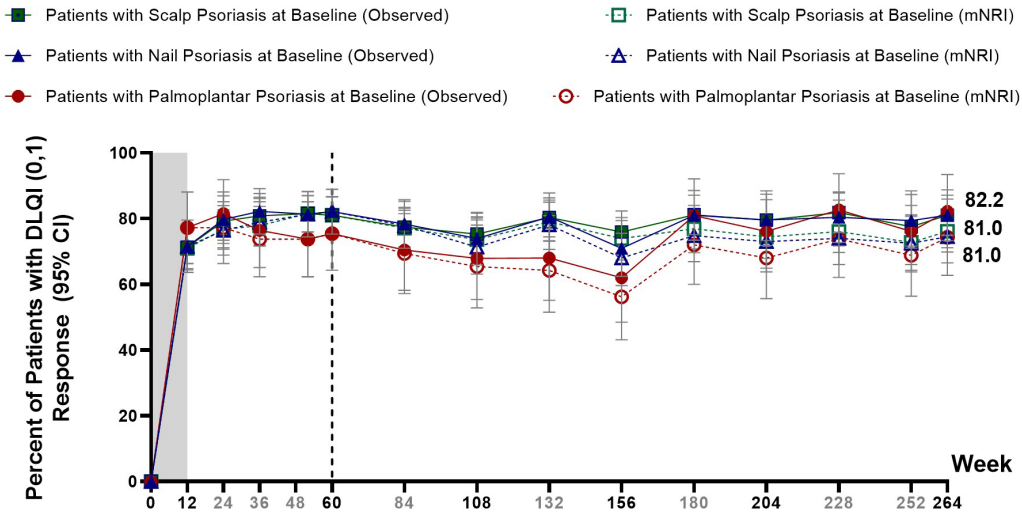
FIGURE 3. Ixekizumab-treated patients in UNCOVER-1 and UNCOVER-2 rapidly achieved and sustained percentage improvement from baseline in scalp, nail, and palmoplantar psoriasis for up to 5 years—Percent improvement (Observed and LOCF). The shaded area indicates the treatment induction period (0–12 weeks) and the solid line at week 60 indicates the beginning of the long-term extension period. The values represented on the graph at week 264 are observed values.



Nx		W0	W12	W60	W108	W156	W204	W264
PSSI	Obs	189	189	189	179	169	161	159
	LOCF	189	189	189	189	189	189	189
PPASI	Obs	57	57	57	54	50	46	46
	LOCF	57	57	57	57	57	57	57
NAPSI	Obs	123	122	122	115	109	103	101
	LOCF	123	123	123	123	123	123	123

Abbreviations: LOCF=last observation carried forward; NAPSI=Nail Psoriasis Severity Index; Nx=number of patients at a particular timepoint; Obs=observed; PPASI=Palmoplantar Psoriasis Area and Severity Index; PSSI=Psoriasis Scalp Severity Index; W=week.

FIGURE 4. Ixekizumab-treated patients with scalp, nail, and palmoplantar psoriasis in UNCOVER-1 and UNCOVER-2 rapidly achieved and sustained DLQI (0,1) for up to 5 years (Observed and mNRI). The shaded area indicates the treatment induction period (0–12 weeks) and the solid line at week 60 indicates the beginning of the long-term extension period. The values represented on the graph at week 264 are observed values.



Nx	W0	W12	W60	W108	W156	W204	W264
Scalp	189	188	189	178	170	161	158
Palmoplantar	57	57	57	53	50	46	45
Nail	123	123	123	115	110	103	100

Abbreviations: CI=confidence interval; DLQI=Dermatology Life Quality Index; mNRI=modified non-responder imputation; Nx=number of patients (observed) at a particular timepoint; Obs=observed; W=week.

PSSI, NAPSI, which was maintained up to 5 years, while slightly less improvement up to 5 years was evident for PPASI (Figure 3). Up to 80% of patients reported DLQI (0,1) response at week 12, which was sustained through week 264 for patients in each of the three burdensome areas (Figure 4).

Safety

Safety in each subpopulation was consistent with the safety in the general trial population which has been previously described.[15,16] No deaths were reported through year 5. The incidence rates of TEAEs and SAEs were generally consistent through year 5 in patients with scalp, nail, or palmoplantar psoriasis, and most TEAEs were of mild or moderate severity (Table 2). Pre-defined categories of TEAEs of special interest considering all patients were infection, cytopenias, hepatic, injection site reaction, and allergic reaction/hypersensitivity (anaphylaxis, non-anaphylaxis). Incidence rates across the three patient populations were generally consistent with previous reports of the overall IXE Q2W/IXE Q4W population during the long-term extension period for infection (25.2 – 28.2 per 100 patient years), cytopenias (0.8-2.1), and hepatic TEAEs (2.5-4.1). Allergic reaction/hypersensitivity (non-anaphylaxis) incidence rates ranged from 4.7 to 6.2 per 100 patient years and no events of anaphylaxis were reported. Injection site reactions were also consistent (1.6-3.4) with previously published IRs (data not shown.[16]

DISCUSSION

The long-term efficacy and safety of IXE in patients with moderate-to-severe psoriasis is well established through 5 years.[13,15,16] IXE demonstrated significant responses in patients with burdensome types of psoriasis in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 studies up to week 60,[3,7,8,17] and in UNCOVER-3 up to 5 years. Our analyses integrated UNCOVER-1 and UNCOVER-2 data to report efficacy and safety in patients with baseline scalp, nail, or palmoplantar psoriasis and adds to this body of data supporting long-term IXE treatment. These findings indicate that IXE maintained up to 5 years of high rates in improvement of scalp, nail and palmoplantar psoriasis and QOL.

Scalp psoriasis occurs frequently in patients with psoriasis and is associated with symptoms that negatively effect social activities due to the visibility of lesions and itching.[18] Here, we report that more than 90% of patients with baseline scalp psoriasis had symptom improvement at week 24, which was maintained for up to 5 years, and up to 80% of patients had no impact of symptoms on QoL. Response rates with IXE for up to 5 years in patients with scalp psoriasis were consistent with those previously reported at 60 weeks.[8]

Due to the slow rate of nail growth, a longer duration of treatment of patients with nail psoriasis for optimal response is required.[5,19]

Considering that PASI does not include nail assessment, it is possible that patients with PASI 100, or complete clearance, may have residual nail involvement. In patients with moderate-to-severe psoriasis, significant reductions in NAPSI scores in patients treated with IXE were seen as early as 2 weeks and maintained through 5 years.[7,17] Additionally, IXE was superior to ustekinumab in providing earlier complete clearance of nail psoriasis, with continued improvement through 52 weeks.[20]

Moderate-to-severe palmoplantar psoriasis is ill-defined. However, palmoplantar plaque psoriasis can be more debilitating than generalized plaque psoriasis. Patients with palmoplantar psoriasis experience significant functional impairment from the plaques on their palms and soles, which negatively affects their QoL.[21] Our data suggest that high levels of response have been achieved with IXE in a large percentage of patients with palmoplantar psoriasis through 5 years, which is consistent with what has been reported previously.[3] We also show here that high response rates were indicative of improved DLQI response throughout 5 years of treatment with IXE.

Taken together, long-term IXE treatment positively impacts QoL in patients with burdensome psoriasis. Clinical improvements in symptoms and QoL in patients with burdensome psoriasis with other biologics, specifically IL-17 inhibitors, up to week 80 have also been reported.[9,11,12,19,22,23] Specifically, more than 74% of patients with nail psoriasis reported at least a moderate benefit and significant improvement with secukinumab at week 80.[12] About 33% of patients with palmoplantar psoriasis achieved complete/almost complete clearance and improved QoL at 4 months with secukinumab.[11]

No new safety signals were reported over 5 years of IXE treatment in patients with burdensome psoriasis. The number of patients with either scalp, nail, or palmoplantar involvement reporting TEAEs generally decreased each year, which is consistent with what has been previously reported in IXE-treated patients with moderate-to-severe psoriasis up to 3 years[24] and 5 years.[16]

While advances in psoriasis treatment have improved skin clearance, burdensome areas remain a challenge for patients. Long-term treatment recommendations and algorithms to guide prescribing decisions are lacking. Our study confirms that most patients present with psoriasis lesions in more than one burdensome area at baseline. Healthcare professionals should consider full skin clearance, including psoriasis in these burdensome locations that often go overlooked, as a primary goal for treatment.[25] These data are relevant to dermatologists and healthcare professionals in terms of treatment selection for long-term management of scalp, nail, and palmoplantar psoriasis.

Our analyses included small numbers of patients presenting with one or multiple burdensome psoriasis areas at baseline, which was a limiting factor. Additionally, we were unable to separate the effects on QOL or function based on psoriasis location and disease severity at that location. Because the assessment of disease severity in burdensome psoriasis conditions is generally lacking, making comparisons among treatment options was not feasible.

CONCLUSION

Management of patients with burdensome psoriasis requires long-term treatment strategies that are effective without substantially increasing the risk of adverse events. Patients receiving IXE for 5 years sustained high rates of improvement in baseline scalp, nail, and palmoplantar psoriasis. Overall, QoL benefit was sustained with no unexpected safety signals. IXE is effective for long-term management of patients with baseline burdensome psoriasis.

DISCLOSURES

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