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CONCISE COMMUNICATION

Efficacy and safety of ixekizumab treatment in Japanese patients with moderate-to-severe plaque psoriasis: Subgroup analysis of a placebo-controlled, phase 3 study (UNCOVER-1)

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ABSTRACT

The present study describes a subgroup analysis of 33 Japanese patients participating in UNCOVER-1, an international, placebo-controlled, phase 3 study of ixekizumab in patients with moderate-to-severe psoriasis. Patients were randomized to a placebo (*n* = 13) or ixekizumab 80 mg every 4 (IXEQ4W, *n* = 12) or 2 (IXEQ2W, *n* = 8) weeks, from week 0–12. At week 12, ixekizumab-treated patients with a static Physician Global Assessment score 0 or 1 (sPGA [0,1]; *n* = 16) were re-randomized to a placebo (*n* = 6), ixekizumab 80 mg every 12 (IXEQ12W, *n* = 5) or 4 (IXEQ4W, *n* = 5) weeks, from week 12–60. At week 12, more ixekizumab-treated versus placebo-treated patients achieved sPGA (0,1) (≥66.7% *vs* 0%), ≥75% improvement in Psoriasis Area and Severity Index (≥75% *vs* 0%), and sPGA (0) or 100% improvement in Psoriasis Area and Severity Index (both ≥33.3% *vs* 0%), with improved symptoms and quality of life. At week 60, 100% (IXEQ4W), 40.0% (IXEQ12W) and 16.7% (placebo) had maintained sPGA (0,1). From week 0–12, treatment-emergent adverse events were 76.9% (placebo), 75.0% (IXEQ4W) and 87.5% (IXEQ2W), and from week 12–60 were 66.7% (placebo) and 100% (IXEQ12W, IXEQ4W). Ixekizumab-treated patients had no severe treatment-emergent adverse events, and one serious TEAE (IXEQ4W); infection was the most frequent treatment-emergent adverse event. In conclusion, ixekizumab for 60 weeks was effective and safe for Japanese patients with moderate-to-severe psoriasis, in line with the overall findings from UNCOVER-1.

Key words: **interleukin-17A, ixekizumab, Japan, psoriasis, randomized controlled trial.**

INTRODUCTION

Psoriasis is a chronic, immune-mediated, skin condition characterized by red scaly plaques.[1] In Japan, 4.43% of patients (*n* = 67 448) attending dermatology clinics in 2007–2008 had psoriasis,[2] which was estimated to affect 0.34% of the population in 2011.[3] In international phase 3 trials, ixekizumab markedly improved the clinical signs and symptoms of moderate-to-severe psoriasis.[4,5] In a single-arm study of ixekizumab in Japanese patients (UNCOVER-J), 98.7% with moderate-to-severe psoriasis achieved ≥75% improvement in the Psoriasis Area and Severity Index (PASI 75) at week 12,[6] which was maintained up to 52 weeks with no unexpected safety signals.[7] Herein, we assess the efficacy and safety of ixekizumab for 60 weeks in Japanese patients participating in UNCOVER-1, an ongoing, placebo-controlled phase 3 study (NCT01474512; JapicCTI-121952).[4]

METHODS

Study design

Protocol approval and ethics have been described.[4] Eligible patients (aged ≥18 years) had moderate-to-severe psoriasis ≥6 months before randomization, were candidates for phototherapy and/or systemic therapy, and had body surface area involvement ≥10%, static Physician's Global Assessment (sPGA) score ≥3, and PASI score ≥12 at screening and baseline.[4]

Patients were randomized (1:1:1) to receive a placebo or ixekizumab 80 mg (160 mg at week 0) every 4 weeks (IXEQ4W) or every 2 weeks (IXEQ2W) from week 0–12 (induction period). At week 12, ixekizumab-treated patients with sPGA (0,1) (responders) were re-randomized (1:1:1) to a placebo, ixekizumab 80 mg every 12 weeks (IXEQ12W) or IXEQ4W from week 12–60 (maintenance period). Placebo-treated responders (sPGA [0,1]) received a placebo until

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relapse (sPGA [≥3]), then IXEQ4W, and non-responders (sPGA [≥2]) received IXEQ4W.

Outcome measures

Co-primary measures were PASI 75 and sPGA (0,1) at week 12. Secondary measures were sPGA (0), ≥90% and 100% improvement in PASI (PASI 90, PASI 100) at week 12; ≥4-point improvement in Itch Numeric Rating Scale,[8] change in Dermatology Life Quality Index,[9] change in Nail Psoriasis Severity Index (NAPSI)[10] from week 0–12 and maintenance of sPGA (0,1) from week 12–60. Safety measures were treatment-emergent adverse events (TEAE), serious adverse events and protocol-specified TEAE of special interest.[4]

Statistical analysis

Statistical methods have been described elsewhere.[4] Efficacy analyses included all randomized patients. Safety analyses included all patients who received at least one study dose. Data were summarized using descriptive statistics (SAS version ≥9.2; SAS Institute, Cary, NC, USA). For week 12–60, only data for ixekizumab-treated responders re-randomized at week 12 are presented; data for placebo-treated responders and non-responders, and ixekizumab-treated non-responders are not presented. Missing data for categorical efficacy variables (e.g. treatment discontinuation for any reason, no post-baseline observations) were imputed as non-responders (i.e. did not meet clinical response criteria).

RESULTS

Patient characteristics

At week 0, 33 Japanese patients participating in UNCOVER-1 (n = 1296) were randomized to a placebo (n = 13), IXEQ4W (n = 12) or IXEQ2W (n = 8). At week 12, 16 responders (IXEQ4W n = 8, IXEQ2W n = 8) were re-randomized to a placebo (n = 6), IXEQ12W (n = 5) or IXEQ4W (n = 5). By week 60, three placebo-treated and three IXEQ12W-treated patients had relapsed. Eight patients discontinued the study, most commonly because of adverse events (n = 5).

Demographics and disease characteristics were similar among treatment groups (Table 1). The mean duration of psoriasis was longer for the IXEQ4W group, and previous non-biological + biological therapy was more common in the placebo group.

Efficacy

At week 12, eight (100%) IXEQ2W-treated and eight (66.7%) IXEQ4W-treated patients achieved sPGA (0,1), and eight (100%) IXEQ2W-treated and nine (75.0%) IXEQ4W-treated patients achieved PASI 75 (Table 2). No placebo-treated patient achieved sPGA (0,1) or PASI 75, nor sPGA (0), PASI 90 or PASI 100. Furthermore, six (75.0%) IXEQ2W-treated patients and seven (58.3%) IXEQ4W-treated patients achieved PASI 90, with at least three (37.5%) IXEQ2W-treated and four (33.3%) IXEQ4W-treated patients achieving complete resolution of psoriasis plaques (sPGA [0] or PASI 100).

Five (all) IXEQ4W-treated, two IXEQ12W-treated and one placebo-treated patient maintained sPGA (0,1) until week 60 (Table 2). PASI response rates were numerically greater for IXEQ4W than IXEQ12W and the placebo.

At week 12, improvements in Itch Numeric Rating Scale and Dermatology Life Quality Index scores were numerically greater for IXEQ2W than IXEQ4W, and were minimal for the placebo (Table 2). Improvement in NAPSI scores were minimal for the placebo and IXEQ4W, but more marked for IXEQ2W.

Safety

In the Japanese subgroup, TEAE were reported by 10 placebo-treated and 16 ixekizumab-treated patients from week 0–12, and four placebo-treated and 10 (all) ixekizumab-treated patients from week 12–60; for ixekizumab-treated patients, none were considered severe (Table 3). TEAE considered possibly drug-related were reported by nine (week 0–12) and two (week 12–60) ixekizumab-treated patients. Three IXEQ4W-treated patients discontinued because of generalized pruritus (mild severity), allergic edema (moderate severity) and bronchopneumonia (moderate severity, also considered a serious adverse event). No deaths were reported.

In ixekizumab-treated patients, infection, particularly nasopharyngitis, was the most frequently reported TEAE of special interest (Table 3). All infections were mild, except for moderate cases of bronchopneumonia (n = 1), nasopharyngitis (n = 2), tinea pedis (n = 1) and influenza (n = 1). Cytopenias (leukopenia and neutropenia [n = 1], leukopenia and lymphopenia [n = 1]) were mild, all allergic/hypersensitivity reactions were non-anaphylactic, and all injection-site reactions were mild and resolved within 1–3 days. One case of elevated alanine aminotransferase and aspartate aminotransferase concentrations above normal limits during the induction period resulted in study discontinuation at week 44 after re-randomization from IXEQ4W to a placebo at week 12, and two cases of mild increases in alanine aminotransferase concentrations resolved during the study. No patients had tuberculosis.

DISCUSSION

Ixekizumab effectively reduced the symptoms and signs of moderate-to-severe psoriasis in Japanese patients participating in UNCOVER-1. At week 12, high levels of psoriasis clearance (sPGA [0,1], PASI 75) were seen in ≥66.7% of ixekizumab-treated patients and were maintained through to week 60 (sPGA [0,1]), with IXEQ2W (induction) and IXEQ4W (maintenance) providing the highest response rates. Furthermore, ixekizumab improved nail psoriasis, itch severity and quality of life with an acceptable safety profile.

Efficacy findings for the 33 Japanese patients were in line with those for the overall UNCOVER-1 population.[4] Both populations achieved high levels of psoriasis clearance at week 12; in the overall population, sPGA (0,1) and PASI 75 were significantly ($P < 0.001$) greater for ixekizumab than the placebo, and numerically greater for IXEQ2W than IXEQ4W (Table 2).[4] Doses of ixekizumab every 4 weeks provided the best opportunity for maintaining psoriasis clearance (sPGA [0,1]) in both populations (Table 2). The low mean baseline NAPSI score of

Table 1. Patient demographics and baseline disease characteristics of Japanese patients and all patients with moderate-to-severe plaque psoriasis participating in UNCOVER-1

	Placebo		IXEQ4W		IXEQ2W	
Variable	JPN (*n* = 13)	All[†] (*n* = 431)	JPN (*n* = 12)	All[†] (*n* = 432)	JPN (*n* = 8)	All[†] (*n* = 433)
Age, years (mean ± SD)	51.4 ± 14.9	46.4 ± 13.4	44.5 ± 10.6	45.6 ± 13.0	45.5 ± 10.4	45.3 ± 12.7
Male, *n* (%)	9 (69.2)	303 (70.3)	10 (83.3)	289 (66.9)	8 (100)	291 (67.2)
Weight, kg (mean ± SD)	65.0 ± 14.1	91.8 ± 25.0	74.6 ± 15.7	92.5 ± 23.9	71.7 ± 10.9	92.4 ± 22.7
Duration of psoriasis, years (mean ± SD)	13.2 ± 8.7	19.5 ± 11.7	18.7 ± 7.2	19.5 ± 11.9	13.9 ± 8.3	19.9 ± 11.9
Previous systemic therapy, *n* (%)						
Non-biological[‡] only	4 (30.8)	118 (27.4)	7 (58.3)	132 (30.6)	5 (62.5)	152 (35.1)
Biological only	0	57 (13.2)	0	62 (14.4)	0	49 (11.3)
Non-biological[‡] + biological	5 (38.5)	124 (28.8)	2 (16.7)	106 (24.5)	1 (12.5)	124 (28.6)
Never used	4 (30.8)	132 (30.6)	3 (25.0)	132 (30.6)	2 (25.0)	108 (24.9)
sPGA, *n* (%)						
3 (Moderate)	6 (46.2)	204 (47.3)	5 (41.7)	197 (45.6)	4 (50.0)	231 (53.3)
4 (Severe)	5 (38.5)	193 (44.8)	7 (58.3)	205 (47.5)	3 (37.5)	179 (41.3)
5 (Very severe)	2 (15.4)	34 (7.9)	0	30 (6.9)	1 (12.5)	23 (5.3)
PASI (mean ± SD)	24.8 ± 12.9	20.3 ± 8.6	22.3 ± 9.4	20.0 ± 7.3	27.6 ± 14.7	20.1 ± 8.0
Itch NRS (mean ± SD)	7.2 ± 3.0	7.0 ± 2.6	7.0 ± 2.5	7.0 ± 2.5	7.4 ± 2.6	7.2 ± 2.4
DLQI (mean ± SD)	12.9 ± 7.9	12.8 ± 7.1	11.5 ± 7.6	13.2 ± 7.0	13.9 ± 8.0	13.4 ± 7.0
NAPSI (if nail psoriasis present)						
Patients, *n* (%)	10 (76.9)	283 (65.7)	9 (75.0)	283 (65.5)	7 (87.5)	284 (65.6)
Mean ± SD	36.8 ± 28.6	26.1 ± 20.5	11.9 ± 9.3	24.1 ± 18.2	25.6 ± 11.5	24.6 ± 18.9
PSSI (if scalp psoriasis present)						
Patients, *n* (%)	13 (100)	393 (91.2)	12 (100)	413 (95.6)	8 (100)	393 (90.8)
Mean ± SD	34.2 ± 16.9	21.8 ± 15.7	28.8 ± 17.6	19.9 ± 14.8	30.1 ± 15.8	21.1 ± 14.7

DLQI, Dermatology Life Quality Index; IXEQ2W, ixekizumab 80 mg once every 2 weeks; IXEQ4W, ixekizumab 80 mg once every 4 weeks; JPN, Japanese; NAPSI, Nail Psoriasis Severity Index; NRS, Numeric Rating Scale; PSSI, Psoriasis Scalp Severity Index; SD, standard deviation; sPGA, static Physician Global Assessment.

[†]Patient demographic (age, sex, weight) and baseline disease characteristics (duration of psoriasis, Psoriasis Area and Severity Index [PASI] score, previous therapy) for the overall UNCOVER-1 population have been reported previously.[4]

[‡]Previous non-biological therapies were methotrexate, cyclosporine, retinoids and psoralen plus ultraviolet light of A (long) wavelength.

Table 2. Efficacy outcomes of ixekizumab treatment in Japanese patients and all patients with moderate-to-severe plaque psoriasis participating in UNCOVER-1

	Induction period (week 0–12)						Maintenance period (week 12–60)					
	Placebo		IXEQ4W		IXEQ2W		IXE → placebo		IXE → IXEQ12W		IXE → IXEQ4W	
Variable	JPN (n = 13)	All† (n = 431)	JPN (n = 12)	All† (n = 432)	JPN (n = 8)	All† (n = 433)	JPN (n = 6)	All (n = 226)	JPN (n = 5)	All (n = 227)	JPN (n = 5)	All (n = 229)
sPGA (0,1), n (%)	0	14 (3.2)	8 (66.7)	330 (76.4)**	8 (100)	354 (81.8)**	1 (16.7)	17 (7.5)	2 (40.0)	85 (37.4)**	5 (100)	167 (72.9)**
sPGA (0), n (%)	0	0	4 (33.3)	149 (34.5)**	5 (62.5)	160 (37.0)**	NR	NR	NR	NR	NR	NR
PASI 75, n (%)	0	17 (3.9)	9 (75.0)	357 (82.6)**	8 (100)	386 (89.1)**	1 (16.7)	20 (8.8)	2 (40.0)	104 (45.8)**	5 (100)	178 (77.7)**
PASI 90, n (%)	0	2 (0.5)	7 (58.3)	279 (64.6)**	6 (75.0)	307 (70.9)**	1 (16.7)	10 (4.4)	2 (40.0)	83 (36.6)**	5 (100)	162 (70.7)**
PASI 100, n (%)	0	0	4 (33.3)	145 (33.6)**	3 (37.5)	153 (35.3)**	0	6 (2.7)	2 (40.0)	46 (20.3)**	3 (60.0)	119 (52.0)**
Itch NRS (change from BL)												
n (with measurement)	10	405	9	406	8	417	NR	NR	NR	NR	NR	NR
Mean (SD)	−1.1 (2.81)	−0.3 (0.12)‡	−5.2 (2.68)	−5.4 (0.12)**‡	−6.6 (2.56)	−5.6 (0.12)**‡	NR	NR	NR	NR	NR	NR
Itch NRS (≥4-point improvement from BL)												
n (BL score ≥4)	11	374	11	379	7	391	NR	NR	NR	NR	NR	NR
n (%)	2 (18.2)	58 (15.5)	5 (45.5)	305 (80.5)**	7 (100)	336 (85.9)**	NR	NR	NR	NR	NR	NR
DLQI (change from BL)												
n (with measurement)	10	403	9	407	8	414	NR	NR	NR	NR	NR	NR
Mean (SD)	−2.6 (8.22)	−1.0 (0.27)‡	−9.0 (6.91)	−10.7 (0.27)**‡	−13.3 (7.38)	−11.1 (0.26)**‡	NR	NR	NR	NR	NR	NR
NAPSI (change from BL)												
n (with measurement)	8	267	7	266	7	275	NR	NR	NR	NR	NR	NR
Mean (SD)	−1.0 (12.52)	2.17 (0.67)‡	−1.14 (5.96)	−7.19 (0.66)**‡	−11.29 (7.99)	−7.24 (0.66)**‡	NR	NR	NR	NR	NR	NR

BL, baseline; DLQI, Dermatology Life Quality Index; IXE, ixekizumab; IXEQ2W, ixekizumab 80 mg once every 2 weeks; IXEQ4W, ixekizumab 80 mg once every 4 weeks; JPN, Japanese; NAPSI, Nail Psoriasis Severity Index; NR, not reported; NRS, Numeric Rating Scale; SD, standard deviation.

**$P < 0.001$, *$P < 0.05$ compared with placebo; P-values are from logistic regression analyses or Fisher's exact test, if the response rate for placebo was 0, of categorical efficacy variables, and mixed model repeated measures (MMRM) analyses of continuous efficacy variables. For categorical efficacy variables, missing data were imputed with non-responder imputation (NRI).

†Efficacy outcomes (static Physician Global Assessment [sPGA] [0], [0,1]; Psoriasis Area and Severity Index [PASI 75, PASI 90, PASI 100) for the overall UNCOVER-1 population have been reported previously.[4]

‡Values are least square mean (standard error) from MMRM analyses.

Table 3. Safety overview of ixekizumab treatment in Japanese patients and all patients with moderate-to-severe plaque psoriasis participating in UNCOVER-1

	Induction period (week 0–12)						Maintenance period (week 12–60)					
	Placebo		IXEQ4W		IXEQ2W		IXE → Placebo		IXE → IXEQ12W		IXE → IXEQ4W	
Variable[†]	JPN (*n* = 13)	All (*n* = 431)	JPN (*n* = 12)	All (*n* = 432)	JPN (*n* = 8)	All (*n* = 433)	JPN (*n* = 6)	All (*n* = 226)	JPN (*n* = 5)	All (*n* = 227)	JPN (*n* = 5)	All (*n* = 229)
Patients with ≥1 TEAE, *n* (%)	10 (76.9)	210 (48.7)	9 (75.0)	264 (61.1)	7 (87.5)	257 (59.4)	4 (66.7)	123 (54.4)	5 (100)	168 (74.0)	5 (100)	182 (79.5)
TEAE by severity, *n* (%)												
Mild	9 (69.2)	104 (24.1)	7 (58.3)	147 (34.0)	7 (87.5)	164 (37.9)	4 (66.7)	59 (26.1)	2 (40.0)	72 (31.7)	3 (60.0)	78 (34.1)
Moderate	0	88 (20.4)	2 (16.7)	100 (23.1)	0	79 (18.2)	0	55 (24.3)	3 (60.0)	84 (37.0)	2 (40.0)	85 (37.1)
Severe	1 (7.7)	18 (4.2)	0	17 (3.9)	0	14 (3.2)	0	9 (4.0)	0	12 (5.3)	0	19 (8.3)
TEAE possibly related to study drug, *n* (%)	0	49 (11.4)	6 (50.0)	111 (25.7)	3 (37.5)	127 (29.3)	1 (16.7)	39 (17.3)	1 (20.0)	42 (18.5)	1 (20.0)	71 (31.0)
Discontinuation because of TEAE, *n* (%)	1 (7.7)	6 (1.4)	3 (25.0)	10 (2.3)	0	10 (2.3)	1 (16.7)	4 (1.8)	0	2 (0.9)	0	9 (3.9)
Death, *n* (%)	0	0	0	0	0	0	0	0	0	0	0	2 (0.9)
SAE, *n* (%)	1 (7.7)	5 (1.2)	1 (8.3)	12 (2.8)	0	6 (1.4)	0	7 (3.1)	0	9 (4.0)	0	15 (6.6)
Selected TEAE of special interest, *n* (%)[‡]												
Infection	3 (23.1)	106 (24.6)	3 (25.0)	128 (29.6)	2 (25.0)	124 (28.6)	2 (33.3)	74 (32.7)	5 (100)	116 (51.1)	3 (60.0)	129 (56.3)
Cytopenias	0	6 (1.4)	0	3 (0.7)	0	4 (0.9)	0	2 (0.9)	1 (20.0)	3 (1.3)	1 (20.0)	7 (3.1)
Allergic/ hypersensitivity reactions	0	10 (2.3)	1 (8.3)	19 (4.4)	1 (12.5)	14 (3.2)	1 (16.7)	7 (3.1)	1 (20.0)	10 (4.4)	1 (20.0)	21 (9.2)
Injection-site reactions	0	13 (3.0)	1 (8.3)	52 (12.0)	1 (12.5)	69 (15.9)	0	2 (0.9)	0	12 (5.3)	0	16 (7.0)
Malignancies	1 (7.7)	2 (0.5)	0	3 (0.7)	0	0	0	0	0	2 (0.9)	0	0
Abnormal liver function	0	6 (1.4)	1 (8.3)	7 (1.6)	0	4 (0.9)	0	4 (1.8)	0	5 (2.2)	2 (40.0)	12 (5.2)
CVD	0	0	0	3 (0.7)	0	0	0	1 (0.4)	0	3 (1.3)	0	3 (1.3)
IBD	0	0	0	1 (0.2)	0	1 (0.2)	0	1 (0.4)	0	0	0	0

CVD, cerebrocardiovascular disease; IBD, inflammatory bowel disease; IXE, ixekizumab; IXEQ2W, ixekizumab 80 mg once every 2 weeks; IXEQ4W, ixekizumab 80 mg once every 4 weeks; IXEQ12W, ixekizumab 80 mg once every 12 weeks; JPN, Japanese; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[†]For all variables, *n* (%) refers to the number (%) of patients.

[‡]Adverse events were coded and summarized using the Medical Dictionary for Regulatory Activities, Version 16.1.

IXEQ4W-treated Japanese patients (Table 1) might have influenced the difference in mean change in NAPSI scores from week 0–12 between Japanese patients and the overall population (Table 2). The present findings were also in line with those of UNCOVER-J, including high levels of psoriasis clearance (PASI 75, sPGA [0,1]) after 12 weeks of IXEQ2W,[6] which were maintained up to 52 weeks with IXEQ4W,[7] and improved the Dermatology Life Quality Index and Itch Numeric Rating Scale.[6,7]

Ixekizumab was well tolerated, with no Japanese-specific safety findings. A higher proportion of ixekizumab-treated Japanese patients reported TEAE than the overall UNCOVER-1 population (Table 3). However, most TEAE were mild to moderate. In addition, serious adverse event incidence was low; TEAE of special interest incidence was similar to that of the overall population; infection was the most common TEAE of special interest, a finding similar for the overall[4] and UNCOVER-J[6,7] populations, and other biological therapies tested in Japanese patients;[11–14] TEAE-related study discontinuations were few; no deaths were reported.

In conclusion, ixekizumab-treated Japanese patients with moderate-to-severe psoriasis attained clinically meaningful reductions in symptoms and severity for up to 60 weeks with an acceptable safety profile. These findings are in line with the overall UNCOVER-1[4] and UNCOVER-J[6,7] populations, further supporting the favorable benefit/risk profile of ixekizumab in Japanese patients.

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