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Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study

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Summary

Background It has been shown that the interleukin (IL)-23/IL-17 axis is critical in the pathogenesis of psoriasis.
Objectives To present the primary end point (week 12) and safety and efficacy data up to week 24 from a head-to-head trial (IXORA-S) of the IL-17A inhibitor ixekizumab (IXE) vs. the IL-12/23 inhibitor ustekinumab (UST).
Methods Randomized patients received IXE (160-mg starting dose, then 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks, n = 136) or UST (45 mg or 90 mg weight-based dosing per label, n = 166). The primary end point was the proportion of patients reaching ≥ 90% Psoriasis Area and Severity Index improvement (PASI 90). Hommel-adjusted key secondary end points at week 12 included PASI 75, PASI 100, static Physician's Global Assessment (sPGA) score of 0 or 1, sPGA score of 0, Dermatology Life Quality Index (DLQI) score of 0 or 1, ≥ 4-point reduction on the itch numerical rating scale (NRS) and changes in itch NRS and skin pain visual analogue scale.
Results At week 12, IXE (n = 99, 72·8%) was superior to UST (n = 70, 42·2%) in PASI 90 response (response difference 32·1%, 97·5% confidence interval 19·8–44·5%, $P < 0·001$). Response rates for PASI 75, PASI 100 and sPGA (0,1) were significantly higher for IXE than for UST (adjusted $P < 0·05$). At week 24, IXE-treated patients had significantly higher response rates than UST-treated patients for PASI, sPGA and DLQI (unadjusted $P < 0·05$). No deaths were reported, and the treatments did not differ with regard to overall incidences of adverse events ($P = 0·299$).
Conclusions The superior efficacy of IXE demonstrated at week 12 persisted up to week 24. The safety profiles were consistent with those previously reported for both treatments.

What's already known about this topic?

- With the advancements in new biologics targeting the interleukin (IL)-17A pathway, the majority of patients with moderate-to-severe psoriasis are now able to achieve complete or near complete clearance of psoriasis.

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Conflicts of interest
See Appendix 1.

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What does this study add?

- The IL-17A inhibitor ixekizumab provides superior efficacy over the IL-12/23 inhibitor ustekinumab, with a similar safety profile after 24 weeks of treatment.

Recent advancements in the understanding of signalling pathways involved in psoriasis pathogenesis have revealed key roles for the interleukin (IL)-23/IL-17 axis.[1–7] This has led to the development of biological treatments specifically targeting these cytokines,[8–11] enabling higher levels of skin improvement than those provided by antitumour necrosis factor agents.[12–16]

Ustekinumab, a monoclonal antibody targeting p40, the subunit shared by IL-12 and IL-23, was the first successful attempt to target the IL-23/IL-17 axis.[17] Randomized controlled studies have shown that ustekinumab enabled 40–50% of patients to achieve ≥ 90% improvement of Psoriasis Area and Severity Index (PASI 90) after 12 weeks.[18,19]

IL-17A is a cytokine that directly activates keratinocytes and stimulates the production of chemokines, cytokines and antimicrobial peptides, which contribute to the clinical manifestations of psoriasis.[3–5] Blocking IL-17A represents the most recent approach to control this disease effectively. Ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A,[8] has already demonstrated greater efficacy than the tumour necrosis factor-α inhibitor etanercept in two phase III clinical trials,[12,13] showing that 70·7% of patients treated with ixekizumab 80 mg every 2 weeks achieved PASI 90 after 12 weeks, compared with 18·7% of etanercept-treated patients.[13]

These data, as well as recent data with secukinumab,[14,15] another anti-IL-17A monoclonal antibody, provide evidence that reaching PASI 90 is now an achievable treatment outcome for a majority of patients. With the availability of new biological agents, a PASI 90 response could therefore be considered as the treatment goal in clinical practice in the near future.[20–22]

The current study, IXORA-S, is the first head-to-head trial including ixekizumab and ustekinumab over 52 weeks, with a primary objective of comparing PASI 90 at week 12. The week 12 primary end point data is presented here. Additionally, due to the dosing schedule of ustekinumab, we also present efficacy and safety results up to week 24 for a more accurate comparison between the two treatments. Safety and efficacy data from week 52 will be disclosed at a future date, as the study is still ongoing.

Patients and methods

Study population

Eligible study participants were aged ≥ 18 years, had a diagnosis of chronic plaque psoriasis for ≥ 6 months, had a PASI score ≥ 10 and had previously failed or had a contraindication or intolerability to at least one systemic therapy (including ciclosporin, methotrexate and phototherapy). Key exclusion criteria were a predominant presence of nonplaque psoriasis, a contraindication for ustekinumab, or prior treatment with ustekinumab, ixekizumab or any other IL-17 or IL-12/23 antagonists.

The study was approved by applicable ethical review boards, and all patients signed informed consent forms before undergoing study-related procedures. The study was conducted in compliance with the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. The first patient randomization took place on 21 October 2015, and the last week 24 patient visit was on 3 August 2016.

Study design

This 52-week, phase IIIb, multicentre, controlled, double-blind, parallel-group trial (IXORA-S, NCT02561806) was conducted at 51 sites across 13 countries. Patients were randomized (1 : 1) via an interactive web-response system to receive either ixekizumab or ustekinumab. Randomization was stratified by study centre and patient weight (≤ 100·0 kg vs. > 100·0 kg). The clinical trial details can be accessed at www.clinicaltrials.gov.

During the induction period (weeks 0–12), patients randomized to ixekizumab received two subcutaneous (SC) injections of ixekizumab 80 mg (160 mg total) at week 0, followed by one SC injection of ixekizumab 80 mg every 2 weeks through week 12, and 80 mg every 4 weeks thereafter (Fig. 1). Patients randomized to ustekinumab were dosed at weeks 0, 4, 16, 28 and 40, in accordance with the label, with patients weighing ≤ 100·0 kg receiving 45 mg SC injections and patients weighing > 100·0 kg receiving 90 mg SC injections. To maintain the blinding, patients randomized to ixekizumab received placebo injections matching the ustekinumab dose regimen, and patients in the ustekinumab group received dummy injections of ixekizumab. Unblinded site personnel responsible for ustekinumab and ustekinumab placebo injections were involved in neither the clinical assessments nor the treatment decisions, and kept the patients and investigators blinded from treatment allocation.

Study objectives

The primary objective of IXORA-S was to demonstrate firstly that ixekizumab is noninferior to ustekinumab (inferiority

margin: −12·6%) and secondly that ixekizumab is superior to ustekinumab, as measured by the proportion of patients achieving a PASI 90 response at week 12.

Eight key secondary end points at week 12 were defined. These were the proportion of patients achieving: (i) PASI 75 response; (ii) PASI 100 response; (iii) static Physician's Global Assessment (sPGA) 0 response; (iv) sPGA 0 or 1 response with at least a 2-point improvement in patients with baseline sPGA ≥ 3; (v) Dermatology Life Quality Index (DLQI) 0 or 1; and (vi) itch numerical rating scale (NRS) ≥ 4-point improvement in patients with baseline itch NRS ≥ 4; and changes from baseline in (vii) the itch NRS and (viii) the skin pain visual analogue scale (VAS).

PASI is a primary efficacy measurement for psoriasis that combines assessments of the extent of body surface involvement and severity of scaling, erythema and plaque thickness in four regions (head, trunk, arms and legs); scores range from 0 (no psoriasis) to 72 (most severe disease). The sPGA assesses the severity of psoriatic lesions by categorizing them by induration, erythema and scaling; scores are 0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe) or 5 (very severe).

The DLQI is a 10-question, validated health-related quality of life (HRQoL) questionnaire, with scores ranging from 0 to 30 (less to more impairment); scores of 0 or 1 represent no impact of disease on HRQoL.[23] The itch NRS is a validated,[24] single-item 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable); an improvement of ≥ 4 points is considered clinically meaningful.[24] The skin pain VAS assesses patient skin pain on a horizontal scale of 0 mm (no pain) to 100 mm (severe skin pain).

Safety and tolerability were evaluated by the incidence of adverse events (including severity), laboratory measurements, vital signs and physical examinations. Adverse events were coded using the Medical Dictionary for Regulatory Activities terminology.

Sample size

A sample size of 150 patients per treatment group was required to achieve a power of at least 95% for a two-sided χ^2-test at the 5% alpha level, with estimated response rates for PASI 90 at week 12 being 70% for ixekizumab and 43% for ustekinumab.

Statistical analyses

Patients were analysed according to the treatment they were assigned at randomization (intention-to-treat population). The primary-analysis model was a logistic regression for the PASI 90 response end point after 12 weeks of treatment, with terms for treatment group, weight and geographical region. Missing data were imputed via nonresponder imputation (NRI), assuming that patients without data had no response. This primary logistic regression model used 97·5% confidence intervals to estimate the difference in proportions between ixekizumab and ustekinumab (Appendix S2; see Supporting Information).

The eight key secondary end point comparisons (for points i–viii above) were assessed via logistic regression with NRI for binary end points, or ANCOVA with modified baseline observation carried forward for continuous end points. Logistic regression models included terms for treatment group, weight and geographical region. ANCOVA models included terms for baseline value, treatment group, weight and geographical region. To avoid inflation of type I error (i.e. to limit the chance of an overall false-positive result) at the 5% level, the Hommel procedure was used to adjust P-values for key secondary end points at week 12.[25] Comparisons of secondary outcomes over time were made using Fisher's exact test, after data were imputed via the NRI method. Safety analyses were performed in patients who received at least one dose of the study treatment (safety population). Safety events were analysed using Fisher's exact test.

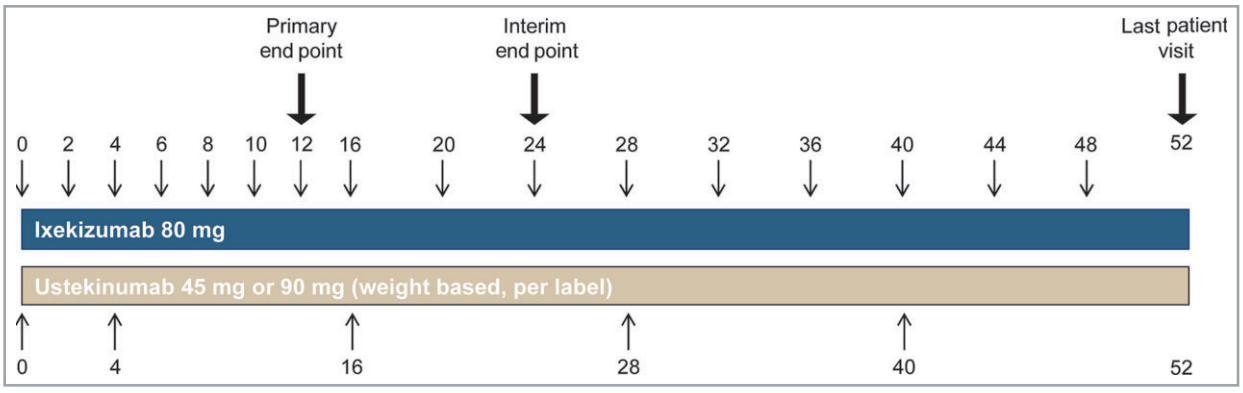

Fig 1. Study design for IXORA-S. Patients were randomized 1 : 1 to receive either ixekizumab or ustekinumab. Ixekizumab patients received a subcutaneous (SC) 160-mg starting dose (two SC injections of 80 mg) at week 0. This was followed by 80-mg SC injections every 2 weeks until week 12. After week 12, ixekizumab patients received 80-mg SC injections every 4 weeks. Ustekinumab patients were dosed, per label, based on weight. Patients weighing ≤ 100·0 kg received 45-mg SC injections and patients weighing > 100·0 kg received 90-mg SC injections. All ustekinumab patients received active SC injections at weeks 0, 4, 16, 28 and 40. The primary end point of the study was at week 12. Arrows indicate weeks when active injections were given for both treatment arms. The last patient visit was at week 52; no injections were given at that visit.

P-values were considered statistically significant at the 5% alpha level and confidence intervals were, unless otherwise noted, at the 95% level. All analyses were conducted using SAS 9.4 software (SAS Institute Inc., Cary, NC, U.S.A.).

Results

Study population

In total, 355 patients were screened (Fig. 2), of whom 302 were randomized to receive ustekinumab (n = 166) or ixekizumab (n = 136). The slight imbalance between the two treatment groups could have resulted from having more incomplete randomization blocks than anticipated; however, there were no signs of a loss of randomization. One patient randomized to ixekizumab discontinued before treatment was administered. Of the patients receiving a study drug, five (1·7%) discontinued prior to week 12, and discontinuation rates were similar between treatment groups (ustekinumab n = 2, ixekizumab n = 3). Between week 12 and week 24, seven patients discontinued from the study (ustekinumab n = 6, ixekizumab n = 1). At week 24, 95·2% of ustekinumab-treated patients and 96·3% of ixekizumab-treated patients remained in the study. The baseline

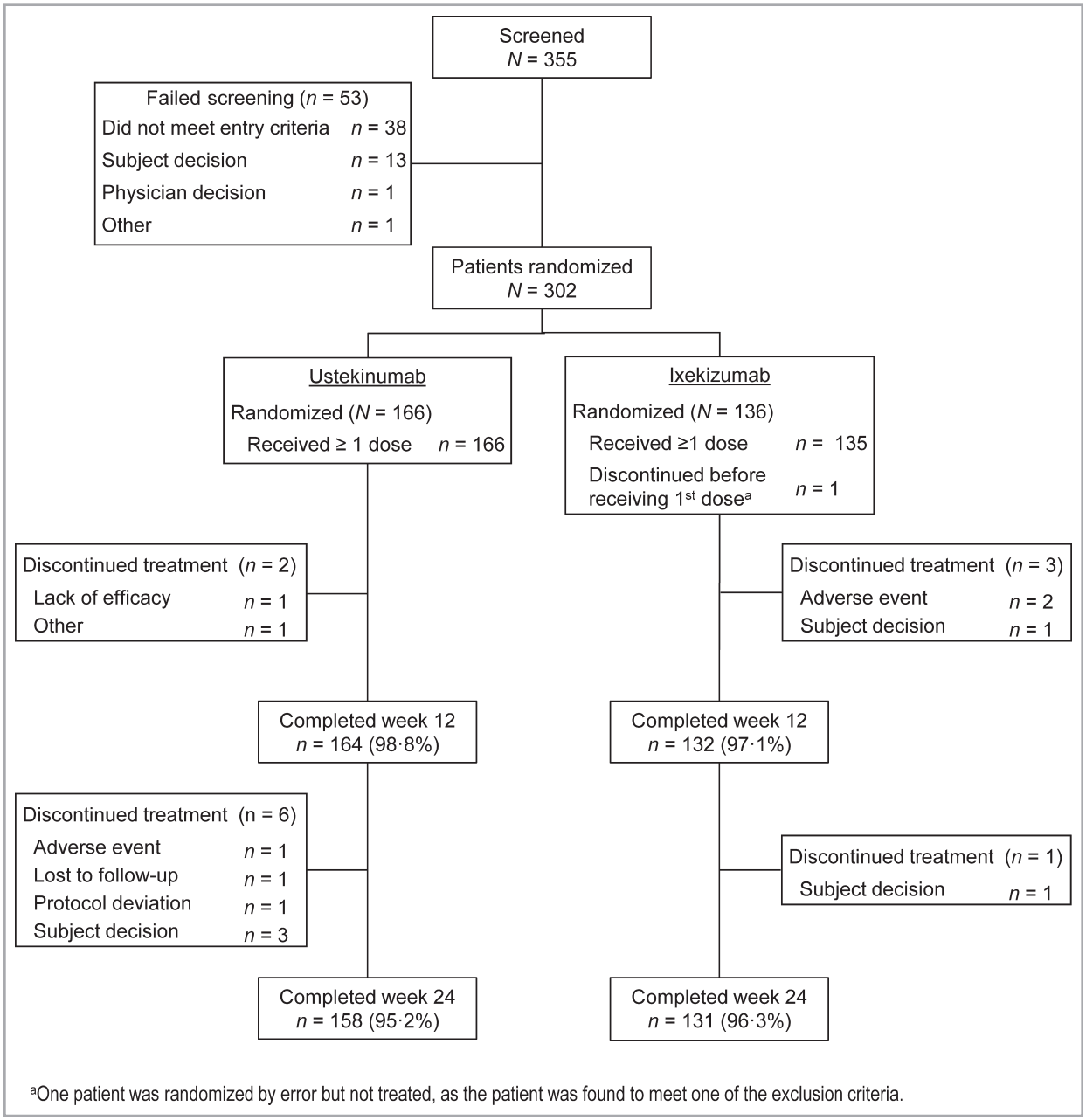

Fig 2. CONSORT flow diagram of participation in the study.

characteristics were overall similar between the treatment arms (Table 1).

Primary end point: week 12

At week 12, significantly more patients in the ixekizumab group (n = 99, 72·8%) than in the ustekinumab group (n = 70, 42·2%) achieved PASI 90 (response difference 32·1%, 97·5% confidence interval 19·8–44·5%, P < 0·001; Figs 3, 4). A significant difference in PASI 90 response was seen as early as week 4 (Fig. 4).

Key secondary end points: week 12

At week 12, ixekizumab showed superiority over ustekinumab in five of the eight key secondary end points (Table 2), with significantly more patients treated with ixekizumab achieving PASI 75, PASI 100, sPGA 0, sPGA (0,1) and DLQI (0,1) compared with ustekinumab. After multiplicity adjustment, three of the eight secondary end points confirmed superiority: PASI 75, PASI 100 and sPGA (0,1) (Table 2).

Ixekizumab provided rapid onset of action, as significantly more patients treated with ixekizumab achieved PASI 75 as early as week 2 (ustekinumab n = 3, 1·8%; ixekizumab n = 22, 16·2%; P < 0·001) and PASI 100 as early as week 4, compared with ustekinumab (ustekinumab n = 0; ixekizumab n = 9, 6·6%; P < 0·001; Fig. 4). Similarly, significantly (P < 0·001) more ixekizumab-treated patients (n = 11, 8·1%) compared with ustekinumab-treated patients (n = 0) reported sPGA 0 as early as week 4 (Fig. S1; see Supporting Information). Among patients with a baseline sPGA score ≥ 3, significantly more patients treated with ixekizumab achieved sPGA (0,1) as early as week 2 (ustekinumab n = 3, 1·8%; ixekizumab n = 16, 11·9%; P < 0·001; Fig. S1).

At week 12, the mean changes from baseline in itch NRS and skin pain VAS, as well as the percentage of patients with ≥ 4-point reduction in itch NRS, were not significantly different between the two treatment groups (itch NRS change: ustekinumab −4·2, ixekizumab −4·8; skin pain VAS change: ustekinumab −29·1, ixekizumab −35·4; itch ≥ 4-point improvement: ustekinumab n = 101, 74·3%; ixekizumab n = 84, 76·4%). However, ixekizumab-treated patients reported faster improvements than ustekinumab-treated patients in itch and skin pain, as illustrated in Figure 5.

Furthermore, a significantly greater proportion of ixekizumab-treated patients reported DLQI (0,1), indicating no impact of psoriasis on HRQoL, as early as week 2 (ustekinumab n = 16, 9·6%; ixekizumab n = 39, 28·7%; P < 0·001; Fig. 5).

Efficacy: week 24

Between weeks 12 and 24, patients treated with ixekizumab continued to have significantly greater PASI improvements than ustekinumab-treated patients (Fig. 4; Table S1; see

Table 1 Baseline demographics and clinical characteristics

	Ustekinumab (N = 166)	Ixekizumab (N = 136)
Age (years), mean ± SD	44·0 ± 13·3	42·7 ± 12·7
Sex (male), n (%)	112 (67·5)	90 (66·2)
Race (white), n (%)	157 (95·7)	125 (93·3)
Weight (kg), mean ± SD	89·4 ± 24·8	85·8 ± 20·3
Weight > 100·0 kg, n (%)	45 (27·1)	31 (23·0)
Body mass index (kg m^{-2}), mean ± SD	29·7 ± 7·0	28·8 ± 5·6
PASI score, mean ± SD	19·8 ± 9·0	19·9 ± 8·2
sPGA score, mean ± SD	3·6 ± 0·6	3·6 ± 0·7
Affected body surface area (%), mean ± SD	27·5 ± 16·7	26·7 ± 16·5
Duration of psoriasis (years), mean ± SD	18·2 ± 12·0	18·0 ± 11·1
Itch numerical rating scale, mean ± SD	6·2 ± 2·6	6·3 ± 2·7
DLQI total score, mean ± SD	12·0 ± 7·3	11·1 ± 7·2
Skin pain visual analogue scale, mean ± SD	39·4 ± 30·8	42·9 ± 33·3
Previous psoriasis treatment (≥ 1), n (%)		
Nonbiologic systemic[a]	152 (91·6)	126 (92·6)
Phototherapy[b]	89 (61·0)	74 (59·7)
Biologics	25 (15·1)	18 (13·2)

Due to missing data, some percentages are calculated from available data only. DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment. [a]Nonbiologic systemic treatments include ciclosporin, methotrexate, corticosteroids, acitretin, fumaric acid derivatives and apremilast. [b]Phototherapy includes psoralen–ultraviolet A and ultraviolet B.

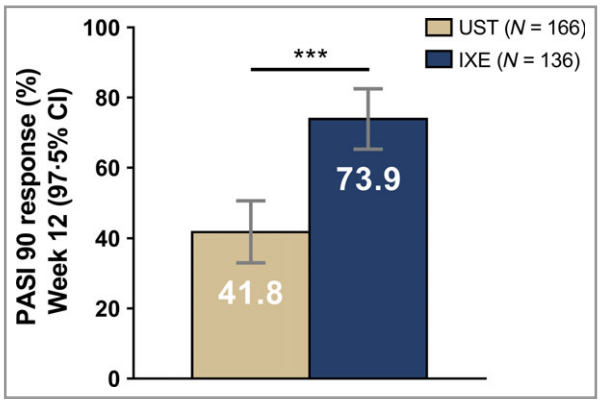

Fig 3. Primary end point: ≥ 90% improvement in Psoriasis Area and Severity Index (PASI 90) response at week 12. A logistic regression model (adjusting for treatment group, weight and geographical region) was used to test for (i) noninferiority of ixekizumab (IXE) compared with ustekinumab (UST) and (ii) the superiority of IXE over UST. The model used a 97·5% confidence interval (CI) to estimate the difference in proportions between IXE and UST. After confirming noninferiority, the superiority of IXE was demonstrated to be significant (***P < 0·001). UST, 41·8% (97·5% CI 33·0–50·6); IXE, 73·9% (97·5% CI 65·3–82·5).

Supporting Information). At week 24, 91·2% (n = 124) of ixekizumab-treated patients and 81·9% (n = 136) of ustekinumab-treated patients achieved PASI 75 (P = 0·029); 83·1% (n = 113) of patients receiving ixekizumab and 59·0% (n = 98) of patients treated with ustekinumab reached PASI 90 (P < 0·001). Complete clearance, as measured by PASI 100, was achieved by 49·3% (n = 67) of patients treated with ixekizumab compared with 23·5% (n = 39) of those receiving ustekinumab (P < 0·001). Consistent results were seen for sPGA 0 and sPGA (0,1) response rates (P < 0·001 for each; Fig. S1).

Patient-reported outcomes: week 24

During weeks 12–24, patient-reported outcome measures continued to improve for both treatment groups. At week 24, significantly more ixekizumab-treated patients (n = 90, 66·2%) than patients treated with ustekinumab (n = 88, 53·0%) reported a DLQI score of 0 or 1 (P = 0·025; Fig. 5).

Irrespective of baseline values, the changes from baseline in itch NRS and skin pain VAS remained numerically higher for all patients receiving ixekizumab compared with those receiving ustekinumab, but were not statistically different at week 24 between the two treatment groups (Fig. 5). However, among the patients with baseline itch NRS ≥ 4, significantly more ixekizumab-treated patients reached ≥ 4-point reduction on the itch NRS (n = 94, 85·5%) compared with the ustekinumab treatment group at week 24 (n = 98, 72·1%; P = 0·013; Fig. 5).

Safety

After 24 weeks of treatment, no deaths were reported. Serious adverse events were experienced by five (3·0%) patients in the ustekinumab group and three (2·2%) patients in the ixekizumab group (P = 0·735; Table 3). As this is an ongoing study, details related to serious and/or rare adverse events are not reported to maintain blinding.

Adverse events leading to discontinuation were reported by one (0·6%) ustekinumab-treated patient and two (1·5%) patients treated with ixekizumab (P = 0·589; Table 3).

Overall, there was no statistically significant difference in treatment-emergent adverse events (TEAEs) between the treatment groups (P = 0·299; Table 3). TEAEs were reported by 125 patients (75·3%) in the ustekinumab group and 94 patients (69·6%) in the ixekizumab group. There was also no significant difference (P = 0·613) in TEAEs rated as severe between the two groups (ustekinumab n = 10, 6·0%;

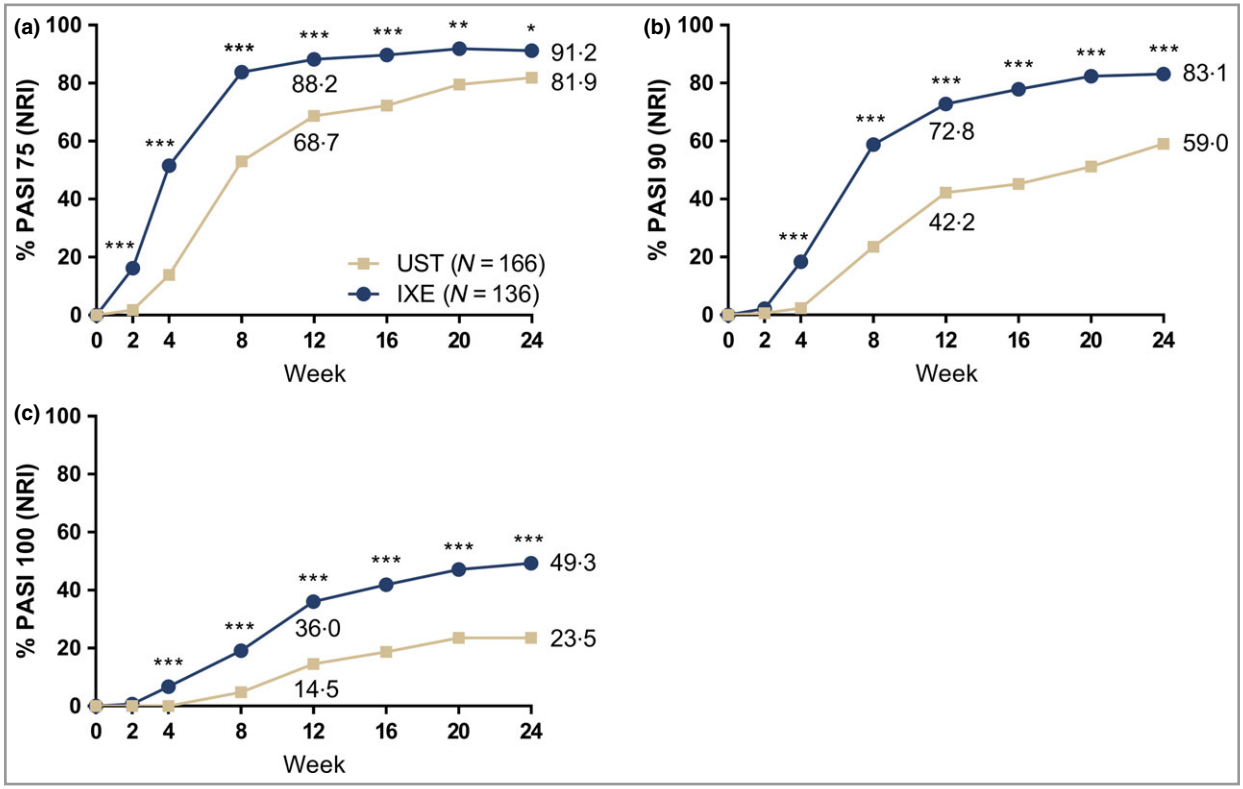

Fig 4. Psoriasis Area and Severity Index (PASI) response rates for patients treated with ixekizumab (IXE; N = 136) or ustekinumab (UST; N = 166) from week 0 to week 24; the primary end point was at week 12. At week 12, IXE patients switched from 80 mg every 2 weeks to 80 mg every 4 weeks. (a) PASI 75; (b) PASI 90; (c) PASI 100. PASI response rates were calculated via nonresponder imputation (NRI). ***P < 0·001, **P < 0·01, *P < 0·05 via Fisher's exact test.

Table 2 Clinical responses at week 12 and week 24

	Week 12				Week 24		
	Ustekinumab (N = 166)	Ixekizumab (N = 136)	P-value[c]	Adjusted P-value[d]	Ustekinumab (N = 166)	Ixekizumab (N = 136)	P-value[c]
PASI response, n (%)							
PASI 100	24 (14·5)	49 (36·0)	0·009	0·044	39 (23·5)	67 (49·3)	0·001
PASI 90	70 (42·2)	99 (72·8)	< 0·001	–	98 (59·0)	113 (83·1)	< 0·001
PASI 75	114 (68·7)	120 (88·2)	< 0·001	0·002	136 (81·9)	124 (91·2)	0·015
sPGA response							
sPGA 0, n (%)	30 (18·1)	57 (41·9)	0·021	0·085	40 (24·1)	73 (53·7)	< 0·001
sPGA 0 or 1, n (%)[a]	95 (57·2)	112 (83·6)	< 0·001	< 0·001	115 (69·3)	116 (86·6)	< 0·001
DLQI (0,1), n (%)	74 (44·6)	83 (61·0)	0·012	0·053	88 (53·0)	90 (66·2)	0·030
Itch NRS							
At least 4-point improvement from baseline, n (%)[b]	101 (74·3)	84 (76·4)	0·704	0·704	98 (72·1)	94 (85·5)	0·018
Change from baseline, mean ± SD	−4·2 ± 3·0	−4·8 ± 3·0	0·085	0·170	−4·6 ± 2·8	−5·0 ± 2·9	0·214
Skin pain VAS change from baseline, mean ± SD	−29·1 ± 30·7	−35·4 ± 32·1	0·072	0·144	−31·4 ± 29·9	−36·4 ± 32·7	0·340

The response and change values shown were computed via nonresponder imputation (NRI) and modified baseline observation carried forward, respectively. P-values < 0·05 are statistically significant. DLQI, Dermatology Life Quality Index; NRS, numerical rating scale; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment; VAS, visual analogue scale. [a]Among patients with baseline score ≥ 3, and ≥ 2-point improvement from baseline. [b]Among patients with a baseline score ≥ 4. [c]P-value for categorical data (PASI, sPGA, DLQI, itch improvement) based on relative risk of logistic regression (95% confidence interval) with terms for weight, treatment and geographical region; P-value for continuous data (change from baseline) based on least squares mean using an ANCOVA model (95% confidence interval), with terms for baseline, weight, treatment and geographical region. [d]Adjusted P-value generated using the Hommel procedure.

ixekizumab n = 6, 4·4%). The most common TEAE was nasopharyngitis (ustekinumab n = 45, 27·1%, ixekizumab n = 33, 24·4%).

Discussion

Patients enrolled in the IXORA-S study were highly representative of those receiving biological treatments in clinical practice throughout Europe. This study demonstrated the rapid and superior efficacy of ixekizumab compared with ustekinumab at week 12, as assessed by PASI 90 response (primary end point), which was maintained through week 24. Similar observations were made for total clearance (PASI 100). Overall, ixekizumab was found to be statistically superior to ustekinumab as early as week 2 and/or week 4 for all key secondary end points. During the first 24 weeks of IXORA-S, both drugs were generally well tolerated. These data indicate that ixekizumab can provide a faster and greater level of improvement than ustekinumab in patients with plaque psoriasis, while maintaining a safety profile consistent with previous reports.

The clinical relevance of these observations relies upon the accumulating evidence that higher levels of skin clearance allow patients to reach a better quality of life,[22,26–28] which was confirmed in IXORA-S with concurrent DLQI improvement. The IXORA-S study also adds to the knowledge on comparative efficacy between IL-17 inhibitors and existing biologics, as recently investigated in the CLEAR[14,16] and AMAGINE[29] studies, which may be important to guide treatment decisions. The efficacy results obtained with ixekizumab in the IXORA-S study are consistent with the observations made during the UNCOVER phase III programme.[12,13]

The ustekinumab efficacy data are slightly lower in IXORA-S than the results recently reported in the CLEAR study, which compared secukinumab with ustekinumab, where PASI 90 was reached by 66·3% of the patients treated with ustekinumab by week 24.[16] However, in the CLEAR trial, the efficacy of secukinumab was also higher than reported in the ERASURE and FIXTURE studies.[14,15] Of note, the patient population in CLEAR was different from the population recruited for the IXORA-S study; patients in the CLEAR study could be naive to any systemic treatment,[15] while IXORA-S enrolled patients who met the European label for ustekinumab (i.e. must have failed to respond to, have a contraindication to, or are intolerant to other systemic therapies).

To allow for better comparison with the ixekizumab UNCOVER phase III studies, the end of the ixekizumab induction period at week 12 was chosen as the primary end point in the IXORA-S study. However, we concede that a primary comparison with ustekinumab at week 12 may be too early with respect to the ustekinumab dose regimen, as there is evidence that ustekinumab reaches peak efficacy around 24 weeks.[18,19] Thus, for a more accurate comparison between the two treatments, data up to week 24 are reported.

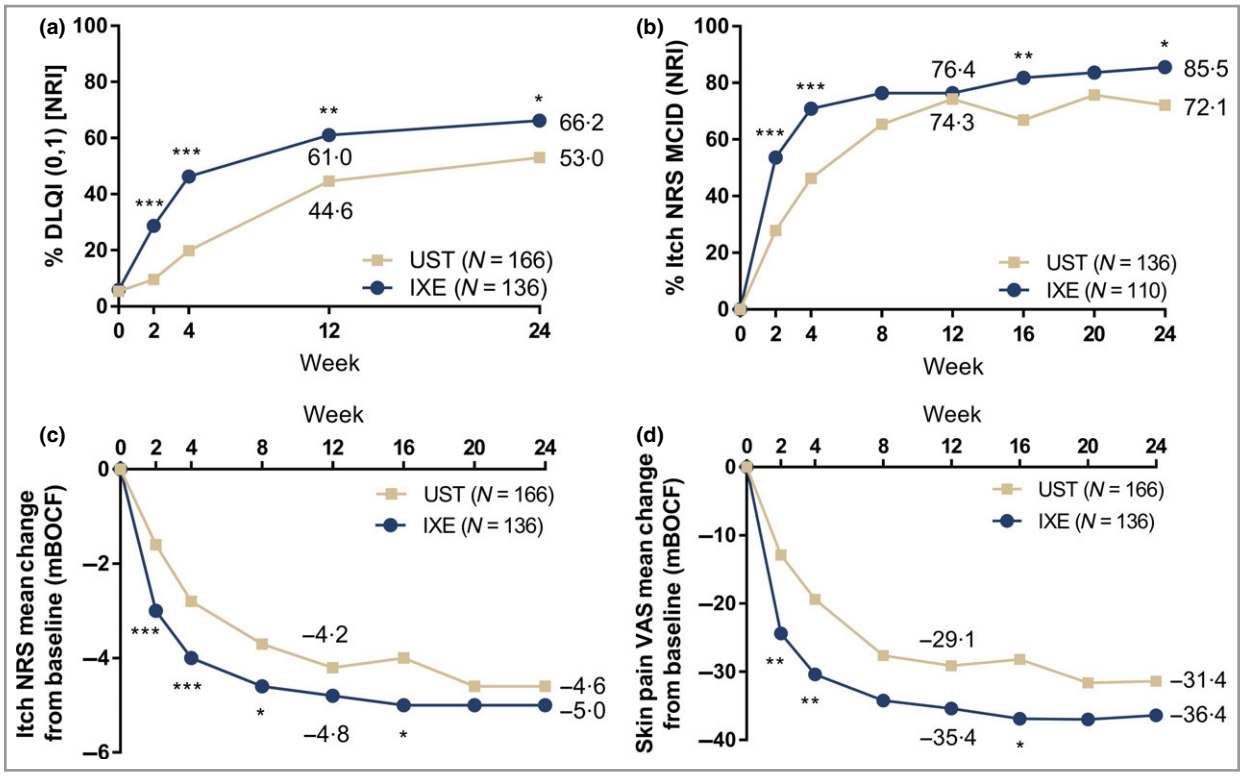

Fig 5. Patient-reported outcomes for ixekizumab (IXE; N = 136) and ustekinumab (UST; N = 166) from week 0 to week 24; the primary end point was at week 12. At week 12, IXE patients switched from 80 mg every 2 weeks to 80 mg every 4 weeks. (a) Dermatology Life Quality Index (DLQI) (0,1) response rates via nonresponder imputation (NRI). (b) Percentage of patients achieving the itch numerical rating scale (NRS) minimally clinical important difference (MCID) of ≥ 4-point improvement, among patients with a baseline itch NRS score ≥ 4 (IXE, N = 110; UST, N = 136) via NRI. (c) Itch NRS mean change from baseline via the modified baseline observation carried forward (mBOCF) method. (d) Skin pain visual analogue scale (VAS) mean change from baseline via the mBOCF method. ***P < 0·001, **P < 0·01, *P < 0·05 via Fisher's exact test (a, b) or Wilcoxon rank sum test (c, d).

Table 3 Adverse events during the 24-week treatment period

	Ustekinumab (N = 166)	Ixekizumab (N = 135)	P-value[b]
Any TEAE	125 (75·3)	94 (69·6)	0·299
Severe TEAE	10 (6·0)	6 (4·4)	0·613
Death	0	0	n.a.
Nonfatal serious AE	5 (3·0)	3 (2·2)	0·735
Discontinuation due to AE	1 (0·6)	2 (1·5)	0·589
Infections	87 (52·4)	57 (42·2)	0·083
Selected common TEAEs[a]			
Nasopharyngitis	45 (21·7)	33 (24·4)	n.a.
Headache	13 (7·8)	10 (7·4)	n.a.
Arthralgia	10 (6·0)	6 (4·4)	n.a.
Hypertension	8 (4·8)	4 (3·0)	n.a.
Rhinitis	7 (4·2)	3 (2·2)	n.a.
Back pain	7 (4·2)	1 (0·7)	n.a.

Values are n (%). AE, adverse event; n.a., not applicable; TEAE, treatment-emergent adverse event. [a]Common TEAEs were defined as having a frequency ≥ 4% in either treatment arm during the 24-week treatment period; any TEAEs that met the 4% threshold but had events in only one treatment arm were excluded from this analysis in order to maintain the blinding of this ongoing study. [b]Calculated by Fisher's exact test.

Some limitations should be considered with regard to the interpretation of the data, mainly the lack of a placebo group. However, both treatments (ixekizumab and ustekinumab) have previously demonstrated superior efficacy over placebo in large phase III clinical trials,[12,13,18,19] which might have made the inclusion of an additional placebo arm questionable from an ethical perspective.

In conclusion, the IXORA-S study has demonstrated the superiority of ixekizumab over ustekinumab at week 12 with regard to PASI 90 improvement. PASI 90 response was significantly higher as early as week 4 and was maintained through to week 24. These data confirm the rapid and sustained levels of high skin clearance observed with ixekizumab during the UNCOVER programme and further demonstrate that PASI 90 is an achievable goal for a majority of patients with moderate-to-severe plaque psoriasis.

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References

1 Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of psoriasis. *Annu Rev Immunol* 2014; **32**:227–55.
2 Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. *J Invest Dermatol* 2009; **129**:1339–50.
3 Raychaudhuri S. Role of IL-17 in psoriasis and psoriatic arthritis. *Clin Rev Allergy Immunol* 2013; **44**:183–93.
4 Cai Y, Shen X, Ding C *et al.* Pivotal role of dermal IL-17-producing γδ T cells in skin inflammation. *Immunity* 2011; **35**:596–610.
5 Cai Y, Fleming C, Yan J. Dermal γδ T cells – a new player in the pathogenesis of psoriasis. *Int Immunopharmacol* 2013; **16**:388–91.
6 Di Meglio P, Nestle FO. The role of IL-23 in the immunopathogenesis of psoriasis. *F1000 Biol Rep* 2010; **2**:40.
7 Piskin G, Sylva-Steenland RMR, Bos JD, Teunissen MBM. *In vitro* and *in situ* expression of IL-23 by keratinocytes in healthy skin and psoriasis lesions: enhanced expression in psoriatic skin. *J Immunol* 2006; **176**:1908–15.
8 Liu L, Lu J, Allan BW *et al.* Generation and characterization of ixekizumab, a humanized monoclonal antibody that neutralizes interleukin-17A. *J Inflamm Res* 2016; **9**:39–50.
9 Hueber W, Patel DD, Dryja T et al. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. *Sci Transl Med* 2010; **2**:52ra72.
10 Papp KA, Leonardi C, Menter A *et al.* Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med* 2012; **366**:1181–9.
11 Krueger GG, Langley RG, Leonardi C *et al.* A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med* 2007; **356**:580–92.
12 Gordon KB, Blauvelt A, Papp KA *et al.* Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med* 2016; **375**:345–56.
13 Griffiths CEM, Reich K, Lebwohl M *et al.* Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet* 2015; **386**:541–51.
14 Thaçi D, Blauvelt A, Reich K *et al.* Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol* 2015; **73**:400–9.
15 Langley RG, Elewski BE, Lebwohl M *et al.* Secukinumab in plaque psoriasis – results of two phase 3 trials. *N Engl J Med* 2014; **371**:326–38.
16 Blauvelt A, Reich K, Tsai TF *et al.* Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: results from the CLEAR study. *J Am Acad Dermatol* 2017; **76**:60–9.
17 Griffiths CEM, Strober BE, van de Kerkhof P *et al.* Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med* 2010; **362**:118–28.
18 Papp KA, Langley RG, Lebwohl M *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; **371**:1675–84.
19 Leonardi CL, Kimball AB, Papp KA *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008; **371**:1665–74.
20 Nast A, Gisondi P, Ormerod AD *et al.* European S3-guidelines on the systemic treatment of psoriasis vulgaris – update 2015 – short version – EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol* 2015; **29**:2277–94.
21 Blauvelt A, Armstrong AW, Krueger GG. Essential truths for the care and management of moderate-to-severe psoriasis. *J Drugs Dermatol* 2015; **14**:805–12.
22 Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. *J Eur Acad Dermatol Venereol* 2015; **29**:645–8.
23 Hongbo Y, Thomas CL, Harrison MA *et al.* Translating the science of quality of life into practice: what do Dermatology Life Quality Index scores mean? *J Invest Dermatol* 2005; **125**:659–64.
24 Kimball AB, Naegeli AN, Edson-Heredia E *et al.* Psychometric properties of the Itch Numeric Rating Scale in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol* 2016; **175**:157–62.
25 Hommel G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika* 1988; **75**:383–6.
26 Edson-Heredia E, Banerjee S, Zhu B *et al.* A high level of clinical response is associated with improved patient-reported outcomes in psoriasis: analyses from a phase 2 study in patients treated with ixekizumab. *J Eur Acad Dermatol Venereol* 2016; **30**:864–5.
27 Takeshita J, Callis Duffin K, Shin DB *et al.* Patient-reported outcomes for psoriasis patients with clear versus almost clear skin in the clinical setting. *J Am Acad Dermatol* 2014; **71**:633–41.
28 Viswanathan HN, Chau D, Milmont CE *et al.* Total skin clearance results in improvements in health-related quality of life and reduced symptom severity among patients with moderate to severe psoriasis. *J Dermatolog Treat* 2015; **26**:235–9.
29 Lebwohl M, Strober B, Menter A *et al.* Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med* 2015; **373**:1318–28.

Appendix 1

Conflicts of interest

K.R. has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, Medac, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Takeda, UCB Pharma and Xenoport. A.P. has served as an advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, Medac, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron and UCB. J.P.L. has served as an advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Amgen, Boehringer Ingelheim, Celgene, Galderma, Janssen, LEO Pharma, Lilly, Merck-Serono, Novartis, Pfizer, Regeneron, Roche and UCB Pharma. C.F. has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Amgen, Celgene, Centocor, Janssen-Cilag, LEO Pharma, Lilly, Merck Sharp & Dohme, Novartis and Pfizer. G.M. has served as an investigator for Lilly. L.E.F. has served as an advisor for and/or participated in clinical trials sponsored by AbbVie, Amgen, Celgene, Eli Lily and Company, Galderma, Janssen-Cilag and Novartis. M.L. has worked as a consultant and/or clinical trial investigator for AbbVie, Allergan,

Amgen, Anacor, Boehringer Ingelheim, Celgene, Dr Reddy's, Janssen, LEO Pharma, Lilly, Merck-Serono, Novartis, Oncobiologics, Pfizer, Regeneron, Roche, Xenon Pharma, Valeant, Bayer, L'Oreal and Galderma. Y.D, C.H., S.W. and S.H. are employees of Eli Lilly and Company, and receive salary from and own stock in the company. C.P. has served as a consultant and/or investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis and Pfizer. A full list of the IXORA-S investigators is provided in Appendix S1 (see Supporting Information).

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1. The IXORA-S investigators.

Appendix S2. Supplementary methods.

Fig S1. Static Physician's Global Assessment response rates.

Table S1. Efficacy results at each time point.

Video S1. Author video.