PROFESSOR KRISTIAN REICH (Orcid ID : 0000-0001-5248-4332)

PROFESSOR CARLE F PAUL (Orcid ID : 0000-0003-0165-5263)

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Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a Phase 3 study

K. Reich,[1] A. Pinter,[2] J. P. Lacour,[3] C. Ferrandiz,[4] G. Micali,[5] L. E. French,[6] M. Lomaga,[7] Y. Dutronc,[8] C. Henneges,[8] S. Wilhelm,[8] S. Hartz,[8] C. Paul[9] on behalf of the IXORA-S investigators*

[1]*Dermatologikum Hamburg, Hamburg, Germany and Georg-August-University, Göttingen, Germany*
[2]*Department of Dermatology, Venereology, and Allergology, Universitiy Clinic Frankfurt, Frankfurt am Main, Germany*
[3]*Department of Dermatology, University Hospital of Nice, Nice, France*
[4]*Servicio de Dermatología, Hospital Universitario Germans Trias i Pujol, Universitat Autónoma de Barcelona, Badalona, Barcelona, Spain*
[5]*Dermatology Clinic, University of Catania, University Hospital Policlinico-Vittorio Emanuele, Catania, Sicily, Italy*
[6]*Department of Dermatology, University of Zurich Hospital, Zurich, Switzerland*
[7]*DermEdge Research, Mississauga, Ontario, Canada*
[8]*Eli Lilly and Company, Indianapolis, IN, USA*
[9]*Dermatology Department, CHU, Paul Sabatier University, Toulouse, France*

*Investigators listed in supplement

Corresponding Author:
Kristian Reich, MD
Dermatologikum Hamburg
Stephansplatz 5
20354, Hamburg, Germany
Phone: +49 40-35 10 75-0
Fax: +49 40-35 10 75-10
Email: kreich@dermatologikum.de

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IRB: Study protocol was approved by the Institutional Review Board at each study centre. Written, informed consent was obtained from each patient at study entry before any study procedures took place**.**

Trial registration: NCT02561806

- With the advancements in new biologics targeting the IL-17A pathway, the majority of patients with moderate-to-severe psoriasis are now able to achieve complete or near complete clearance of psoriasis.
- The IL-17A inhibitor ixekizumab provides superior efficacy compared to the IL-12/23 inhibitor ustekinumab, with a similar safety profile after 24 weeks of treatment.

Keywords: psoriasis, ixekizumab, ustekinumab, PASI 90, clinical trial

ABSTRACT

Background: The interleukin (IL)-23/IL-17 axis has been shown critical in the pathogenesis of psoriasis.

Objectives: To present the primary endpoint (Week 12) and safety/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: Randomised patients received IXE (160-mg starting dose, then 80 mg every two weeks for 12 weeks, then 80 mg every four weeks, N=136) or UST (45 mg/90 mg weight-based dosing per label, N=166). The primary endpoint was the proportion of patients reaching ≥90% Psoriasis Area and Severity Index improvement (PASI 90). Hommel-adjusted key secondary endpoints at Week 12 included PASI 75, PASI 100, static physician global assessment (sPGA) (0,1), sPGA (0), Dermatology Life Quality Index (DLQI) score of (0,1), ≥4-point reduction on the itch Numeric Rating Scale (NRS), and changes in itch NRS and skin pain Visual Analog Scale (VAS).

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<.001). Response rates for PASI 75, PASI 100, and sPGA (0,1) were significantly higher for IXE vs. UST (adjusted p<.05). At Week 24, IXE-treated patients had significantly higher response rates than UST-treated patients for PASI, sPGA, and DLQI (unadjusted p<.05). No deaths were reported, and treatments did not differ with regard to overall incidences of adverse events (p=.299).

Conclusions: The superior efficacy of IXE demonstrated at Week 12 persisted up to Week 24. Safety profiles were consistent with what has been previously reported for both treatments.

INTRODUCTION

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 biologic treatments specifically targeting these cytokines,[8-11] enabling higher levels of skin improvement than those provided by anti-tumour necrosis factor (TNF) agents.[12-16]

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

Blocking IL-17A, a cytokine that directly activates keratinocytes and stimulates the production of chemokines, cytokines, and antimicrobial peptides that contribute to the clinical manifestations of psoriasis, represents the most recent approach to effectively control this disease.[3-5] Ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A,[8] has already demonstrated greater efficacy than the TNF alpha-inhibitor etanercept in two Phase 3 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 to 18.7% of ETN 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 biologic 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 endpoint data is presented herein. 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.

METHODS

Study Population

Eligible study participants were 18 years of age or older, had a diagnosis of chronic plaque psoriasis for ≥6 months, a PASI score ≥10, and had previously failed, had a contraindication, or intolerability to at least one systemic therapy (including cyclosporine, methotrexate or phototherapy). Key exclusion criteria were a predominant presence of non-plaque 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. First patient randomisation took place on October 21, 2015 and Week 24 last patient visit was on August 3, 2016.

Study Design

This 52-week, Phase 3b, multicentre, controlled, double-blind, parallel-group trial (IXORA-S, NCT02561806) was conducted at 51 sites across 13 countries. Patients were randomised (1:1) via an interactive web-response system (IWRS) to receive either ixekizumab (IXE) or ustekinumab (UST). Randomisation was stratified by study centre and patient weight (≤100.0 kg vs. >100.0 kg). Clinical trial details can be accessed at www.clinicaltrials.gov.

During the induction period (weeks 0-12), patients randomised to ixekizumab received two subcutaneous (SC) injections of 80 mg ixekizumab (160-mg total) at Week 0, followed by one SC injection of 80 mg ixekizumab every two weeks, through Week 12 and 80 mg every four weeks thereafter (Fig. 1). Patients randomised 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 randomised 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/ustekinumab placebo injections were neither involved in clinical assessments nor treatment decisions and kept patients and investigators blinded from treatment allocation.

Study Objectives

The primary objective of IXORA-S was to demonstrate first that ixekizumab is non-inferior (inferiority margin: -12.6%) and second that ixekizumab is superior to ustekinumab, as measured by the proportion of patients achieving a PASI 90 response at Week 12.

Eight key secondary endpoints at Week 12 were defined: the proportion of patients achieving [1] PASI 75 response, [2] PASI 100 response, [3] static physicians global assessment (sPGA) (0) response, [4] sPGA (0,1) response with at least a 2-point improvement in patients with a baseline sPGA ≥3, [5] Dermatology Life Quality Index (DLQI) (0,1), [6] itch Numeric Rating Scale (NRS) ≥4-point improvement in patients with baseline itch NRS ≥4, and the changes from baseline in [7] the itch NRS, as well as [8] the skin pain Visual Analog Scale (VAS).

The PASI is a primary efficacy measurement for psoriasis which 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 categorising 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 – 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 0 (no pain) to 100 (severe skin pain) millimetre horizontal scale.

Safety and tolerability were evaluated via incidence of adverse events (AEs) (including severity), laboratory measurements, vital signs, and physical examinations. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) 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 Chi-squared 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 randomisation (intent-to-treat population, ITT). The primary analysis model was a logistic regression for the PASI 90 response endpoint after 12 weeks of treatment, with terms for treatment group, weight, and geographic region. Missing data were imputed via non-responder 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 (see Supplemental Methods).

The eight key secondary endpoint (points 1-8 above) comparisons were assessed via logistic regression with NRI for binary endpoints or analysis of covariance (ANCOVA) with modified baseline observation carried forward (mBOCF) for continuous endpoints. Logistic regression models included terms for treatment group, weight, and geographic region. ANCOVA models included terms for baseline value, treatment group, weight, and geographic region. To avoid inflation of type I error (i.e. to limit the chance for an overall false positive result) at the 5% level, the Hommel procedure was used to adjust p-values for key secondary endpoints 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 Fishers exact test.

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.

RESULTS

Study Population

A total of 355 patients were screened (Fig. 2), of which 302 patients were randomised to receive ustekinumab (N=166) or ixekizumab (N=136). The slight imbalance between the two treatment groups could result from having more incomplete randomisation blocks than anticipated; however, there were no signs for a loss of randomisation. One patient randomised to ixekizumab discontinued before treatment was administered. Of the patients receiving study

drug, a total of five (1.7%) discontinued prior to Week 12, and discontinuation rates were similar between treatment groups (UST n=2, IXE n=3). Between Week 12 and Week 24, seven patients discontinued from the study (UST n=6, IXE n=1). At Week 24, 95.2% of ustekinumab-treated patients and 96.3% of ixekizumab-treated patients remained in the study. Baseline characteristics were overall similar between the treatment arms (Table 1).

Primary Endpoint – 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% CI: 19.8%−44.5%, p<.001; Figs. 3-4). A significant difference in PASI 90 response was seen as early as Week 4 (Fig. 4).

Key Secondary Endpoints – Week 12

At Week 12, ixekizumab showed superiority over ustekinumab in five of eight key secondary endpoints (Table 2), with significantly more patients treated with ixekizumab achieving PASI 75, PASI 100, sPGA (0), sPGA (0,1) and DLQI (0,1) compared to ustekinumab. After multiplicity adjustment, three of the eight secondary endpoints 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 (UST n=3, 1.8%, IXE n=22, 16.2%; p<.001) and PASI 100 as early as Week 4, compared to ustekinumab (UST n=0, IXE n=9, 6.6%; p<.001; Fig. 4). Likewise, significantly (p<.001) more ixekizumab-treated patients (n=11, 8.1%) compared to ustekinumab-treated patients (n=0) reported sPGA (0) as early as Week 4 (Supp. Fig. 1). Among patients with a baseline sPGA score ≥3, significantly more patients treated with ixekizumab achieved sPGA (0,1) as early as Week 2 (UST n=3, 1.8%, IXE n=16, 11.9%; p<.001; Supp. Fig. 1).

At Week 12, the mean change from baseline in itch NRS and skin pain VAS, as well as the percentage of patients with a ≥4-point reduction in itch NRS, were not significantly different between the two treatment groups (itch NRS change: UST -4.2, IXE -4.8; skin pain VAS change: UST -29.1, IXE -35.4; itch ≥4-point improvement: UST n=101, 74.3%, IXE 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 (UST n=16, 9.6%, IXE n=39, 28.7%; p<.001; Fig. 5).

Efficacy – Week 24

Between weeks 12 and 24, patients treated with ixekizumab continued to have significantly better PASI improvements compared to ustekinumab-treated patients (Fig. 4; Supplemental Table 1). At Week 24, 91.2% (n=124) of ixekizumab-treated patients and 81.9% (n=136) of ustekinumab-treated patients achieved PASI 75 (p=.029); 83.1% (n=113) of patients receiving ixekizumab and 59.0% (n=98) of patients treated with ustekinumab reached PASI 90 (p<.001). Complete clearance, as measured by PASI 100, was achieved by 49.3% (n=67) of patients treated with ixekizumab compared to 23.5% (n=39) of those receiving ustekinumab (p<.001). Consistent results were seen for sPGA (0) and sPGA (0,1) response rates (p<.001 for each; Supp. Fig. 1).

Patient Reported Outcomes – Week 24

During weeks 12 to 24, patient reported outcome measures continued to improve for both treatment groups. At Week 24, significantly more ixekizumab-treated patients (n=90, 66.2%) compared to patients treated with ustekinumab (n=88, 53.0%) reported a DLQI (0,1) (p=.025; Fig. 5).

Irrespective of baseline values, change from baseline in itch NRS and skin pain VAS remained numerically higher for all patients receiving ixekizumab compared to those receiving ustekinumab, but was 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 a ≥4-point reduction on the itch NRS (n=94, 85.5%) compared to the ustekinumab treatment group at Week 24 (n=98, 72.1%; p=.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=.735; Table 3). Since 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=.589; Table 3).

Overall, there was no statistically significant difference in treatment-emergent adverse events (TEAEs) between the treatment groups (p=.299; Table 3). TEAEs were reported by 125 patients (75.3%) in the ustekinumab group and 94 (69.6%) patients in the ixekizumab group. There was also no significant difference (p=.613) in TEAEs rated as severe between the two groups (UST n=10, 6.0%, IXE n=6, 4.4%). The most common TEAE was nasopharyngitis (UST n=45, 27.1%, IXE n=33, 24.4%).

DISCUSSION

Patients enrolled in the IXORA-S study were highly representative of those receiving biologic treatments in clinical practice throughout Europe. This study demonstrated the rapid and

superior efficacy of ixekizumab compared to ustekinumab at Week 12, as assessed by PASI 90 response (primary endpoint), 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 endpoints. 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 suffering from 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 in 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. Efficacy results obtained with ixekizumab in the IXORA-S study are consistent with the observations made during the UNCOVER phase 3 program.[12, 13] Ustekinumab efficacy data are slightly lower in IXORA-S than the results recently reported in the CLEAR study, which compared secukinumab to 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 naïve to any systemic treatment, [15] while IXORA-S enrolled patients met the European label for ustekinumab (i.e. must have failed to respond to, or who have a contraindication to or are intolerant to other systemic therapies).

To allow for a better comparison with the ixekizumab UNCOVER phase-3 studies, the end of the ixekizumab induction period at Week 12 was chosen as the primary endpoint 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.

Some limitations should be considered with regard to the interpretation of the data, mainly the lack of a placebo group. However, both treatments, i.e. ixekizumab and ustekinumab, have previously demonstrated superior efficacy when compared to placebo in large Phase 3 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 compared to ustekinumab at Week 12 with regard to PASI 90 improvement. PASI 90 response was significantly higher as early as Week 4 and maintained through to Week 24. These data confirm the rapid and sustained levels of high skin clearance observed with ixekizumab during the UNCOVER program and further demonstrate that PASI 90 is an achievable goal for a majority of patients suffering from moderate-to-severe plaque psoriasis.

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FIGURE LEGENDS

Figure 1. Study design for IXORA-S. Patients were randomised 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 on weeks 0, 4, 16, 28, and 40. The primary endpoint of the study was at Week 12. Arrows indicate weeks when active injections were given for both treatment arms. Last patient visit was at Week 52; no injections given at that visit.

Figure 3. Primary endpoint – PASI 90 response at Week 12. A logistic regression model (adjusting for treatment group, weight, and geographic region) was used to test for (1) non-inferiority of ixekizumab compared to ustekinumab and (2) the superiority of ixekizumab (IXE) to ustekinumab (UST). The model used a 97.5% confidence interval (CI) to estimate the difference in proportions between ixekizumab and ustekinumab. After confirming non-inferiority, the superiority of ixekizumab was demonstrated to be significant (***p<.001) as shown above (97.5% CI). UST: 41.8% (33.0%, 50.6%); IXE: 73.9% (65.3%, 82.5%).

Figure 4. PASI response rates. PASI response rates for ixekizumab (IXE)-treated (N=136) and ustekinumab (UST)-treated (N=166) patients from Week 0 to Week 24; primary endpoint was 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 non-responder imputation (NRI); ***p<.001, **p<.01, *p<.05 via Fisher's exact test.

Figure 5. Patient reported outcomes. Patient reported outcomes for ixekizumab (IXE)-treated (N=136) and ustekinumab (UST)-treated (N=166) patients from Week 0 to Week 24; primary endpoint was Week 12. At Week 12, IXE patients switched from 80 mg every 2 weeks to 80 mg every 4 weeks. **(a)** DLQI (0,1) response rate via non-responder imputation (NRI); ***p<.001, **p<.01, *p<.05 via Fisher's exact test **(b)** Percent of patients achieving the itch NRS minimally clinical important difference (MCID) of at least a 4-point improvement, among patients with a baseline itch NRS score ≥4 at baseline (IXE: n=110, UST: n=136) via NRI; ***p<.001, **p<.01, *p<.05 via Fisher's exact test **(c)** Itch NRS mean change from baseline via modified baseline carried forward (mBOCF) method; ***p<.001, *p<.05 via Wilcoxon rank sum test **(d)** Skin pain VAS mean change from baseline via mBOCF method; **p<.01, *p<.05 via Wilcoxon rank sum test.

Supplemental Figure 1. sPGA Response Rates. sPGA response rates for ixekizumab (IXE)-treated and ustekinumab (UST)-treated patients from Week 0 to Week 24; primary endpoint was Week 12. At Week 12, IXE patients switched from 80 mg every 2 weeks to 80 mg every 4 weeks. **(b)** sPGA (0) among all patients **(b)** sPGA (0,1) response rates among patients with a baseline sPGA score ≥3 and had a ≥2 point improvement from baseline. sPGA response rates were calculated via non-responder imputation (NRI); ***p<.001 via Fisher's exact test.

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)
Gender (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)
BMI [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)
% BSA, 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 NRS, 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 VAS, mean (SD)	39.4 (30.8)	42.9 (33.3)
Previous psoriasis treatment		
Non-biologic systemic[†] (≥1), n (%)	152 (91.6)	126 (92.6)
Phototherapy[‡] (≥1), n (%)	89 (61.0)	74 (59.7)
Biologics (≥1), n (%)	25 (15.1)	18 (13.2)

BMI=body mass index, BSA=body surface area, DLQI=Dermatology Life Quality Index, NRS=Numeric Rating Scale, PASI=Psoriasis Area and Severity Index, SD=standard deviation, sPGA=static Physician's Global Assessment, VAS=Visual Analog Scale

[†]Non-biologic systemic treatments include cyclosporine, methotrexate, corticosteroids, acitretin, fumaric acid derivatives, and apremilast

[‡]Phototherapy includes PUVA and UVB therapy

Table 2. Clinical responses at Week 12 and Week 24

	Week 12				Week 24		
	Ustekinumab (N=166)	Ixekizumab (N=136)	p-value*	Adjusted p-value¶	Ustekinumab (N=166)	Ixekizumab (N=136)	p-value*
PASI Response, n (%)							
PASI 100	24 (14.5)	49 (36.0)	**.009**	**.044**	39 (23.5)	67 (49.3)	**.001**
PASI 90	70 (42.2)	99 (72.8)	**<.001**	---	98 (59.0)	113 (83.1)	**<.001**
PASI 75	114 (68.7)	120 (88.2)	**<.001**	**.002**	136 (81.9)	124 (91.2)	**.015**
sPGA response							
sPGA (0), n (%)	30 (18.1)	57 (41.9)	**.021**	.085	40 (24.1)	73 (53.7)	**<.001**
sPGA (0,1)†, n (%)	95 (57.2)	112 (83.6)	**<.001**	**<.001**	115 (69.3)	116 (86.6)	**<.001**
DLQI (0,1), n (%)	74 (44.6)	83 (61.0)	**.012**	.053	88 (53.0)	90 (66.2)	**.030**
Itch NRS							
≥4 point improvement from baseline,‡ n (%)	101 (74.3)	84 (76.4)	.704	.704	98 (72.1)	94 (85.5)	**.018**
Change from baseline, mean (SD)	-4.2 (3.0)	-4.8 (3.0)	.085	.170	-4.6 (2.8)	-5.0 (2.9)	.214
Skin Pain VAS change from baseline, mean (SD)	-29.1 (30.7)	-35.4 (32.1)	.072	.144	-31.4 (29.9)	-36.4 (32.7)	.340

DLQI=Dermatology Life Quality Index, NRS=Numeric Rating Scale, PASI=Psoriasis Area and Severity Index, SD=standard deviation, sPGA=static Physician's Global Assessment, VAS=Visual Analog Scale

Note: response and change values shown in table are computed via non-responder imputation (NRI) and modified Baseline Observation Carried Forward (mBOCF), respectively; bolded p-values denote statistical significance

†Among patients with baseline score ≥3 and ≥2-point improvement from baseline

‡Among patients with a baseline Itch NRS score ≥4

*p-value for categorical data (PASI, sPGA, DLQI, Itch improvement) based on relative risk of logistic regression (95% CI) with terms for weight, treatment, and geographic region; p-value for continuous data (change from baseline) based on LS mean using ANCOVA model (95% CI), with terms for baseline, weight, treatment, and geographic region

¶Adjusted p-value generated using Hommel procedure

Table 3. Adverse events during the 24-week treatment period

	Ustekinumab (N=166) n (%)	Ixekizumab (N=135) n (%)	p-value*
Any TEAE	125 (75.3)	94 (69.6)	.299
Severe TEAE	10 (6.0)	6 (4.4)	.613
Death	0	0	n/a
Nonfatal serious AE	5 (3.0)	3 (2.2)	.735
Discontinuation due to AE	1 (0.6)	2 (1.5)	.589
Infections	87 (52.4)	57 (42.2)	.083
Selected common TEAEs†			
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

AE=adverse event, n/a=not applicable, TEAE=treatment-emergent adverse event

†Common TEAEs were defined as having a frequency of 4% or greater in either treatment arm during the 24-week treatment period; any TEAEs which 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

*p-value calculated via Fisher's exact test

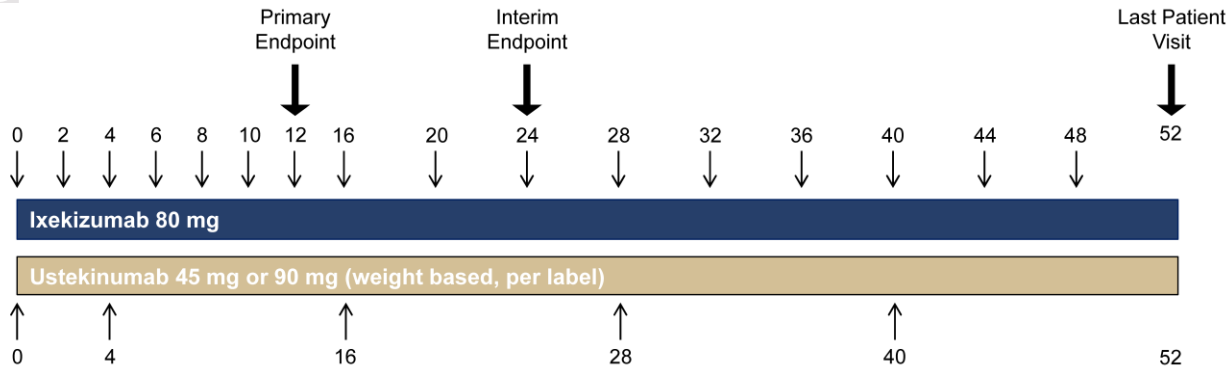
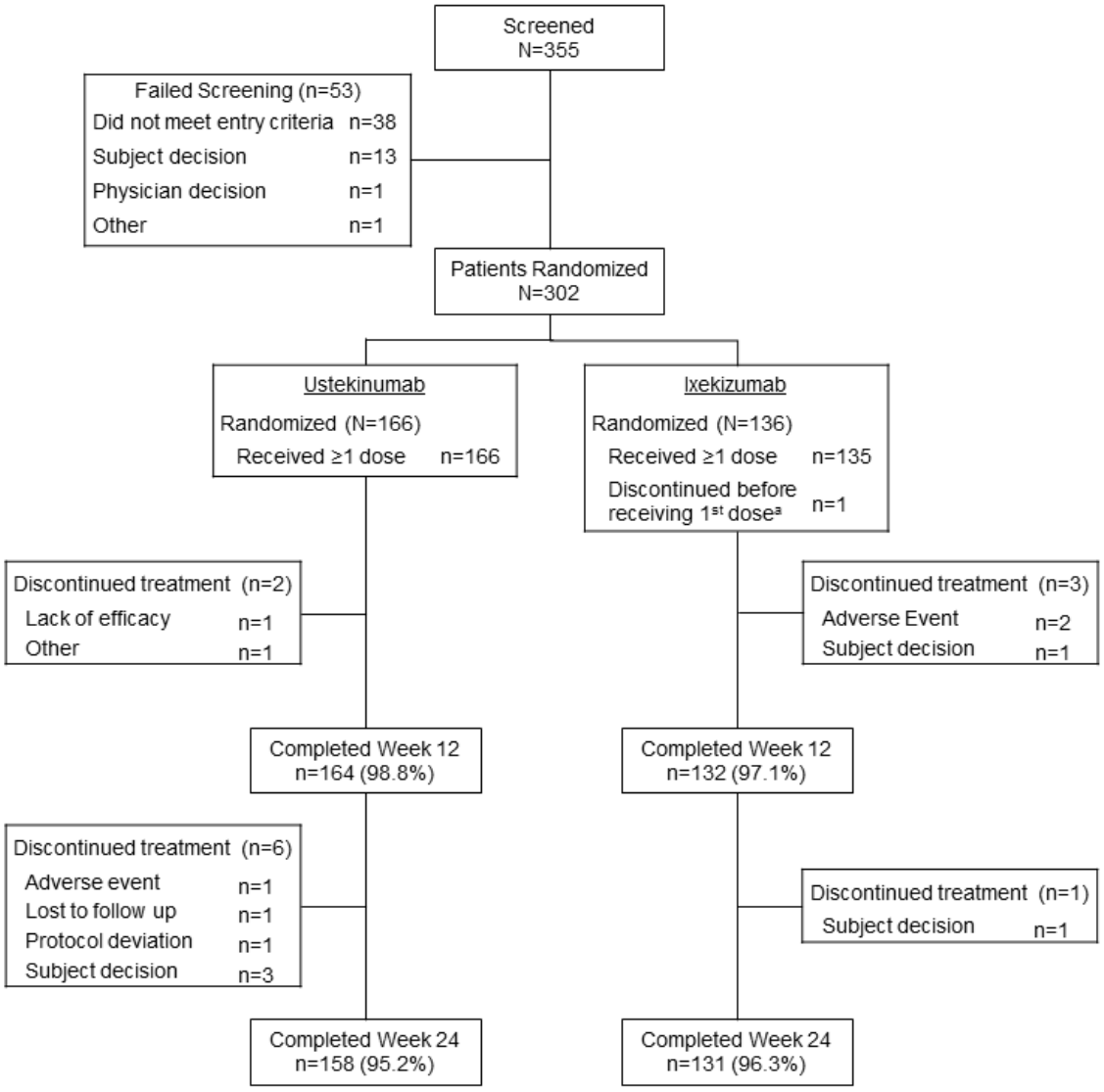


Figure 2. Consort diagram



[a]One patient was randomised by error but not treated, as the patient was found to meet one of the exclusion criteria.

Figure 3. Primary endpoint PASI 90 response at Week 12

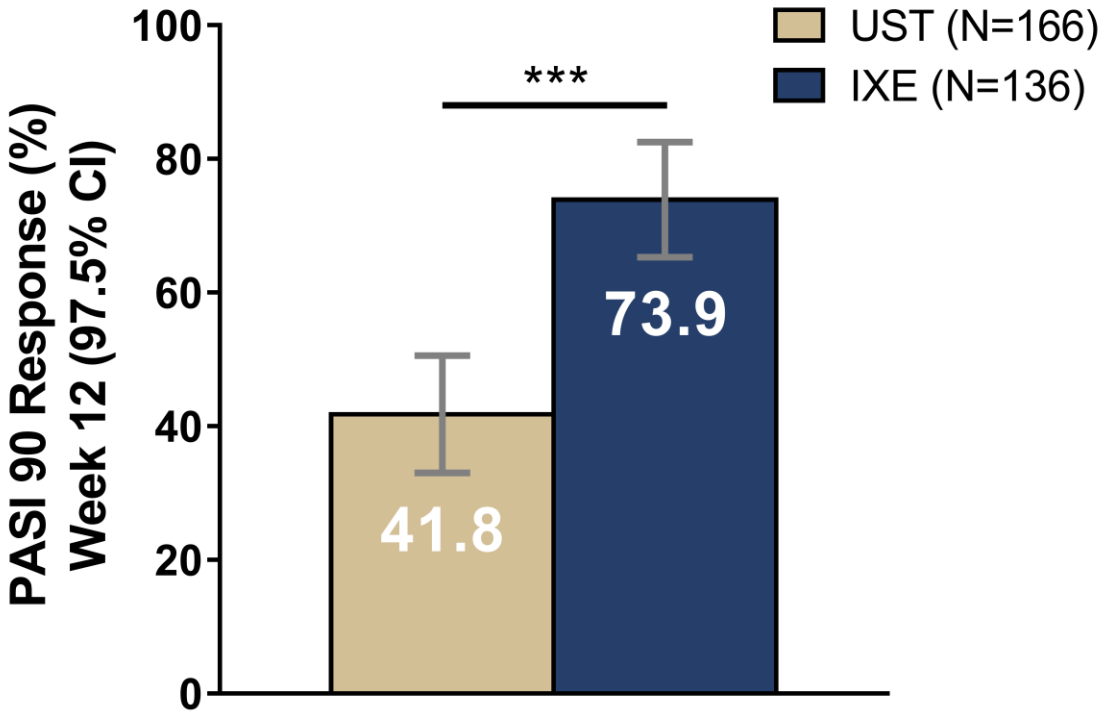


Figure 4. PASI response rates

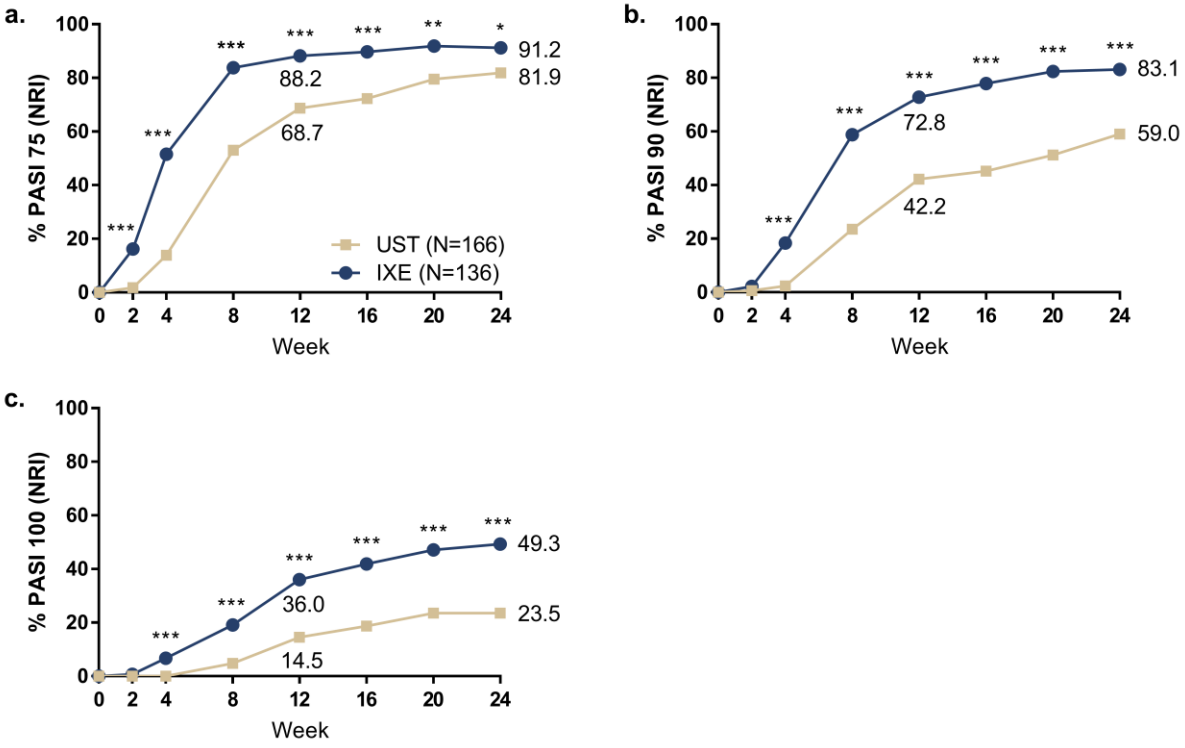


Figure 5. Patient reported outcomes