
Ixekizumab provides superior efficacy compared with ustekinumab over 52 weeks of treatment: Results from IXORA-S, a phase 3 study



Carle Paul, MD, PhD,^a Christopher E. M. Griffiths, MD,^b Peter C. M. van de Kerkhof, MD, PhD,^c Lluís Puig, MD, PhD,^d Yves Dutronc, MD,^e Carsten Hennes, PhD,^e Martin Dossenbach, MD,^e Kristin Hollister, PhD,^e and Kristian Reich, MD, PhD^f

Toulouse, France; Manchester, United Kingdom; Nijmegen, The Netherlands; Barcelona, Spain; Indianapolis, Indiana; and Göttingen, Germany

Background: Biologics targeting interleukin 17A (IL-17A) allow for rapid clearance of psoriatic plaques, with a clinically favorable safety profile.

Objectives: To compare the safety and efficacy of ixekizumab, an IL-17A antagonist, with the safety and efficacy of the IL-12/23 inhibitor ustekinumab through 52 weeks of treatment in the head-to-head trial IXORA-S.

Methods: Patients were randomized to ixekizumab (n = 136) or ustekinumab (n = 166) and dosed per the approved labels. After 1 year, efficacy was assessed via improvements in Psoriasis Area and Severity Index (PASI) score (with PASI 90 indicating a 90% or greater improvement from baseline PASI score) and a static Physician's Global Assessment (sPGA) response of either 0 or 0 or 1, with dropouts counted as nonresponders. Safety analyses included treatment-emergent adverse events (AEs).

From the Dermatology Department, CHU, Paul Sabatier University, Toulouse^a; Dermatology Centre, Salford Royal Hospital, University of Manchester, Manchester Academic Health Science Centre^b; Department of Dermatology, Radboud University Nijmegen Medical Centre^c; Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona^d; Eli Lilly and Company, Indianapolis^e; and Dermatologikum Berlin and Georg-August-University Göttingen.^f

Funding sources: Supported in full by Eli Lilly and Company, Indianapolis, Indiana. Dr Griffiths is a National Institute for Health Research senior investigator.

Disclosure: Dr Paul has served as consultant and/or investigator for AbbVie, Amgen, Boehringer, Celgene, Eli Lilly and Company, Janssen, Leo, Novartis, and Pfizer. Dr Griffiths reports grants and personal fees from Eli Lilly and Company during the conduct of the study and grants and personal fees from AbbVie, Janssen, Celgene, Novartis, Pfizer, and GSK-Stiefel; grants from Sandoz, LEO Pharma, MMS, MSD, Sanofi, and Roche; personal fees from Amgen, UCB Pharma, Sun Pharmaceuticals, and Medscape; and, stock/stock options from CG Skin outside the submitted work. Dr van de Kerkhof has served as a consultant for Celgene, Centocor, Allmiral, Amgen, Pfizer, Philips, Abbott, Eli Lilly and Company, Galderma, Novartis, Jansen Cilag, Leo Pharma, Sandoz, and Mitsubishi and has worked as an investigator for Basilea, Pfizer, Eli Lilly and Company, Amgen, Abbvie, Philips Lighting, Jansen Cilag, and Leo Pharma. Dr Puig has been a clinical trial investigator for AbbVie, Amgen, GSK, Janssen, Eli Lilly and Company, MSD, Novartis, Pfizer, Regeneron, and VBL; he has also been a paid adviser/speaker for AbbVie, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, GSK, Janssen,

Leo-Pharma, Eli Lilly and Company, Merck-Serono, MSD, Novartis, Pfizer, Regeneron, Sandoz, Sanofi, and VBL. Dr Dutronc, Dr Hennes, Dr Dossenbach, and Dr Hollister are employees of Eli Lilly and Company and receive a salary from and own stock in the company. Dr Reich has served as adviser and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Leo, Eli Lilly and Company, Medac, Merck Sharp & Dohme Corp, Novartis, Pfizer, Regeneron, Takeda, UCB Pharma, and Xenoport.

Although the primary objective of this paper is to disclose efficacy and safety for IXORA-S at week 52, data for weeks 0 to 24 are provided for context. The data for weeks 0 to 24 data were previously published in the following article: Reich K, Pinter A, Lacour JP, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *Br J Dermatol.* 2017;177:1014-1023.

Accepted for publication June 26, 2018.

Reprints not available from the authors.

Correspondence to: Carle Paul, MD, PhD, Department of Dermatology, Toulouse University, Hôpital Larrey, 24 chemin de Pourville, 31059 Toulouse, France. E-mail: paul.c@chu-toulouse.fr.

Published online June 30, 2018.

0190-9622/\$36.00

© 2018 Published by Elsevier on behalf of the American Academy of Dermatology, Inc.

<https://doi.org/10.1016/j.jaad.2018.06.039>

Results: At week 52, significantly more ixekizumab-treated patients ($P < .01$) reported PASI 90 (104 [76.5%]), an sPGA response of 0 (72 [52.9%]), or an sPGA response of 0 or 1 (110 [82.1%]) responses than did ustekinumab-treated patients (PASI 90, 98 [59.0%]; sPGA response of 0, 60 [36.1%]; and sPGA response of 0 or 1, 108 [65.1%]). Treatment-emergent AEs, serious AEs, and discontinuation rates were not different between the treatment groups. Injection site reactions occurred more frequently in the ixekizumab-treated group (ixekizumab, 22 [16.3%]; ustekinumab, 2 [1.2%]) ($P < .001$).

Limitations: This study was not designed to compare safety end points related to rare events.

Conclusions: Compared with ustekinumab, ixekizumab showed superior efficacy and comparable safety outcomes through 52 weeks of treatment. (J Am Acad Dermatol 2019;80:70-9.)

Key words: biologic; clinical trial; efficacy; ixekizumab; IXORA-S; psoriasis; safety; ustekinumab.

Recent advances in understanding of the pathophysiology of psoriasis have highlighted a key role for the interleukin 23 (IL-23)/IL-17 pathway.¹⁻⁶ New treatments targeting these cytokines have allowed for high levels of clearance, with a favorable safety profile.⁷⁻¹³

Ixekizumab is a high-affinity, monoclonal IL-17A antagonist¹⁴ that has demonstrated efficacy at both short- and long-term time points in 3 phase 3 clinical trials, with a favorable safety profile.^{7,8,15} IXORA-S is the first head-to-head trial providing 52-week comparative data between ixekizumab and another biologic targeting the IL-23/IL-17 pathway.¹⁶ As psoriasis is a lifelong disease, long-term comparison of therapeutic agents is important and clinically relevant.

Efficacy and high-level safety data up to week 24 from IXORA-S have been previously reported.¹⁶ Herein, we present the safety and efficacy of ixekizumab compared with ustekinumab from a 1-year, double-blind, randomized, controlled trial.

METHODS

Study design and treatments

In this 52-week, phase 3b, double-blind, head-to-head trial (IXORA-S [NCT02561806]), eligible patients¹⁶ with moderate-to-severe plaque psoriasis were randomized 1:1 to receive subcutaneous injections of either ixekizumab or ustekinumab per the recommended dosing regimen (Fig 1).^{17,18} Matching placebo injections were used to maintain blinding. The study methods were previously described in depth.¹⁶

CAPSULE SUMMARY

- The interleukin 17 antagonist ixekizumab is effective in the clearance of plaque psoriasis.
- The superior efficacy of ixekizumab over ustekinumab observed at earlier time points is maintained through week 52.
- Over 52 weeks, the overall safety of ixekizumab was comparable to that of ustekinumab.

Study population

Eligibility and exclusion criteria have been reported previously.¹⁶ Of note, eligible study participants had to have previously failed or had a contraindication to or intolerance of at least 1 systemic therapy; in addition, they had to have had a baseline Psoriasis Area and Severity Index (PASI) score of 10 or higher and could not have had prior treatment with ustekinumab, ixekizumab, or any other IL-17 or IL-12/23 antagonists.

The study was approved by the 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 occurred on October 21, 2015, and the week 52 last patient visit was on May 15, 2017.

Efficacy assessments

The primary objective of IXORA-S was to demonstrate superiority of ixekizumab over ustekinumab at week 12, as assessed by the proportion of patients achieving a 90% or greater improvement from baseline PASI score (PASI 90).¹⁶ Here, results of the primary end point and key secondary end points are presented through week 52, which was the final assessment time point. These end points include the proportion of patients achieving a 75% or greater improvement from baseline PASI score (PASI 75), PASI 90, or a 100% improvement from baseline PASI score (PASI 100) and a static Physician's Global

Abbreviations used:

AE:	adverse event
CI:	confidence interval
IL:	interleukin
NNT:	number needed to treat
NRI:	nonresponder imputation
PASI:	Psoriasis Area and Severity Index
sPGA:	static Physician's Global Assessment
TEAE:	treatment-emergent adverse events

Assessment (sPGA) response of 0 or 1 or an sPGA response of 0.

Safety assessments

Safety was assessed on the basis of patient-reported adverse events (AEs), laboratory values, and vital signs obtained at study visits. Treatment-emergent AEs (TEAEs) were defined as those that first occurred or worsened after baseline (ie, first injection) and on or before the date of last visit. AEs of special interest included cytopenias, changes in liver function test results or elevations of enzyme levels, infections, injection site reactions, malignancies, depression, allergic or hypersensitivity reactions, cerebrovascular and cardiovascular events, inflammatory bowel disease, and *Pneumocystis pneumonia* and interstitial lung disease. Medical Dictionary for Regulatory Activities preferred terms associated with major cerebrovascular and

cardiovascular events were independently adjudicated by an external committee.

Statistical analyses

Patients were analyzed according to their assigned treatment at randomization (intent-to-treat population). Binary end points at week 52 were assessed via logistic regression with nonresponder imputation (NRI). Logistic regression models included terms for treatment group, weight, and geographic region (Eastern Europe, Western Europe, or North America). Analysis of covariance models included terms for baseline value, treatment group, weight, and geographic region. Subgroup analyses were performed by including a term for subgroup and its subgroup-by-treatment interaction in the logistic regression or analysis of covariance model. Comparisons of secondary outcomes over time were made by using Fisher's exact test. Unless otherwise noted, all analyses were prespecified. Post hoc, the number of patients needed to treat (NNT) for 1 additional patient to benefit of PASI 75, PASI 90, or PASI 100 was estimated by using the published methodology.¹⁹

Safety analyses were performed in patients who received at least 1 dose of study treatment (the safety population) and according to the treatment received. Safety events were analyzed by using Fisher's exact test.

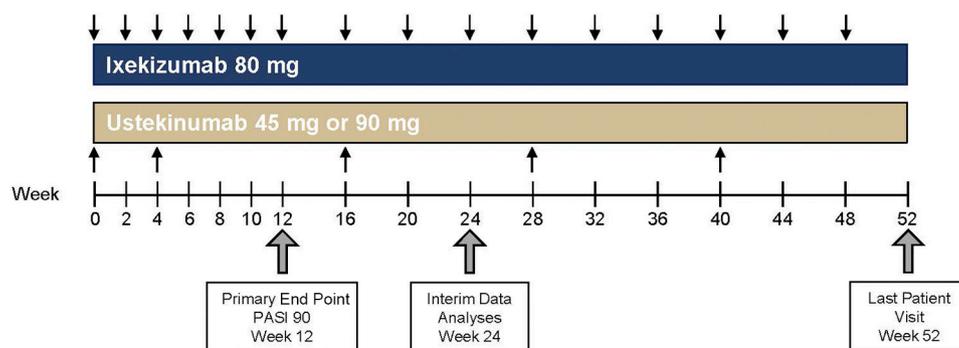
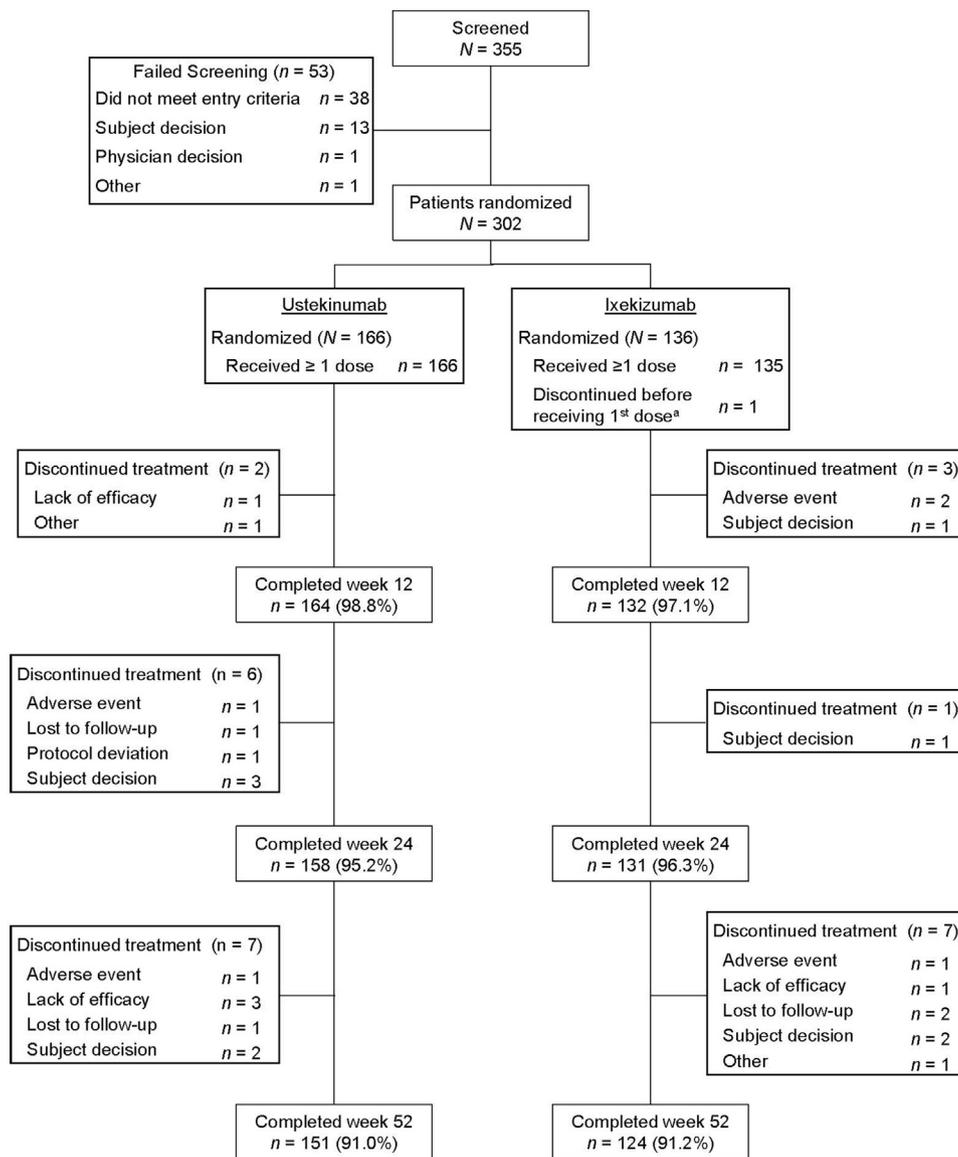


Fig 1. Study design for IXORA-S. Patients were randomized 1:1 to receive either ixekizumab or ustekinumab. Arrows indicate active injections. Ixekizumab-treated patients received a subcutaneous (SC) 160-mg starting dose (2 SC injections of 80 mg) at week 0. This was followed by 80-mg SC injections given every 2 weeks until week 12 and every 4 weeks thereafter. The dose of ustekinumab administered to patients in the ustekinumab group was per the label and based on weight. Patients weighing 100.0 kg or less received 45-mg SC injections and patients weighing more than 100.0 kg received 90-mg SC injections. The primary end point of the study was the proportion of patients achieving a 90% or greater improvement in Psoriasis Area Severity Index from baseline at week 12 (PASI 90); an interim database analysis was done and published for week 24.¹⁶ The last active injections were given at week 48 for the ixekizumab-treated patients and at week 40 for the ustekinumab-treated patients; the last patient visit was at week 52 for both treatment groups.



^aOne patient was randomized by error but not treated, as the patient was found to meet one of the exclusion criteria.

Fig 2. IXORA-S Consolidated Standards of Reporting Trials diagram.

P values were considered statistically significant at the 2-sided 5% α level, and confidence intervals (CIs) were at the 95% level. All analyses were conducted with SAS software (version 9.4, SAS Institute Inc, Cary, NC).

RESULTS

Study population

Of the 355 patients screened for IXORA-S (Fig 2), 302 were randomized to receive ustekinumab (n = 166) or ixekizumab (n = 136). The numbers of patients in both treatment groups who discontinued during the maintenance period were comparable, with 91% of patients completing the study through

week 52 (151 of those who received ustekinumab [91.0%] and 124 of those who received ixekizumab [91.2%]). The most common reasons for discontinuation during the maintenance period were subject decision (8 [2.6%]), lack of efficacy (4 [1.3%]), and lost to follow-up (4 [1.3%]).

Baseline characteristics were balanced between treatment groups (Table I).¹⁶

Clinical efficacy

For all clinical efficacy measurements, the superiority of ixekizumab that was demonstrated at weeks 12 and 24¹⁶ persisted at all time points through week 52 (Table II and Fig 3). Of the ustekinumab-treated patients, 59.0% (n = 98) and

Table I. Baseline demographics and clinical characteristics

Characteristic	Ustekinumab (n = 166)	Ixekizumab (n = 136)
Mean age, y (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)
Mean weight, kg (SD)	89.4 (24.8)	85.8 (20.3)
Weight (>100.0 kg), n (%)	45 (27.1)	31 (23.0)
Mean BMI, kg/m ² (SD)	29.7 (7.0)	28.8 (5.6)
Mean PASI score (SD)	19.8 (9.0)	19.9 (8.2)
Mean sPGA score (SD)	3.6 (0.6)	3.6 (0.7)
Mean % BSA (SD)	27.5 (16.7)	26.7 (16.5)
Mean duration of psoriasis, y (SD)	18.2 (12.0)	18.0 (11.1)
Previous psoriasis treatment, n (%)	166 (100)	134 (98.5)
Nonbiologic systemic* (≥1)	100 (60.2)	84 (61.8)
Phototherapy [†] (≥1)	113 (68.1)	89 (65.4)
Biologic (≥1)	25 (15.1)	18 (13.2)

BMI, Body mass index; BSA, body surface area; PASI, Psoriasis Area and Severity Index; SD, standard deviation; sPGA, static Physician's Global Assessment.

*Nonbiologic systemic agents include cyclosporine, methotrexate, corticosteroids, acitretin, fumaric acid derivatives, and apremilast.

[†]Phototherapy includes psoralen plus ultraviolet A and ultraviolet B therapy.

35.5% (n = 59) showed PASI 90 and PASI 100 responses, respectively, at week 52, whereas 76.5% of patients in the ixekizumab treatment group (n = 104) maintained PASI 90 and 52.2% (n = 71) had completely clear skin (PASI 100). The rates of an sPGA response of 0 or 1 and an sPGA response of 0 at week 52 were 65.1% and 36.1% (n = 108 and 60), respectively, for ustekinumab and 82.1% and 52.9% (n = 110 and 72), respectively, for ixekizumab. Logistic regression analyses at week 52 are available in Table II.

Significantly more patients in the ixekizumab treatment group than in the ustekinumab treatment group achieved an absolute PASI score of 2 or lower at week 4 and every subsequent time point in a post hoc analysis (Fig 3, F). At week 52, 62.7% of the ustekinumab-treated patients (n = 104) had a PASI score of 2 or lower compared with 79.4% of the ixekizumab-treated patients (n = 108). Significantly greater proportions of ixekizumab patients also achieved an absolute PASI score of 5 or lower, 3 or lower, and 1 or lower compared with those in the ustekinumab treatment group (Supplemental Fig 1; available at <http://www.jaad.org>).

In a post hoc analysis, calculation of the NNT showed that by week 52, treatment with ixekizumab

versus with ustekinumab was associated with 1 additional patient reaching PASI 90 and PASI 100 for every 6 treated (95% CI for PASI 90, 2-5; 95% CI for PASI 100, 3-8); for PASI 75, the NNT at week 52 was 8 patients (95% CI, 4-9).

Efficacy by subgroup. Patients entering IXORA-S who had previously received a biologic (25 in the ustekinumab treatment group and 18 in the ixekizumab treatment group) reported significantly ($P = .028$) higher PASI 90 response rates at week 52 when treated with ixekizumab than when treated with ustekinumab; significant differences were not seen at an earlier time point or for PASI 100 response rates (Fig 4). For patients naive to biologic therapies (141 in the ustekinumab treatment group and 118 in the ixekizumab treatment group), treatment with ixekizumab resulted in significantly greater PASI 90 and PASI 100 response rates at both week 12 ($P < .001$) and week 52 ($P < .05$) (Fig 4).

Patients weighing 100.0 kg or less at baseline (121 of those who received ustekinumab and 104 of those who received ixekizumab) reported significantly greater PASI 90 and PASI 100 response rates when treated with ixekizumab than when treated with ustekinumab at both weeks 12 ($P < .05$) and 52 ($P < .05$) (Fig 4). With regard to those patients weighing more than 100.0 kg (45 of those who received ustekinumab and 31 of those who received ixekizumab), significantly more of them achieved PASI 90 ($P < .05$) and PASI 100 ($P < .001$) at week 12 with ixekizumab treatment than with ustekinumab treatment (Fig 4, A). At week 52, there was no statistically significant difference in PASI response rates between the ixekizumab-treated patients and the ustekinumab-treated patients (Fig 4, B).

Regarding baseline severity, patients with a baseline PASI score lower than 20 (107 of those who received ustekinumab and 85 of those who received ixekizumab) were significantly more likely to achieve PASI 90 ($P < .001$) or PASI 100 ($P < .01$) at week 12 with ixekizumab treatment than with ustekinumab treatment; no significant differences were seen at week 52 (Fig 4, A and B). Of those patients with a baseline PASI score of 20 or higher (59 of those who received ustekinumab and 51 of those who received ixekizumab), a significantly higher proportion achieved PASI 90 and PASI 100 at week 12 ($P < .01$) with ixekizumab treatment than with ustekinumab treatment (Fig 4, A). The same applied for PASI 90 ($P < .001$) and PASI 100 ($P < .01$) (Fig 4, B) at week 52.

Treatment-by-subgroup interactions were observed involving PASI 100 for prior biologic use at week 12, PASI 90 for baseline PASI score and prior biologic use at week 52, and PASI 100 for baseline PASI score

Table II. Clinical responses at week 52

Endpoint	Response rate in ustekinumab	Response rate in ixekizumab	Estimated relative risk	95% CI	P value*
PASI 75	0.763	0.892	1.169	1.048-1.290	.006
PASI 90	0.592	0.774	1.308	1.102-1.513	.003
PASI 100	0.352	0.527	1.499	1.100-1.897	.014
sPGA response of 0 or 1 [†]	0.658	0.836	1.271	1.100-1.442	.002
sPGA response of 0	0.358	0.535	1.494	1.102-1.885	.013

CI, Confidence interval; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment.

*P value based on relative risk of logistic regression (95% CI) with terms for weight, treatment, and geographic region; bolded values denote statistical significance.

[†]Among patients with a baseline score of 3 or higher and at least a 2-point improvement from baseline.

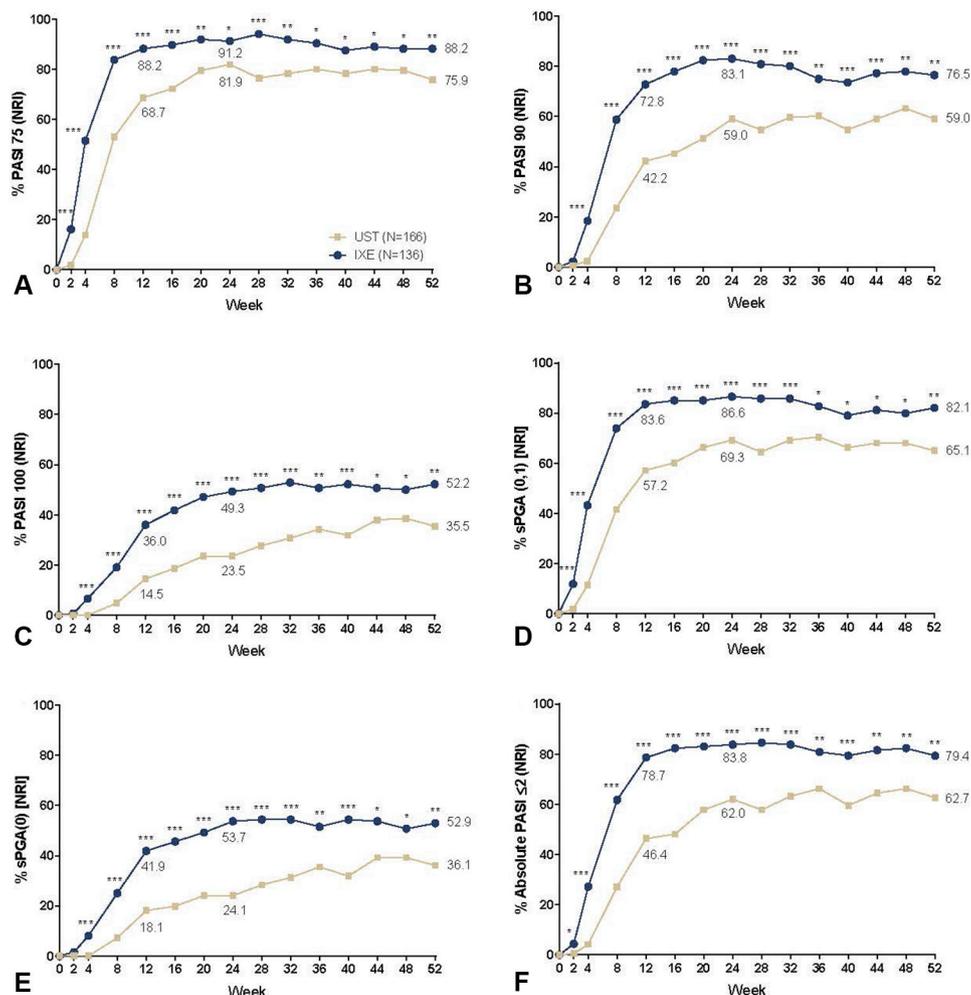


Fig 3. Clinical efficacy through week 52. Psoriasis Area Severity Index (PASI) and static Physician's Global Assessment (sPGA) response rates for ixekizumab (IXE)-treated (n = 136) and ustekinumab (UST)-treated (n = 166) patients from week 0 to week 52. **A**, A 75% or greater improvement from baseline PASI score (PASI 75). **B**, A 90% or greater improvement from baseline PASI score (PASI 90). **C**, A 100% improvement from baseline PASI score (PASI 100). **D**, An sPGA response of 0 or 1. **E**, An sPGA response of 0. **F**, An absolute PASI score of 2 or lower (post hoc analysis). Response rates calculated with nonresponder imputation (NRI); ***P < .001, **P < .01, and *P < .05 by Fisher's exact test.

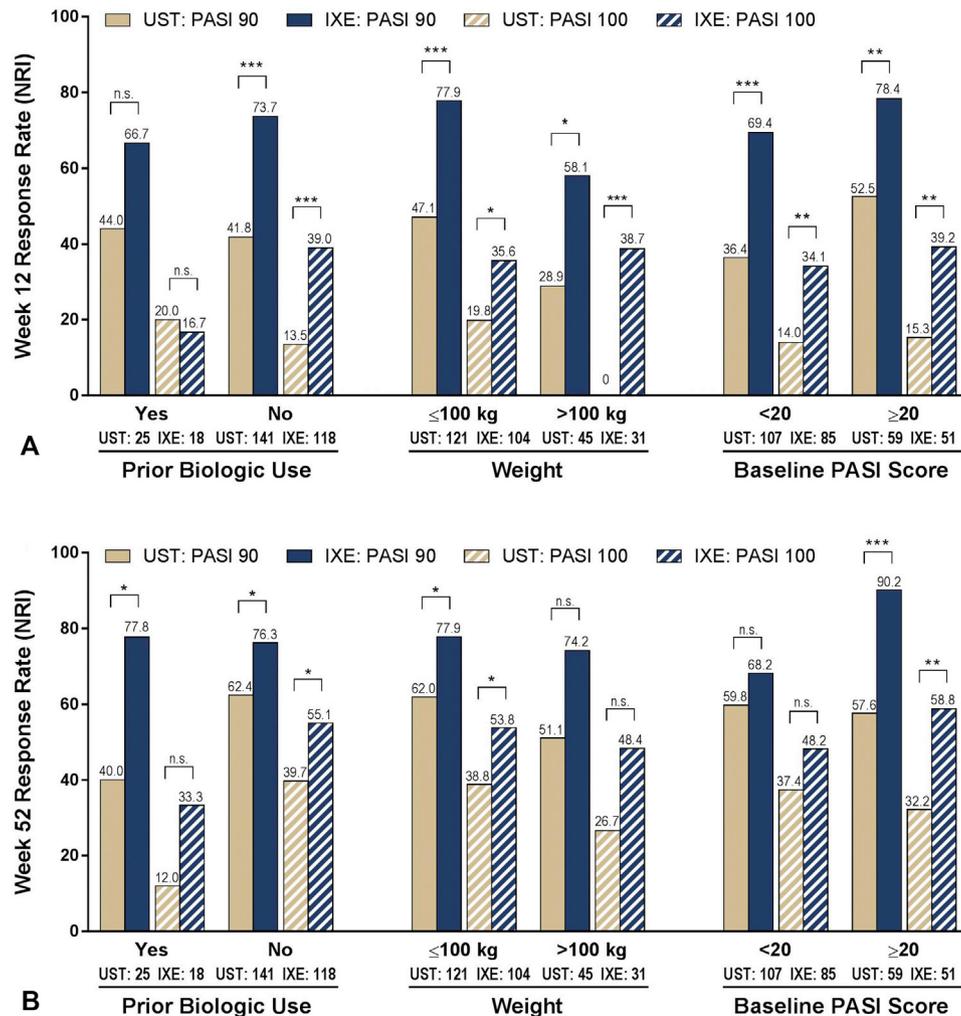


Fig 4. Subgroups at weeks 12 and 52. Select subgroup analyses for ixekizumab (IXE)-treated ($n = 136$) and ustekinumab (UST)-treated ($n = 166$) patients at week 52. Rates of a 90% or greater improvement from baseline PASI score (PASI 90) (solid bars) and a 100% improvement from baseline PASI score (PASI 100) (striped bars) at week 52 are shown for patients according to prior biologic use (left), baseline weight (middle), and baseline PASI score (right). For prior biologic use, “Yes” indicates prior use and “No” indicates no prior use. The weight subgroups were 100.0 kg or less and more than 100.0 kg. The baseline PASI subgroups were patients with a total score lower than 20 and patients with a total score of 20 or higher. The numeric values for each subgroup are shown along the x axis label. **A**, Response rates for each at week 12. **B**, Response rates for each at week 52. Response rates calculated with nonresponder imputation (NRI); * $P < .05$, ** $P < .01$, and *** $P < .001$ by Fisher’s exact test. *n.s.*, Not significant.

at week 52 (Supplemental Table I; available at <http://www.jaad.org>).

Safety

AEs. Up to week 52, no deaths were reported. There was no difference in TEAE rates between the treatment groups (occurring in 139 [83.7%] of those who received ustekinumab and 117 [86.7%] of those who received ixekizumab) (Table III). The most common TEAEs were nasopharyngitis (occurring in 63 [38.0%] of those who received ustekinumab and

45 [33.3%] of those who received ixekizumab), headache (occurring in 21 [12.7%] of those who received ustekinumab and 15 [11.1%] of those who received ixekizumab), and arthralgia (occurring in 14 [8.4%] of those who received ustekinumab and 11 [8.1%] of those who received ixekizumab). Serious AEs were not different between the 2 treatment groups (occurring in 6 [3.6%] of those who received ustekinumab and 9 [6.7%] of those who received ixekizumab), nor were there any differences in discontinuations due to AEs (occurring in 2 [1.2%]

Table III. AEs at week 52

AE	Ustekinumab (n = 166), n (%)	Ixekizumab (n = 135), n (%)	P value*
Any TEAE	139 (83.7)	117 (86.7)	.519
Death	0	0	—
SAE	6 (3.6)	9 (6.7)	.289
Discontinuation due to an AE	2 (1.2)	3 (2.2)	.660
Common TEAEs [†]			
Nasopharyngitis	63 (38.0)	45 (33.3)	
Headache	21 (12.7)	15 (11.1)	
Arthralgia	14 (8.4)	11 (8.1)	
Hypertension	15 (9.0)	7 (5.2)	
Back pain	13 (7.8)	7 (5.2)	
Diarrhea	9 (5.4)	9 (6.7)	
Influenza	6 (3.6)	8 (5.9)	
Cough	7 (4.2)	6 (4.4)	
Injection site erythema	0	12 (8.9)	
Pruritus	6 (3.6)	6 (4.4)	
Bronchitis	9 (5.4)	3 (2.2)	
Upper respiratory tract infection	7 (4.2)	3 (2.2)	
Rhinitis	7 (4.2)	3 (2.2)	
Injection site reaction	2 (1.2)	7 (5.2)	
Musculoskeletal pain	2 (1.2)	6 (4.4)	

AE, Adverse event; SAE, serious adverse event, TEAE, treatment-emergent adverse event.

*P value calculated via Fisher's exact test; tests were not performed on preferred term level.

[†]Common TEAEs were defined as having a frequency of 4% or greater in either treatment arm during the 52-week treatment period.

of those who received ustekinumab and 3 [2.2%] of those who received ixekizumab).

AEs of special interest. Infections were reported by 107 ustekinumab-treated (64.5%) and 83 ixekizumab-treated (61.5%) patients (Table IV). The vast majority of infections (295 [98.0%]) were mild or moderate in severity, and none resulted in discontinuation from the study. The most common types of infections were nasopharyngitis (also the most common TEAE) (occurring in 63 [38.0%] of those who received ustekinumab and 45 [33.3%] of those who received ixekizumab), influenza (occurring in 6 [3.6%] of those who received ustekinumab and 8 [5.9%] of those who received ixekizumab), and bronchitis (occurring in 9 [5.4%] of those who received ustekinumab and 3 [2.2%] of those who received ixekizumab). *Candida* infections were reported by 3 patients in each treatment group (in 1.8% of those who received ustekinumab and 2.2% of those who received ixekizumab). The types of *Candida* infections included vulvovaginal (in 1 [0.6%] of those who received ustekinumab and 2 [1.5%] of those

who received ixekizumab), oral (in 2 [1.2%] of those who received ustekinumab and 0 of those who received ixekizumab), and skin (in 0 of those who received ustekinumab and 1 [0.7%] of those who received ixekizumab). All reports of candidiasis were mild or moderate in severity.

Injection site reactions were reported by significantly more ixekizumab-treated patients (22 [16.3%]) than by ustekinumab-treated patients (2 [1.2%]) ($P < .001$) (Table IV). Half of the reactions resolved in 1 day or less. Reactions lasting longer than 1 day were predominately associated with redness and swelling at the injection site.

AEs consisting of allergic reactions and hypersensitivity were no different between treatment groups (in 3 [1.8%] of those who received ustekinumab and in 6 [4.4%] of those who received ixekizumab); no instances of anaphylaxis occurred (Table IV).

Instances of worsening depressive symptoms were reported by 4 patients; these included 1 case of apathy (in the ixekizumab treatment group) and 3 cases of depressive episodes (in 1 patient who received ustekinumab and in 2 of those who received ixekizumab); rates were not significantly different between treatment groups (Table IV).

Two cerebrocardiovascular events occurred: 1 myocardial infarction (in the ustekinumab treatment group) and 1 unstable angina (in the ixekizumab treatment group) (Table IV). No malignancies occurred through week 52. One case of inflammatory bowel disease occurred in the ustekinumab treatment group. The patient reported mild ulcerative colitis beginning at week 31. No concomitant treatment was initiated, and by week 52, the patient was still undergoing treatment and recovering; the study investigator did not deem this event related to the study drug.

There were no instances of grade 4 neutropenia during the 52-week study period. One instance of grade 3 neutropenia occurred (in a patient who received ixekizumab), and 3 cases of grade 2 occurred (in 2 [1.2%] of those who received ustekinumab and 1 [0.7%] of those who received ixekizumab) (Supplemental Table II; available at <http://www.jaad.org>). All instances of grade 2 and grade 3 neutropenia were transient and did not result in treatment discontinuation.

DISCUSSION

This 1-year analysis of the IXORA-S study shows that the superiority of ixekizumab over ustekinumab in patients with moderate-to-severe psoriasis was maintained through week 52. A PASI 90 response was sustained through 1 year by 76.5% of the ixekizumab-treated patients, and 52.2% had

Table IV. AEs of special interest at week 52

AESI	Ustekinumab (n = 166), n (%)	Ixekizumab (n = 135), n (%)	P value*
Patients with ≥1 AESI	113 (68.1)	98 (72.6)	.448
Any infection	107 (64.5)	83 (61.5)	.632
Common infections [†]			
Nasopharyngitis	63 (38.0)	45 (33.3)	
Influenza	6 (3.6)	8 (5.9)	
Bronchitis	9 (5.4)	3 (2.2)	
Upper respiratory tract infection	7 (4.2)	4 (3.0)	
Rhinitis	7 (4.2)	3 (2.2)	
Candidiasis	3 (1.8)	3 (2.2)	
Vulvovaginal	1 (0.6)	2 (1.5)	
Oral	2 (1.2)	0	
Skin	0	1 (0.7)	
Injection site reactions	2 (1.2)	22 (16.3)	<.001
Hepatic-related AEs	4 (2.4)	7 (5.2)	.230
Allergic reactions/hypersensitivities [‡]	3 (1.8)	6 (4.4)	.308
Depression	1 (0.6)	3 (2.2)	.329
Cytopenia, including neutropenia	2 (1.2)	1 (0.7)	>.999
Interstitial lung disease	0	1 (0.7)	.449
Cerebrocardiovascular events	1 (0.6)	1 (0.7)	>.999
Myocardial infarction	1 (0.6)	0	
Unstable angina	0	1 (0.7)	
Malignancies	0	0	—
Inflammatory bowel disease	1 (0.6)	0	>.999
Crohn's disease	0	0	
Ulcerative colitis	1 (0.6)	0	

AE, Adverse event; AESI, adverse event of special interest.

*P value based on Fisher's exact test; tests were not performed on preferred term level.

[†]Common infections were defined as those occurring in 4% or more of either treatment group during the 52-week treatment period.

[‡]All allergic reactions were considered nonanaphylaxis.

completely clear skin at week 52 (NRI analysis). When the NNT was considered, the superiority of treatment with ixekizumab over treatment with ustekinumab translated into 1 additional patient reaching PASI 90 for every 3 patients treated at week 12 and for every 6 patients treated by week 52. In terms of absolute PASI, 79.4% of those in the ixekizumab treatment group reported minimal or no disease activity (PASI ≤2) at week 52 compared with 62.7% of the ustekinumab-treated patients (NRI analysis).

Antitumor necrosis factor agents initially provided robust skin improvements; however, the efficacy rates waned over time.²⁰⁻²² Ustekinumab was the first available psoriasis treatment targeting IL-12/23 and has been shown to be efficacious and well-tolerated for the treatment of psoriasis.^{12,13,23} The types of common AEs and rates of discontinuation in IXORA-S for the ustekinumab and ixekizumab treatment groups were comparable and in line with those reported in previous trials of these treatments^{7,8,12,13,23} and those of other biologic agents.^{10,11,24,25}

The IXORA-S study is the second clinical trial establishing superiority of an IL-17A inhibitor to the anti-IL-12/23 antibody ustekinumab.^{9,11} One major

differentiator between this trial and the CLEAR trial, which examined the IL-17A inhibitor secukinumab, is the patient population's experience with a systemic agent. Whereas the CLEAR trial enrolled both systemic experienced (68% of patients) and systemic agent-naïve patients,¹¹ the patients randomized in IXORA-S were required to have previous experience with systemic agents (92% of patients) or a contraindication to them.¹⁶ Of note, in the CLEAR trial, ustekinumab treatment resulted in levels of skin improvements at week 52 that were comparable to those seen here in IXORA-S. Across both trials, secukinumab and ixekizumab treatment resulted in clinically meaningful improvements in skin outcomes, and all 3 treatments had clinically acceptable safety profiles.

Some limitations of this study are that IXORA-S was not designed to compare safety end points related to rare events; thus, any safety comparisons should be considered with caution. However, this trial is the first to provide 52-week comparative data for ixekizumab. Additionally, although 1-year data are informative for patients and physicians, even longer-term efficacy data and real-world registries

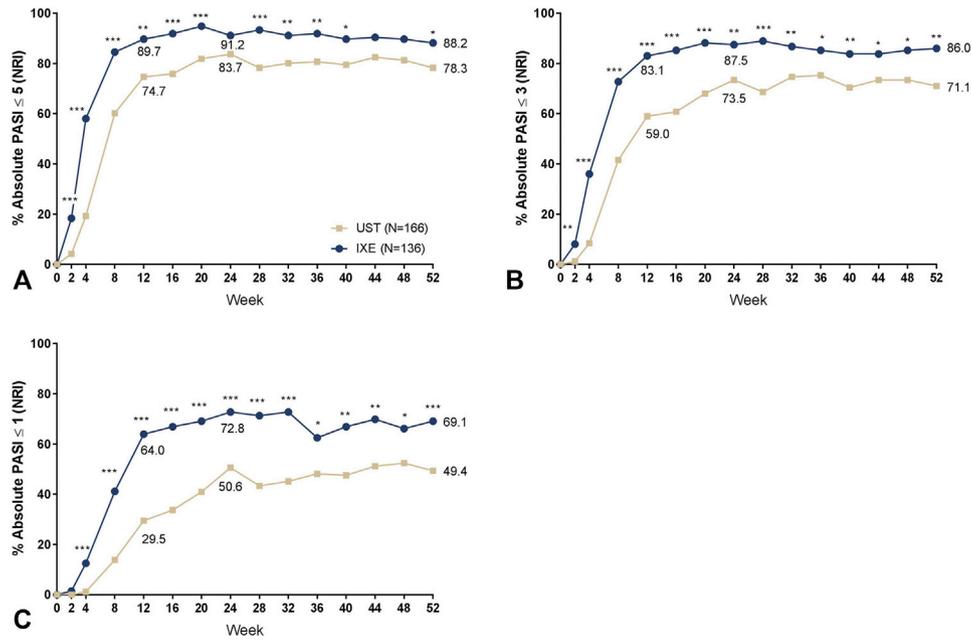
are needed to fully assess sustained efficacy and safety outcomes.

Overall, in the IXORA-S study, ixekizumab provided high efficacy rates, regardless of disease severity at baseline, through 1 year of treatment.

The authors would like to thank the patients and the investigators¹⁶ who participated in this study.

REFERENCES

1. Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of psoriasis. *Annu Rev Immunol*. 2014;32:227-255.
2. Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. *J Invest Dermatol*. 2009;129(6):1339-1350.
3. Di Meglio P, Nestle FO. The role of IL-23 in the immunopathogenesis of psoriasis. *F1000 Biol Rep*. 2010;2(40).
4. Raychaudhuri S. Role of IL-17 in psoriasis and psoriatic arthritis. *Clin Rev Allergy Immunol*. 2013;44(2):183-193.
5. Cai Y, Shen X, Ding C, et al. Pivotal role of dermal IL-17-producing $\gamma\delta$ T cells in skin inflammation. *Immunity*. 2011;35(4):596-610.
6. Cai Y, Fleming C, Yan J. Dermal $\gamma\delta$ T cells—a new player in the pathogenesis of psoriasis. *Int Immunopharmacol*. 2013;16(3):388-391.
7. 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(4):345-356.
8. 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(9993):541-551.
9. 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(3):400-409.
10. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. *N Engl J Med*. 2014;371(4):326-338.
11. 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(1):60-69.e69.
12. 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(9625):1675-1684.
13. 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(9625):1665-1674.
14. 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.
15. Strober B, Leonardi C, Papp KA, et al. Short- and long-term safety outcomes with ixekizumab from 7 clinical trials in psoriasis: etanercept comparisons and integrated data. *J Am Acad Dermatol*. 2017;76(3):432-440.e417.
16. Reich K, Pinter A, Lacour JP, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *Br J Dermatol*. 2017;177(4):1014-1023.
17. European Medicines Agency. Stelara European public assessment reports product information. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000958/WC500058513.pdf. Accessed July 31, 2017.
18. European Medicines Agency. Taltz European public assessment reports product information. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003943/WC500205804.pdf. Accessed July 31, 2017.
19. Altman DG. Confidence intervals for the number needed to treat. *BMJ*. 1998;317(7168):1309-1312.
20. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet*. 2005;366(9494):1367-1374.
21. Gordon KB, Langley RG, Leonardi C, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol*. 2006;55(4):598-606.
22. Tyring S, Gordon KB, Poulin Y, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol*. 2007;143(6):719-726.
23. 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(2):118-128.
24. Gordon KB, Leonardi CL, Lebwohl M, et al. A 52-week, open-label study of the efficacy and safety of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with chronic plaque psoriasis. *J Am Acad Dermatol*. 2014;71(6):1176-1182.
25. 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(6):580-592.



Supplemental Fig 1. Absolute Psoriasis Area Severity Index (PASI) score through week 52. PASI response rates for ixekizumab (IXE)-treated (n = 136) and ustekinumab (UST)-treated (n = 166) patients from week 0 to week 52. **A**, PASI score of 5 or lower. **B**, PASI score of 3 or lower. **C**, PASI score of 1 or lower. Response rates calculated with nonresponder imputation (NRI); ****P* < .001, ***P* < .01, **P* < .05 by Fisher's exact test (prespecified analyses).

Supplemental Table I. Treatment-by-subgroup interaction analyses

Time point	Treatment-by-subgroup interaction <i>P</i> values		
	Prior biologic use, Yes vs no	Weight, ≤100.0 kg vs >100.0 kg	Baseline PASI score, <20 vs ≥20
Week 12			
PASI 90	.600	.799	.866
PASI 100	.038	.967	.985
Week 52			
PASI 90	.175	.672	.010
PASI 100	.390	.533	.140

Treatment-by-subgroup interactions were tested using logistic regression with nonresponder imputation including terms for treatment, weight, geographic region, subgroup, and subgroup-by-treatment interaction. *P* values are considered significant if less than .2; significant *P* values are bolded.

PASI 90, 90% or greater improvement in Psoriasis Area Severity Index score from baseline; *PASI 100*, 100% improvement in Psoriasis Area Severity Index score from baseline.

Supplemental Table II. Worsening of neutropenia from baseline

Minimum postbaseline level	Ustekinumab (n = 166)	Ixekizumab (n = 135)
Grade 1 (<2.0 to $\geq 1.5 \times 10^9/L$)	8 (4.8)	11 (8.1)
Grade 2 (<1.5 to $\geq 1.0 \times 10^9/L$)	2 (1.2)	1 (0.7)
Grade 3 (<1.0 to $\geq 0.5 \times 10^9/L$)	0	1 (0.7)
Grade 4 ($<0.5 \times 10^9/L$)	0	0