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DOI:

[10.1016/j.jaad.2018.06.039](https://doi.org/10.1016/j.jaad.2018.06.039)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Paul, C., Griffiths, C. E. M., van de Kerkhof, P. C. M., Puig, L., Dutronc, Y., Hennekes, C., Dossena, M., Hollister, K., & Reich, K. (2018). Ixekizumab provides superior efficacy compared to ustekinumab over 52-weeks of treatment: results from IXORA-S, a phase 3 study. *Journal of the American Academy of Dermatology*.
<https://doi.org/10.1016/j.jaad.2018.06.039>

Published in:

Journal of the American Academy of Dermatology

Citing this paper

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Accepted Manuscript

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PII: S0190-9622(18)32195-9

DOI: [10.1016/j.jaad.2018.06.039](https://doi.org/10.1016/j.jaad.2018.06.039)

Reference: YMJD 12622

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 20 December 2017

Revised Date: 10 June 2018

Accepted Date: 26 June 2018

Please cite this article as: Paul C, Griffiths CEM, van de Kerkhof PCM, Puig L, Dutronc Y, Henneges C, Dossenbach M, Hollister K, Reich K, Ixekizumab provides superior efficacy compared to ustekinumab over 52-weeks of treatment: results from IXORA-S, a phase 3 study, *Journal of the American Academy of Dermatology* (2018), doi: 10.1016/j.jaad.2018.06.039.

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

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Running title: IXORA-S: randomized trial of ixekizumab vs. ustekinumab, results at Week 52

Target Journal: JAAD

Abstract word count: 200

Capsule summary word count: 50

Text word count: 2187

Table count: 6 (4 main paper, 2 supplemental)

Figure count: 5 (4 main paper, 1 supplemental)

Reference Count: 25

Funding sources: This study was funded in full by Eli Lilly and Company, Indianapolis, IN, USA.

Conflict of interest: CP has served as consultant and/or investigator for AbbVie, Amgen, Boehringer, Celgene, Eli Lilly, Janssen, Leo, Novartis, and Pfizer; CEMG reports grants and personal fees from Eli Lilly during the conduct of the study; grants and personal fees from AbbVie, grants and personal fees from Janssen, grants and personal fees from Celgene, grants from Sandoz, grants and personal fees from Novartis, personal fees from Amgen, grants and personal fees from Pfizer, personal fees from UCB Pharma, grants from LEO Pharma, grants

from MMS, grants from MSD, grants from Sanofi, grants from Roche, grants and personal fees from GSK-Stiefel, personal fees from Sun Pharmaceuticals, personal fees from MedScape, stock/stock options from CG Skin outside the submitted work; **PCMvdK** has served as a consultant for Celgene, Centocor, Allmirall, Amgen, Pfizer, Philips, Abbott, Eli Lilly, Galderma, Novartis, Jansen Cilag, Leo Pharma, Sandoz, and Mitsibishu as well as worked as an investigator for Basilea, Pfizer, Eli Lilly, Amgen, Abbvie, Philips Lighting, Jansen Cilag, and Leo Pharma; **LP** 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 advisor/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; **YD, CH, MD, and KH** are employees of Eli Lilly and Company, and receive salary and own stock from the company; **KR** has served as advisor 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, Lilly, Medac, Merck Sharp & Dohme Corp., Novartis, Pfizer, Regeneron, Takeda, UCB Pharma, and Xenoport

Submission declaration: While the primary objective of this paper is to disclose efficacy and safety for IXORA-S at Week 52, data for weeks 0-24 are provided for context. Week 0-24 data was previously published in the following reference:

Reich, K., Pinter, A., Lacour, J.P., Ferrandiz, C., Micali, G., French, L.E., Lomaga, M., Dutronc, Y., Hennes, C., Wilhelm, S., Hartz, S., Paul, C. and on behalf of the IXORA-S investigators (2017), Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *Br J Dermatol*, 177: 1014–1023. doi:10.1111/bjd.15666

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

Trial registration: NCT02561806

Keywords: IXORA-S, ixekizumab, ustekinumab, biologic, psoriasis, clinical trial, safety, efficacy

ABSTRACT

Background: Biologics targeting interleukin (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, versus 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 approved labels. After one year, efficacy was assessed via improvements in Psoriasis Area and Severity Index (PASI; 90% improvement=PASI 90), and static physician global assessment (sPGA) responses of (0) or (0,1), counting drop-outs as non-responders. Safety analyses included treatment-emergent adverse events (TEAEs).

Results: At Week 52, significantly more ixekizumab-treated patients ($p<0.01$) reported PASI 90 (104, 76.5%), sPGA (0) (72, 52.9%), and sPGA (0,1) (110, 82.1%) responses, compared to ustekinumab-treated patients (PASI 90: 98, 59.0%; sPGA (0): 60, 36.1%; sPGA (0,1): 108, 65.1%). TEAE, serious AEs, and discontinuation rates were not different between the treatment groups. Injection site reactions occurred more frequently in the ixekizumab treatment group (IXE: 22, 16.3%, UST: 2, 1.2%; $p<0.001$).

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

Conclusions: Ixekizumab showed superior efficacy and comparable safety outcomes versus ustekinumab through 52 weeks of treatment.

98 INTRODUCTION

99 Recent advances in the understanding of psoriasis pathophysiology have highlighted a key role
100 for the interleukin (IL)-23/IL-17 pathway.¹⁻⁶ New treatments targeting these cytokines have
101 allowed for high levels of clearance, with a favorable safety profile.⁷⁻¹³ Ixekizumab is a high-
102 affinity, monoclonal, IL-17A antagonist,¹⁴ which has demonstrated efficacy at both short- and
103 long-term time points in three Phase 3 clinical trials, with a favorable safety profile.^{7,8,15} IXORA-S
104 is the first head-to-head trial providing 52-week comparative data between ixekizumab and
105 another biologic targeting the IL-23/IL-17 pathway.¹⁶ As psoriasis is a life-long disease, long-
106 term comparison of therapeutic agents is important and clinically relevant.

107 Efficacy and high-level safety data up to Week 24 from IXORA-S have been previously
108 reported.¹⁶ Herein, we present the safety and efficacy of ixekizumab compared to ustekinumab
109 from a one-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 (Figure 1).^{17,18} Matching placebo injections were used to maintain blinding. Study methods were previously described in-depth.¹⁶

Study Population

Eligibility and exclusion criteria have been previously reported.¹⁶ Of note, eligible study participants had to have previously failed, had a contraindication, or intolerance to at least one systemic therapy; had a baseline Psoriasis Area and Severity Index (PASI) score ≥ 10 ; 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 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 randomization occurred October 21, 2015, and Week 52 last patient visit was on May 15, 2017.

Efficacy Assessments

The primary objective of IXORA-S was to demonstrate superiority of ixekizumab compared to ustekinumab at Week 12, as assessed by the proportion of patients achieving $\geq 90\%$ improvement from baseline PASI score (PASI 90).¹⁶ Here, results of the primary endpoint and key secondary endpoints are presented through Week 52, the final assessment time point.

These endpoints include the proportion of patients achieving PASI 75/90/100 response and the static Physician Global Assessment (sPGA) (0,1) and sPGA (0) responses.

Safety Assessments

Safety was assessed based on patient-reported adverse events, laboratory values, and vital signs obtained at study visits. Treatment-emergent adverse events (TEAEs) were defined as those that first occurred or worsened after baseline (i.e., first injection) and on or before the date of last visit. Adverse events of special interest (AESI) included cytopenias, liver function test changes or enzyme elevations, infections, injection site reactions, malignancies, depression, allergic or hypersensitivity reactions, cerebrovascular and cardiovascular events, inflammatory bowel disease, and *Pneumocystis* pneumonia and interstitial lung disease. MedDRA preferred terms associated with major cerebrovascular and cardiovascular events were independently adjudicated by an external committee.

Statistical Analyses

Patients were analyzed according to the treatment they were assigned at randomization (intent-to-treat population). Binary endpoints at Week 52 were assessed via logistic regression with non-responder imputation (NRI). Logistic regression models included terms for treatment group, weight, and geographic region (Eastern Europe, Western Europe, North America). ANCOVA 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 into the logistic regression or ANCOVA model. Comparisons of secondary outcomes over time were made using Fisher's exact test. Unless otherwise noted, all analyses were pre-specified. Post-hoc, the number of patients needed to treat (NNT) for one additional patient to benefit of PASI 75, 90 or 100 was estimated using published methodology.¹⁹

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

159 P-values were considered statistically significant at the two-sided 5% alpha level and confidence
160 intervals were at the 95% level. All analyses were conducted using SAS 9.4 software, SAS
161 Institute Inc., Cary, North Carolina, USA.

RESULTS

Study Population

Of the 355 patients screened for IXORA-S (Figure 2), 302 were randomized to receive ustekinumab (N=166) or ixekizumab (N=136). Numbers of patients in both treatment groups who discontinued during the maintenance period were comparable, with 91% of patients completing through Week 52 (UST: 151, 91.0%; IXE: 124, 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 demonstrated at Weeks 12 and 24¹⁶ persisted at all time points through Week 52 (Table II, Figure 3). Among ustekinumab-treated patients, 59.0% (n=98) and 35.5% (n=59) showed PASI 90 and PASI 100 responses, respectively, at Week 52, while 76.5% (n=104) of patients in the ixekizumab treatment group maintained PASI 90 and 52.2% (n=71) had completely clear skin (PASI 100). Response rates for sPGA (0,1) and sPGA (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 at Week 4 and every following time point, in a post-hoc analysis (Figure 3f). At Week 52, 62.7% (n=104) of ustekinumab-treated patients had a PASI score of ≤ 2 compared to 79.4% (n=108) of ixekizumab-treated patients. Significantly

greater proportions of ixekizumab patients also achieved an absolute PASI score of ≤ 5 , ≤ 3 , and ≤ 1 compared to the ustekinumab treatment group (Supplemental Figure 1).

In a post-hoc analysis, calculation of the NNT showed that by Week 52, treatment with ixekizumab versus ustekinumab was associated with one additional patient reaching PASI 90 and PASI 100 for every 6 treated (95% confidence interval: PASI 90: 2, 5; PASI 100: 3, 8); for PASI 75, the NNT at Week 52 was 8 patients (95% CI: 4, 9).

Efficacy – Subgroups

Patients entering IXORA-S who were biologic experienced (UST: 25, IXE: 18) reported significantly ($p=0.028$) greater PASI 90 response rates at Week 52 when treated with ixekizumab compared to ustekinumab; significant differences were not seen at an earlier time point or for PASI 100 response rates (Figure 4). For patients naïve to biologic therapies (UST: 141, IXE: 118), treatment with ixekizumab resulted in significantly greater PASI 90 and PASI 100 response rates at both Week 12 ($p<0.001$) and Week 52 ($p<0.05$; Figure 4).

Patients weighing 100.0 kg or less at baseline (UST: 121, IXE: 104) reported significantly greater PASI 90 and PASI 100 response rates when treated with ixekizumab, compared to ustekinumab, at both Weeks 12 ($p<0.05$) and 52 ($p<0.05$; Figure 4). For those weighing more than 100.0 kg (UST: 45, IXE: 31), significantly more patients achieved PASI 90 ($p<0.05$) and PASI 100 ($p<0.001$) with ixekizumab treatment at Week 12 (Figure 4a). At Week 52, there was no statistically significant difference in PASI response rates for ixekizumab-treated patients compared to ustekinumab-treated patients (Figure 4b).

Regarding baseline severity, patients with baseline PASI <20 (UST: 107, IXE: 85) were significantly more likely to achieve PASI 90 ($p<0.001$) or PASI 100 ($p<0.01$) at Week 12 with ixekizumab treatment compared to ustekinumab; significant differences were not seen at Week 52 (Figure 4a-b). For patients with baseline PASI ≥ 20 (UST: 59, IXE: 51), a significantly higher

proportion achieved PASI 90 and PASI 100 at Week 12 ($p<0.01$) with ixekizumab treatment compared to ustekinumab (Figure 4a). The same applied for PASI 90 ($p<0.001$) and PASI 100 ($p<0.01$; Figure 4b) 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 at Week 52 (Supplemental Table I #).

Safety – Adverse Events

Up to Week 52, no deaths were reported. There was no difference in TEAE rates between the treatment groups (UST: 139, 83.7%; IXE: 117, 86.7%; Table III). The most common TEAEs were nasopharyngitis (UST: 63, 38.0%; IXE: 45, 33.3%), headache (UST: 21, 12.7%; IXE: 15, 11.1%), and arthralgia (UST: 14, 8.4%; IXE: 11, 8.1%). Serious adverse events were not different between the two treatment groups (UST: 6, 3.6%; IXE: 9, 6.7%), nor were discontinuations due to AEs (UST: 2, 1.2%; IXE: 3, 2.2%).

Safety – Adverse Events of Special Interest

Infections were reported by 107 (64.5%) ustekinumab-treated and 83 (61.5%) ixekizumab-treated patients (Table IV). The vast majority (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; UST: 63, 38.0%; IXE: 45, 33.3%), influenza (UST: 6, 3.6%; IXE: 8, 5.9%), and bronchitis (UST: 9, 5.4%; IXE: 3, 2.2%). *Candida* infections were reported by three patients in each treatment group (UST: 1.8%; IXE: 2.2%). Types included vulvovaginal (UST: 1, 0.6%; IXE: 2, 1.5%), oral (UST: 2, 1.2%; IXE: 0), and skin (UST: 0; IXE: 1, 0.7%). 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 ustekinumab-treated patients (2, 1.2%, $p<0.001$; Table IV). Half of reactions resolved in one day or less. Reactions lasting longer than one day were predominately associated with redness and swelling at the injection site.

Adverse events of allergic reactions and hypersensitivity were not different between treatment groups (UST: 3, 1.8%; IXE: 6, 4.4%); no instances of anaphylaxis occurred (Table IV).

Instances of worsening depressive symptoms were reported by four patients; these included one case of apathy (IXE) and three cases of depressive episodes (UST: 1; IXE: 2); rates were not significantly different between treatment groups (Table IV).

Two cerebro-cardiovascular events occurred: one myocardial infarction (UST) and one unstable angina (IXE) (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; this event was not deemed related to study drug by the study investigator.

There were no instances of Grade 4 neutropenia during the 52-week study period. One instance of Grade 3 neutropenia occurred (IXE), and three cases of Grade 2 occurred (UST: 2, 1.2%; IXE: 1, 0.7%; Supplemental Table II V). All instances of Grade 2 and Grade 3 neutropenia were transient and did not result in treatment discontinuation.

DISCUSSION

This one-year analysis of the IXORA-S study shows that the superiority of ixekizumab over ustekinumab in patients with moderate-to-severe psoriasis is maintained through Week 52. A PASI 90 response was sustained through one year by 76.5% of ixekizumab-treated patients and 52.2% had completely clear skin at Week 52 (NRI analysis). When considering the NNT, ixekizumab superiority translated into an additional patient reaching PASI 90 for every three patients treated at Week 12 and for every six patients treated by Week 52, compared to treatment with ustekinumab. In terms of absolute PASI, 79.4% in the ixekizumab treatment group reported minimal or no disease activity (PASI ≤ 2) at Week 52, compared to 62.7% of ustekinumab-treated patients (NRI analysis).

Anti-tumor necrosis factor agents initially provided robust skin improvements; however, over time, efficacy rates waned.²⁰⁻²² Ustekinumab was the first available treatment targeting IL-12/23 and has been shown to be both safe and effective for the treatment of psoriasis.^{12,13,23} The types of common adverse events and discontinuation rates 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-IL12/23 antibody, ustekinumab.^{9,11} One major differentiator between this trial and the CLEAR trial of the IL-17A inhibitor secukinumab, is the systemic experience of the patient population. While the CLEAR trial enrolled both systemic-experienced (68% of patients) and systemic-naïve patients,¹¹ patients randomized in IXORA-S were required to have previous systemic experience (92% of patients) or a contra-indication to systemic agents.¹⁶ Of note, in the CLEAR trial, ustekinumab treatment resulted in comparable levels of skin improvements at Week 52 to those seen here in IXORA-S. Across both trials, secukinumab and ixekizumab

273 treatment resulted in clinically meaningful skin and quality of life improvements for patients, and
274 all three treatments resulted in clinically acceptable safety profiles.

275 Some limitations of this study are that IXORA-S was not designed to compare safety endpoints
276 related to rare events; thus, any safety comparisons should be considered with caution.

277 However, this trial is the first to provide 52-week comparative data for ixekizumab. Additionally,
278 while one-year data are informative for patients and physicians, even longer-term efficacy data
279 and real-world registries are needed to fully assess sustained efficacy and safety outcomes.

280 Overall, in the IXORA-S study, ixekizumab provided high efficacy rates, regardless of disease
281 severity at baseline, and improved quality of life through one year of treatment, compared to
282 ustekinumab.

283 **ACKNOWLEDGMENTS**

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

286 Christopher E.M. Griffiths is a National Institute for Health Research Senior Investigator.

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ABBREVIATIONS

AESI – Adverse events of special interest

AE – adverse event

ANCOVA – analysis of covariance

IL – interleukin

IXE – ixekizumab

mBOCF – modified baseline observation carried forward

NNT – number needed to treat

PASI – Psoriasis Area and Severity Index

sPGA – static Physician Global Assessment

TEAE – Treatment-emergent adverse events

UST – ustekinumab

FIGURE LEGENDS

Figure 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 (two 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. Ustekinumab-treated 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. The primary endpoint of the study was the proportion of patients achieving PASI 90 at Week 12; an interim database analysis was done and published for Week 24.¹⁶ Last active injections were given at Week 48 for ixekizumab patients and at Week 40 for ustekinumab patients; last patient visit was at Week 52 for both treatment groups.

Figure 2. IXORA-S consort diagram

Figure 3. Clinical efficacy through Week 52. PASI and sPGA response rates for ixekizumab (IXE)-treated (N=136) and ustekinumab (UST)-treated (N=166) patients from Week 0 to Week 52. **(a)** PASI 75; **(b)** PASI 90; **(c)** PASI 100; **(d)** sPGA (0,1); **(e)** sPGA (0). **(f)** Absolute PASI score of ≤ 2 (post hoc analysis). Response rates calculated with non-responder imputation (NRI); *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ by Fisher's exact test

Figure 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. PASI 90 (solid bars) and PASI 100 (striped bars) response rates at Week 52 are shown for patients based on 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. Weight subgroups were ≤ 100.0 kg and >100.0 kg. Baseline PASI subgroups were a total score <20 and a total score ≥ 20 . N-values for each subgroup are shown in x-axis label. **(a)** Response rates for each at

Week 12. **(b)** Response rates for each at Week 52. Response rates calculated with non-responder imputation (NRI); * $p < .05$, ** $p < 0.01$, *** $p < 0.001$ by Fisher's exact test; n.s.=not significant.

Supplemental Figure 1. Absolute PASI 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 ≤ 5 ; **(b)** PASI ≤ 3 ; **(c)** PASI ≤ 1 . Response rates calculated with non-responder imputation (NRI); *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ by Fisher's exact test (pre-specified analyses).

Table I. 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)
Previous psoriasis treatment, n (%)	166 (100)	134 (98.5)
Non-biologic systemic ^a (≥1)	100 (60.2)	84 (61.8)
Phototherapy ^b (≥1)	113 (68.1)	89 (65.4)
Biologics (≥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

^aNon-biologic systemic treatments include cyclosporine, methotrexate, corticosteroids, acitretin, fumaric acid derivatives, and apremilast

^bPhototherapy includes PUVA and UVB therapy

Table II. Probability of clinical responses at Week 52

Probability of response	Ustekinumab	Ixekizumab	Estimate ^a	95% CI	p-value ^b
PASI 75	0.763	0.892	1.169	1.048, 1.290	0.006
PASI 90	0.592	0.774	1.308	1.102, 1.513	0.003
PASI 100	0.352	0.527	1.499	1.100, 1.897	0.014
sPGA (0,1) ^c	0.658	0.836	1.271	1.100, 1.442	0.002
sPGA (0)	0.358	0.535	1.494	1.102, 1.885	0.013

DLQI=Dermatology Life Quality Index, PASI=Psoriasis Area and Severity Index, SE=standard error, sPGA=static Physician's Global Assessment

^aRelative Risk

^bp-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 LSM using ANCOVA model (95% CI), with terms for baseline, weight, treatment, and geographic region; bolded values denote statistical significance

^cAmong patients with baseline score ≥ 3 and ≥ 2 -point improvement from baseline

417 **Table III.** Adverse events at Week 52

	Ustekinumab (N=166) n (%)	Ixekizumab (N=135) n (%)	p-value^a
Any TEAE	139 (83.7)	117 (86.7)	0.519
Death	0	0	---
SAE	6 (3.6)	9 (6.7)	0.289
Discontinuation due to AE	2 (1.2)	3 (2.2)	0.660
Common TEAEs^b			
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)	
Diarrhoea	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)	

418 AE=adverse event, SAE=serious adverse event, TEAE=treatment-emergent adverse event

419 ^ap-value calculated via Fisher's exact test; tests were not performed on preferred term level

420 ^bCommon TEAEs were defined as having a frequency of 4% or greater in either treatment arm during the 52-week
 421 treatment period

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	Ustekinumab (N=166) n (%)	Ixekizumab (N=135) n (%)	p-value ^a
Patients with ≥ 1 AESI	113 (68.1)	98 (72.6)	0.448
Any infection	107 (64.5)	83 (61.5)	0.632
Common Infections ^b			
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)	<0.001
Hepatic-related AEs	4 (2.4)	7 (5.2)	0.230
Allergic reactions/hypersensitivities ^c	3 (1.8)	6 (4.4)	0.308
Depression	1 (0.6)	3 (2.2)	0.329
Cytopenia, including neutropenia	2 (1.2)	1 (0.7)	>0.999
Interstitial lung disease	0	1 (0.7)	0.449
Cerebro-cardiovascular events	1 (0.6)	1 (0.7)	>0.999
Myocardial infarction	1 (0.6)	0	
Unstable angina	0	1 (0.7)	
Malignancies	0	0	---
Inflammatory bowel disease	1 (0.6)	0	>0.999
Crohns disease	0	0	
Ulcerative colitis	1 (0.6)	0	

Table IV. Adverse events of special interest at Week 52

AE=adverse event, AESI=adverse events of special interest

^ap-value based on Fisher's exact test; tests were not performed on preferred term level

426 ^bCommon infections were defined as those occurring in 4% or more of either treatment group during the 52-week
427 treatment period

428 ^cAll allergic reactions were considered non-anaphylaxis

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

Figure 3. Clinical efficacy through Week 52.

Supplemental Table I. Treatment-by-subgroup interaction analyses

Treatment-by-subgroup interaction p-values ^a			
	Prior Biologic Use	Weight	Baseline PASI Score
	Yes vs. No	≤100.0 kg vs. >100.0 kg	<20 vs. ≥20
Week 12			
PASI 90	0.600	0.799	0.866
PASI 100	0.038	0.967	0.985
Week 52			
PASI 90	0.175	0.672	0.010
PASI 100	0.390	0.533	0.140

^aTreatment-by-subgroup interactions were tested using logistic regression with NRI including terms for treatment, weight, geographic region, subgroup, and subgroup-by-treatment interaction; p-values were considered significant if <0.2; significant p-values are bolded

Supplemental Table II. Neutropenia – worsening from baseline

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

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CAPSULE SUMMARY

- The IL-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 and is associated with greater quality of life improvements.
- Over 52 weeks, the overall safety of ixekizumab and ustekinumab was comparable.