



# Ixekizumab and Ustekinumab Efficacy in Nail Psoriasis in Patients with Moderate-to-Severe Psoriasis: 52-Week Results from a Phase 3, Head-to-Head Study (IXORA-S)

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## ABSTRACT

**Introduction:** Patients with plaque psoriasis often have nail psoriasis, which is difficult to treat. Ixekizumab (IXE) and ustekinumab (UST) are biologics with established efficacy in nail psoriasis. We present post hoc data from a head-

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to-head trial of IXE and UST (IXORA-S) to examine the efficacy in nail psoriasis in patients with moderate-to-severe plaque psoriasis over 52 weeks.

**Methods:** In IXORA-S, randomised patients received IXE ( $N = 136$ ) or UST ( $N = 166$ ) per label for 52 weeks. Eighty-four (61.8%) and 105 (63.3%) of the patients treated with IXE or UST, respectively, had baseline fingernail psoriasis (Nail Psoriasis Severity Index [NAPSI]  $> 0$ ); of these, 54 (64.3%) and 63 (60.0%) patients, respectively, had significant baseline fingernail psoriasis (defined as NAPSI  $\geq 16$  with  $\geq 4$  fingernails involved). The proportion of patients achieving NAPSI = 0, a NAPSI score change from baseline and correlations in Psoriasis Area of Severity Index (PASI) and NAPSI improvement over 52 weeks were examined.

**Results:** Progressive improvement occurred in both treatment groups over 52 weeks. Statistically significantly more patients achieved NAPSI = 0 with IXE versus UST by week 16–20, and the proportions continued to increase through week 52 among patients with baseline nail psoriasis (61.9 vs. 28.6%, respectively;  $P < 0.001$ ), including those with significant nail psoriasis (57.4 vs. 17.5%, respectively;  $P < 0.001$ ). Similar results were observed for NAPSI score improvement from baseline to week 52. Interestingly, the presence of nail psoriasis was associated with lower skin response with UST but not with IXE.

**Conclusions:** Ixekizumab was superior to UST in the clearance of nail psoriasis, with earlier improvement continued through 52 weeks regardless of baseline nail severity.

**Trial Registration:** ClinicalTrials.gov identifier; NCT02561806.

**Keywords:** Ixekizumab; Nail psoriasis; Psoriasis; Ustekinumab

### Key Summary Points

#### Why carry out this study?

Nail psoriasis is common in patients with psoriasis but is particularly difficult to treat.

IXORA-S was a randomised, double-blind, head-to-head comparison of the efficacy and safety of ixekizumab (IXE) and ustekinumab (UST) in patients with moderate-to-severe psoriasis.

This post hoc analysis was performed to directly compare IXE and UST efficacy in the clearance of nail psoriasis or significant nail psoriasis up to 52 weeks.

#### What was learned from the study?

Ixekizumab was shown to be superior to UST in providing earlier complete clearance of nail psoriasis with continued improvement through 52 weeks, regardless of baseline nail severity.

The presence of nail psoriasis was associated with a lower rate of skin clearance among UST-treated patients, but this was not the case for IXE-treated patients, who had similar skin response whether nail psoriasis was present or not.

with psoriasis will experience nail psoriasis during their lifetime [1, 2]. Nail psoriasis is also prevalent in patients with psoriatic arthritis (PsA), and it has been considered a predictor for the development of PsA [2–5]. Nail psoriasis can cause pain and can impair hand mobility [6].

Nail psoriasis is difficult to treat. The anatomy of the nail presents therapeutic challenges, as topical agents may not penetrate the nail plate to reach sites of inflammation in the nail bed or matrix [4]. Local injections of therapeutic agents to the nail matrix can be used but these are painful, and the efficacy of systemic therapies is mixed or data are limited [4]. In addition, as nails grow slowly, the resolution of psoriasis lesions with local or systemic treatments may take up to 1 year [4]. Several biologic therapies are approved for the treatment of moderate-to-severe plaque psoriasis [7], including ixekizumab (IXE), a high affinity immunoglobulin (Ig) G4 monoclonal antibody that selectively acts as an interleukin-(IL)-17A antagonist [8, 9], and ustekinumab (UST), an IgG1 $\kappa$  monoclonal antibody that binds with specificity to inhibit the p40 subunit of IL-12/23 [10, 11]. Pivotal phase 3 trials for both IXE [12, 13] and UST [14, 15] have shown a significant efficacy of at least 75% in the Psoriasis Area and Severity Index (PASI 75) for moderate-to-severe psoriasis, ranging from 87% to 90% for IXE and from 65% to 78% for UST [7]. Both drugs also have been shown to statistically significantly improve nail psoriasis within 1 year [16, 17], but they have not been compared directly in a head-to-head trial. Such comparative studies are important for helping make suitable decisions based on specific therapeutic goals [16, 18, 19].

The aim of the analysis presented here was to examine the efficacy of IXE and UST in the treatment of nail psoriasis in patients with moderate-to-severe psoriasis over 52 weeks of treatment.

## INTRODUCTION

Psoriasis is a chronic, inflammatory skin condition that frequently affects the nails. The prevalence of nail psoriasis varies from 10 to 82%, and the majority (80–90%) of patients

## METHODS

### Study Design

IXORA-S was a 52-week, phase 3b, multicentre, randomised, double-blind, head-to-head trial in

which eligible patients with moderate-to-severe plaque psoriasis were randomised (1:1) to receive either IXE (160-mg starting dose administered as two 80-mg injections, then 80 mg every 2 weeks for 12 weeks followed by 80 mg every 4 weeks;  $N = 136$ ) or UST (45-mg/90-mg weight-based dosing at weeks 0, 4 and every 12 weeks thereafter per label;  $N = 166$ ) [20, 21]. No concomitant psoriasis treatments were allowed during the trial. This trial was registered with clinicaltrials.gov (NCT02561806) and EudraCT (2015-000892-28).

The study was approved by the applicable ethical review boards at each participating study site, and was conducted in accordance with the principles expressed in the Declaration of Helsinki of 1964 and its subsequent amendments. Written, informed consent was obtained from each patient at study entry before any study procedures took place.

### Nail Evaluations

The Nail Psoriasis Severity Index (NAPSI) was used to assess fingernail psoriasis for all patients who presented with fingernail psoriasis at baseline. Each fingernail was scored for bed and matrix psoriasis. Scores were summed to obtain total NAPSI fingernail scores ranging from 0 (no nail psoriasis) to 80 (severe nail psoriasis). As some patients may have had limited nail psoriasis, we also looked at patients with moderate-to-severe nail psoriasis (later referred to as “significant nail psoriasis”), defined as fingernail NAPSI  $\geq 16$  and  $\geq 4$  fingernails involved [16]. NAPSI scores were not collected for patients who did not have nail psoriasis.

### Statistical Analyses

Categorical data for treatment groups were assessed via logistic regression, with treatment, weight ( $\leq 100$  kg,  $> 100$  kg), and geographic region (Western European Union [EU], Eastern EU, North America) as factors. Fisher’s exact test was used for comparison. Missing data were imputed using non-responder imputation.

For continuous variables, least squares means [95% confidence interval (CI)] were calculated

for NAPSI, and treatment groups were compared using analysis of covariance, with treatment, weight ( $\leq 100$  kg,  $> 100$  kg), geographic region (Western EU, Eastern EU, North America) and baseline NAPSI score as factors. Missing data were imputed using modified baseline observation carried forward.

Statistical significance was set at  $P$  value  $< 0.05$ . No multiplicity correction was done for the nail endpoints as per study protocol.

## RESULTS

Patients in the IXORA-S intent-to-treat population were treated with IXE ( $N = 136$ ) or UST ( $N = 166$ ) for 52 weeks. Eighty-four (61.8%) patients randomised to IXE and 105 (63.3%) patients randomised to UST had nail psoriasis at baseline; of these, 54 (64.3%) and 63 (60.0%) patients treated with IXE and UST, respectively, had significant nail psoriasis at baseline. Overall, patients with nail psoriasis had higher baseline PASI scores, longer duration of plaque psoriasis and a greater proportion of PsA than patients without nail psoriasis. Mean baseline NAPSI ( $\pm$  standard deviation [SD]) scores were 28.3 ( $\pm 19.9$ ) and 24.8 ( $\pm 20.0$ ) in the IXE and UST treatment groups, respectively (Table 1).

Progressive improvement was observed in both treatment groups (Figs. 1, 2). Statistically significantly more patients with baseline nail psoriasis achieved complete resolution (NAPSI = 0) with IXE than with UST by week 16 (31.0 vs. 16.2%;  $P = 0.02$ ) through week 52 (61.9 vs. 28.6%;  $P < 0.001$ ) (Fig. 1, solid lines). Similarly, statistically significantly more patients with significant baseline nail psoriasis achieved complete resolution with IXE than with UST by week 20 (25.9 vs. 9.5%;  $P = 0.03$ ) through week 52 (57.4 vs. 17.5%;  $P < 0.001$ ) (Fig. 1, dashed lines).

Average improvement in NAPSI score was statistically significantly greater for IXE-treated patients by week 8 ( $- 6.6$ ; 95% CI  $- 8.9, - 4.3$ ) than for UST ( $- 2.1$ ; 95% CI  $- 4.1, - 0.1$ ) ( $P = 0.002$ ) (Fig. 2). Improvement remained statistically significantly greater with IXE through week 52 ( $- 22.4$ ; 95% CI  $- 24.8,$

**Table 1** Baseline characteristics of patients with and without nail involvement at baseline in the IXORA-S intent-to-treat population

Baseline characteristics of patients <sup>a</sup>	Ustekinumab (N = 166)	Ixekizumab (N = 136)
Patients with baseline nail psoriasis	105 (63.3%)	84 (61.8%)
Age (years)	45.4 ± 12.7	43.0 ± 12.0
Sex (male)	80 (76.2%)	60 (71.4%)
Weight (kg)	91.3 ± 24.4	87.5 ± 21.7
Weight > 100.0 kg	34 (32.4%)	22 (26.2%)
PASI score	21.1 ± 9.2	20.2 ± 9.0
sPGA score	3.7 ± 0.6	3.7 ± 0.7
Duration of plaque psoriasis (years)	20.2 ± 11.8	19.4 ± 12.0
NAPSI score	24.8 ± 20.0	28.3 ± 19.9
Significant baseline nail psoriasis <sup>b</sup>	63 (60.0%)	54 (64.3%)
Presence of psoriatic arthritis	18 (17.1%)	17 (20.2%)
Patients without baseline nail psoriasis	61 (36.7%)	52 (38.2%)
Age (years)	41.6 ± 14.0	42.3 ± 13.8
Sex (male)	32 (52.5%)	30 (57.7%)
Weight (kg)	86.1 ± 25.3	83.0 ± 17.7
Weight > 100.0 kg	11 (18.0%)	9 (17.6%)
PASI score	17.7 ± 8.3	19.5 ± 6.6
sPGA score	3.6 ± 0.6	3.5 ± 0.5
Duration of plaque psoriasis (years)	14.9 ± 11.6	15.8 ± 9.2
Presence of psoriatic arthritis	6 (9.8%)	7 (13.5%)

N number of patients, NAPSI Nail Psoriasis Severity Index, PASI Psoriasis Area of Severity Index, sPGA static Physicians Global Assessment

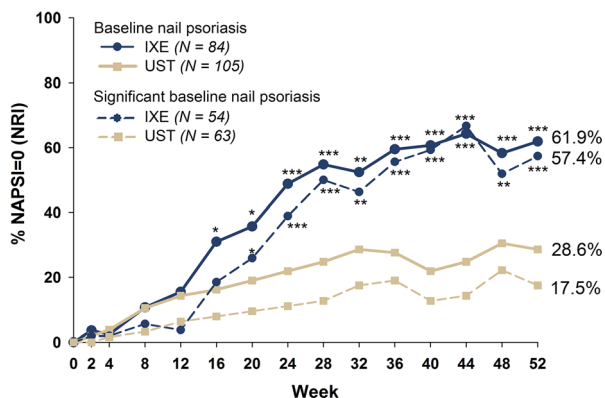
<sup>a</sup> Values for baseline characteristics are presented as the mean ± standard deviation (SD) or as the number of patients with the percentage in parenthesis, as appropriate

<sup>b</sup> Defined as fingernail NAPSI ≥ 16 and ≥ 4 fingernails involved

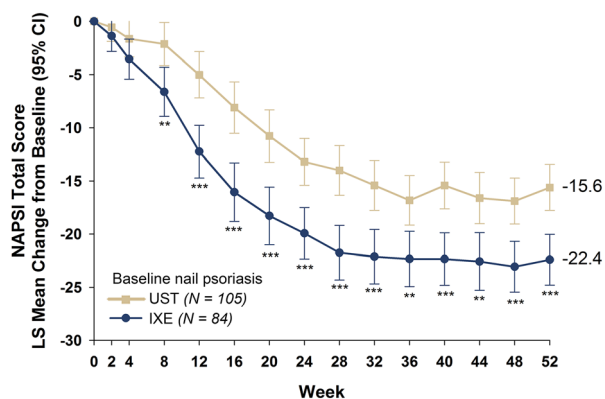
– 20.0) compared with UST (– 15.6; 95% CI – 17.8, – 13.4) ( $P < 0.001$ ) (Fig. 2).

Patients treated with UST had lower clearance of plaque psoriasis when nail psoriasis was present compared to when nail psoriasis was absent. At week 52, PASI 100 response rates, denoting the percentage of patients achieving 100% clearance of skin plaques, were 27.6% when nail psoriasis was present versus 49.2% when nail psoriasis was absent (Fig. 3). In

contrast, patients treated with IXE had similar skin responses throughout the treatment period whether nail psoriasis was present or absent. At week 52, the PASI 100 response rates were 53.6% when nail psoriasis was present and 50.0% when nail psoriasis was absent (Fig. 3). Similar observations were made for PASI 100 response rates at week 24 and for PASI 75/90 response rates at weeks 24 and 52.



**Fig. 1** Complete resolution (Nail Psoriasis Severity Index [NAPSI] = 0) response rates for patients treated with ixekizumab (IXE) or ustekinumab (UST) from week 0 to week 52. Solid lines are patients with baseline nail psoriasis (NAPSI > 0); asterisks are *P* values for solid line. Dashed lines are patients with significant baseline nail psoriasis (NAPSI ≥ 16 and ≥ 4 fingernails involved); asterisks are *P* values for dashed line. NAPSI = 0 response rates were calculated via nonresponder imputation (NRI). \*\*\**P* < 0.001, \*\**P* < 0.01, \**P* < 0.05 via Fisher’s exact test. *N* Number of patients



**Fig. 2** Change from baseline in NAPSI total score for patients with baseline nail psoriasis treated with IXE or UST from week 0 to week 52. Response rates were calculated via analysis of covariance, with missing data imputed using modified baseline observation carried forward. \*\*\**P* < 0.001, \*\**P* < 0.01, \**P* < 0.05, least square (LS) mean difference between treatment groups. CI confidence interval, *N* number of patients

For most patients with nail psoriasis, total NAPSI and PASI scores improved together by week 24, with concurrent improvement continued through week 52 in both treatment

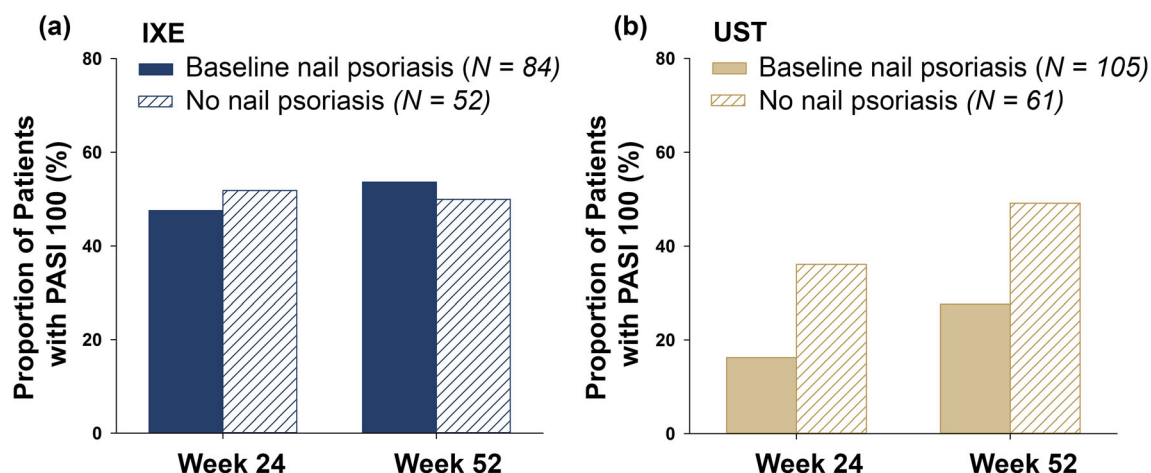
groups. In general, PASI total scores improved more rapidly than NAPSI total scores, and for some patients, NAPSI scores remained higher at week 52 despite reduction in plaque psoriasis burden in both treatment groups. At week 52, the percentages of patients who still presented with significant nail psoriasis were 7.8% and 21.5% (*P* = 0.02) for patients treated with IXE and UST, respectively.

## DISCUSSION

While improvement in nail psoriasis was observed in IXE and UST treatment groups, complete resolution of nail psoriasis was seen in statistically significantly greater percentages of patients treated with IXE compared to UST through 1 year of treatment. Complete clearance was more rapid in patients treated with IXE than UST, as early as week 16 for patients with nail psoriasis or week 20 for patients with significant nail psoriasis. Similarly, there was a statistically significant improvement in the NAPSI total score in the IXE treatment group by week 8 compared with the UST treatment group, and the superior response with IXE continued through week 52. These results suggest that IXE may provide significantly greater clearance of nail psoriasis than UST.

Interestingly, among UST-treated patients, the presence of baseline nail psoriasis was associated with a lower rate of skin clearance. This was not the case for IXE-treated patients. Further studies are required to determine if the presence of nail psoriasis is a predictor of the skin response to UST treatment or if this observation is simply due to the fact that, in this trial, patients with nail psoriasis had overall more severe skin involvement and were heavier than those without nail psoriasis. Of note, nail involvement is more frequent in HLA-Cw6 negative patients [22], while HLA-Cw6 presence is a predictor of better clinical response of plaque psoriasis with UST treatment. No difference was observed in anti-IL-17A (secukinumab)-treated patients with regards to HLA-Cw6 status [23, 24]. These data suggest that patients with nail involvement might have a better predicted outcome in skin plaque psoriasis with IXE





**Fig. 3** Proportion of patients with and without baseline nail psoriasis (solid and pattern bars, respectively) who achieved 100% clearance of skin plaques based on Psoriasis

Area and Severity Index score (*PASI 100*) at weeks 24 and 52 with IXE (a) or UST (b) treatment. *PASI* response rates were calculated via NRI. *N* number of patients

treatment than with UST treatment. Determining HLA-Cw6 status may be of interest in further studies evaluating the efficacy of new biologics in nail psoriasis.

NAPSI and PASI total scores generally improved simultaneously for many patients over 52 weeks. Nevertheless, a dissociation between skin and nail improvement was seen for some patients who had very good skin response but retained significant nail lesions (low PASI total score with high NAPSI total score). This observation highlights the importance of studying nail psoriasis response with approved or emerging therapies, as it cannot be assumed that efficacy in skin lesions will translate to nail psoriasis resolution as well.

IXORA-S was a randomised, controlled, head-to-head trial comparing IXE and UST, but a limitation was that nail psoriasis was not a stratification factor in the trial. Nevertheless, patients with and without baseline nail psoriasis, including those with significant involvement, had comparable representation in each treatment group in the post hoc analyses. IXE and UST were administered in this study per label at the approved dosage regimen for the treatment of adult patients with moderate-to-severe psoriasis [9, 11], but real-world dosing may differ. A longer period of observation is required to determine if nail lesions will

continue to improve beyond 1 year of treatment, as the duration of this observation in the current study may still be too short to assess complete benefit.

## CONCLUSIONS

Ixekizumab showed greater ability to clear both skin and nail psoriasis than UST at 1 year of treatment.

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**Compliance with Ethics Guidelines.** The study was approved by the applicable ethical review boards at each participating study site, and was conducted in accordance with the principles expressed in the Declaration of Helsinki of 1964 and its subsequent amendments. Written, informed consent was obtained from each patient at study entry before any study procedures took place.

**Data Availability.** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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