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A head-to-head comparison of ixekizumab vs. guselkumab in patients with moderate-to-severe plaque psoriasis: 24-week efficacy and safety results from a randomized, double-blinded trial*

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Summary

Background Significantly more patients with moderate-to-severe plaque psoriasis treated with the interleukin (IL)-17A inhibitor ixekizumab vs. the IL-23p19 inhibitor guselkumab in the IXORA-R head-to-head trial achieved 100% improvement in Psoriasis Area and Severity Index (PASI 100) at week 12.

Objectives To compare skin and nail clearance and patient-reported outcomes for ixekizumab vs. guselkumab, up to week 24.

Methods IXORA-R enrolled adults with moderate-to-severe plaque psoriasis, defined as static Physician's Global Assessment ≥ 3, PASI ≥ 12 and involved body surface area ≥ 10%. Statistical comparisons were performed using the Cochran–Mantel–Haenszel test stratified by pooled site. Time-to-first-event comparisons were performed using Kaplan–Meier analysis, and P-values were generated using adjusted log-rank tests stratified by treatment group. Cumulative days at clinical and patient-reported responses were compared by ANCOVA. The trial was registered with ClinicalTrials.gov (NCT03573323).

Results Of the 1027 patients randomly assigned, 90% completed the trial (465 of 520 ixekizumab and 459 of 507 guselkumab). As early as week 2 and through week 16, more patients on ixekizumab achieved PASI 100 ($P < 0{\cdot}01$). At week 24, ixekizumab was noninferior to guselkumab (50% vs. 52%, difference −2·3%), with no statistically significant difference in PASI 100 ($P = 0{\cdot}41$). More patients receiving ixekizumab showed completely clear nails at week 24 (52% vs. 31%, $P = 0{\cdot}007$). The median time to first PASI 50/75/90 and PASI 100 were 2 and 7·5 weeks shorter, respectively, for patients on ixekizumab vs.

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Conflicts of interest
Conflicts of interest statements can be found in the Appendix.

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guselkumab ($P < 0{\cdot}001$). Patients on ixekizumab also had a greater cumulative benefit, with more days at PASI 90 and 100, with Dermatology Life Quality Index of 0 or 1, and itch free ($P < 0{\cdot}05$). The frequency of serious adverse events was 3% for each group, with no new safety signals.

Conclusions Ixekizumab was noninferior to guselkumab in complete skin clearance and superior in clearing nails at week 24. Ixekizumab cleared skin more rapidly in patients with moderate-to-severe plaque psoriasis, with a greater cumulative benefit, than guselkumab. Overall, the safety findings were consistent with the known safety profile for ixekizumab.

What is already known about this topic?

- Patients with plaque psoriasis desire both high levels of clearance and rapid onset of treatment effects.
- Ixekizumab is a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A.
- In the 12-week report of the IXORA-R study, ixekizumab demonstrated significantly higher efficacy at early timepoints than the IL-23p19 inhibitor guselkumab, with more patients achieving 100% improvement in Psoriasis Area and Severity Index (PASI 100) and improved quality of life as early as week 4.

What does this study add?

- Patients on ixekizumab vs. guselkumab achieved similar levels of skin clearance and superior efficacy in the resolution of nail psoriasis at week 24.
- Patients on ixekizumab vs. guselkumab had a greater cumulative benefit, with more days at PASI 90 and 100, more days when psoriasis did not impact their quality of life, and more itch-free days.
- The safety profiles of both drugs were consistent with those in previous studies.

Head-to-head studies are valuable in understanding the differences between therapies. Both interleukin (IL)-17 and IL-23p19 inhibitors are highly effective treatments for moderate-to-severe plaque psoriasis.[1,2] The interim 12-week results of the IXORA-R head-to-head study demonstrated that patients treated with the IL-17A inhibitor ixekizumab showed more rapid achievement of fully clear skin than patients treated with the IL-23p19 inhibitor guselkumab.[3] More rapid relief of itch and skin pain, the most bothersome symptoms indicated by patients, was noted in patients on ixekizumab vs. guselkumab.[3,4]

Twenty-five per cent of patients with psoriasis have coexisting nail psoriasis with pitting, onycholysis, subungual hyperkeratosis, splinter haemorrhages and/or dystrophy.[5] More than a cosmetic concern, nail psoriasis can be painful and physically impairing.[5,6] Nail psoriasis is also strongly associated with psoriatic arthritis (PsA), occurring in 80% of patients with PsA.[7] Given their structure and rate of growth, nails are often more difficult to treat than skin, taking longer to respond to therapy.[5,8] With total skin clearance as the treatment goal, this status should include clearance in all types of psoriasis and conditions associated with it, as residual psoriasis in visible areas can negatively impact quality of life.[9] Here, we build on the initial 12-week report of IXORA-R,[3] presenting not only the 24-week skin and nail clinical outcomes but also patient-reported outcomes and safety results from this study. Early efficacy and safety data that were not reported in the 12-week report, due to the risk of unblinding patients and investigators, are also included, in addition to analyses examining cumulative results over the full study.

Patients and methods

Study design

The study design was previously described by Blauvelt *et al.*[3] Briefly, IXORA-R was a 24-week, multicentre, randomized, double-blinded, parallel-group, phase IV study with the primary endpoint at 12 weeks.[3] The study was conducted between 9 November 2018 and 8 January 2020.

All patients gave informed consent for participation in the study; a subset of patients also consented to have photographs taken. The IXORA-R protocol was approved by local ethical review boards and conducted according to the International Conference on Harmonisation Good Clinical Practice guidelines and Declaration of Helsinki.

Randomization and masking

The randomization details were published previously.[3] Patients were randomly assigned (1: 1) to receive subcutaneous injections of ixekizumab or guselkumab at the approved dosing. From weeks 12 to 24, patients received ixekizumab 80 mg every 4 weeks or guselkumab 100 mg at weeks 12 and 20. To maintain blinding, patients on guselkumab received one placebo injection at week 16.

Participants

Eligible patients were ≥ 18 years old with chronic plaque psoriasis with a static Physician's Global Assessment of Disease (sPGA) score of ≥ 3 (moderate), a Psoriasis Area and Severity Index (PASI) ≥ 12, and ≥ 10% body surface area involvement at screening and baseline. The study excluded patients with prior use of IL-23p19 antagonists or who had any condition or contraindication as addressed in the local labelling for guselkumab. Prior use of biologics was allowed provided the patient did not receive the biologic within specified periods prior to baseline. Prior use of an IL-17 antagonist other than ixekizumab was allowed if the patient had not failed to respond to that therapy. The full list of inclusion and exclusion criteria has been published.[3]

Procedures

Doses were administered subcutaneously with prefilled syringes. Study visits occurred during screening and at weeks 0 (baseline), 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24.

Outcomes

As previously reported, the primary efficacy endpoint (PASI 100 at week 12) and seven of the eight major secondary endpoints were met.[3] The eighth major secondary endpoint is reported here: superiority of ixekizumab in terms of PASI 100 at week 24. A subset of patients was enrolled in a study addendum to document improvement photographically at weeks 0, 1, 2, 4, 8, 12 and 24. The clinical images shown herein were chosen because these patients had similar baseline PASIs, had PASI improvement similar to the median for their treatment group, and had an adequate set of representing photos (Table S1; see Supporting Information). Detailed descriptions of the outcome measures are provided in Appendix S1 (see Supporting Information).

Statistical analyses

As described previously, the sample size was estimated to have 98% power for testing the superiority of ixekizumab over guselkumab for the PASI 100 outcome at week 12 at a two-sided 5% type I error rate.[3]

Unless otherwise stated, efficacy analyses included all randomized patients according to the treatment to which they were assigned (intent-to-treat population). Safety data were summarized using the safety population (all randomized patients who received at least one dose of a trial drug).

Statistical comparisons between the two treatment groups were performed using the Cochran–Mantel–Haenszel test stratified by pooled site. Missing data for binary measures were imputed as nonresponders. Missing values for continuous measures were imputed using a modified baseline-observation-carried-forward method. A multiple-testing strategy to control the overall familywise type I error rate at a two-sided alpha level of 0·05 was implemented for superiority testing of the primary and major secondary endpoints. Nominal P-values are shown for all analyses. A prespecified noninferiority test of ixekizumab vs. guselkumab was performed for PASI 100 at week 24, with a preset noninferiority margin of −11·4%. Exploratory and post hoc analyses were not adjusted for multiple comparisons. Additional details regarding statistical analyses were published previously and are provided in Appendix S1 (see Supporting Information).[3]

Cerebrocardiovascular adverse events (AEs) and suspected inflammatory bowel disease (IBD) were adjudicated by external clinical event committees, as previously described.[3]

The trial was registered with ClinicalTrials.gov (NCT03573323). Requests for access to the study data and protocol can be submitted at www.vivli.org, per the sharing policy of Eli Lilly and Company.

Results

Of the 1027 patients randomized, 89% (465 of 520) in the ixekizumab arm and 91% (459 of 507) in the guselkumab arm completed the 24-week trial (Figure 1). The baseline characteristics were described previously.[3]

Clinical outcomes

The final major secondary outcome for IXORA-R tested the superiority of ixekizumab vs. guselkumab for the proportion of patients achieving PASI 100 at week 24. Similar percentages of patients receiving ixekizumab and guselkumab achieved PASI 100 at week 24: 50% (260 of 520) for ixekizumab vs. 52% (265 of 507) for guselkumab; P = 0·41 (Figure 2a). The superiority test for PASI 100 at week 24 was the last in the hierarchical testing scheme, and thus its result did not affect the other major outcomes. Ixekizumab was noninferior to guselkumab at week 24 (difference of −2·3%; 95% confidence interval −8·4 to 3·8).

Ixekizumab was superior to guselkumab in the primary outcome, PASI 100 at week 12, and the seven other major secondary outcomes.[3] To prevent early unblinding, numerous early clinical outcomes were not reported previously. As the study is now complete, the full results for these clinical outcomes are presented (Figure 2). Significantly more patients receiving ixekizumab than guselkumab achieved PASI 100 and an sPGA score of 0 from weeks 2 to 16 (P < 0·01; Figure 2a, b). Moreover, significantly more patients receiving ixekizumab

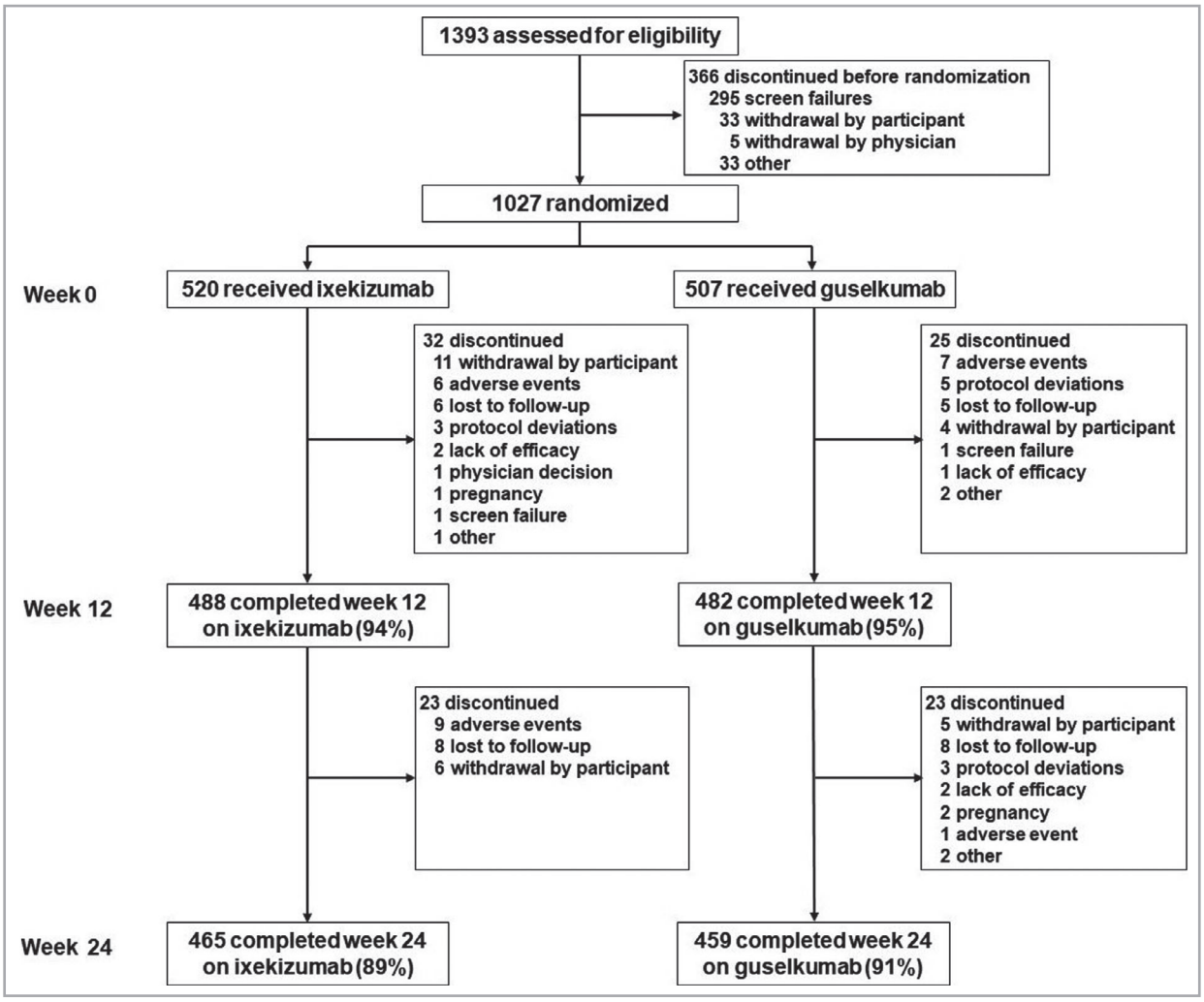

Figure 1 Disposition of the patients. Details are given according to the CONSORT statement for reporting randomized controlled trials.

achieved PASI 90 as early as week 2 (5·2% vs. 0·6%, $P < 0·001$) and PASI 75 as early as week 1 (4·8% vs. 1·0%, $P < 0·001$), and this remained statistically significant through week 12 for PASI 90 ($P < 0·001$; Figure 2c) and through week 10 for PASI 75 ($P < 0·01$; Figure 2d). The proportions of patients achieving PASI 50 were significantly greater for ixekizumab than for guselkumab at weeks 1 to 6 (Figure 2e, $P < 0·01$).

Psoriasis of the fingernails was evaluated using Physician's Global Assessment of Fingernail Psoriasis (PGA-F) at baseline and week 24, a timepoint that allowed for nail regrowth in most patients.[8] At baseline, 16% (83 of 520) in the ixekizumab group and 12% (59 of 507) in the guselkumab group had moderate-to-severe nail psoriasis (PGA-F score ≥ 3). Among these patients, significantly more patients on ixekizumab reached clear nails or minimal nail psoriasis [PGA-F score of 0 or 1 with ≥ 2-point improvement; 75% (62 of 83) vs. 54% (32 of 59); $P = 0·020$; Figure 3] or complete clearance of nail psoriasis at week 24 [PGA-F score of 0; 52% (43 of 83) vs. 31% (18 of 59); $P = 0·007$; Figure 3]. Due to an imbalance between the treatment groups in the number of patients who had baseline PGA-F scores ≥ 3, a post hoc analysis was performed for all patients who had nail psoriasis at baseline (PGA-F > 0), including 51% (264 of 517) of the ixekizumab group and 47% (239 of 507) of the guselkumab group. More patients in the ixekizumab group with any degree of nail psoriasis at baseline reached complete clearance of nail psoriasis than those in the guselkumab group: 63% (165 of 264) vs. 44% (106 of 239); $P < 0·001$ (Figure 3).

Clinical images of skin and nail lesions were obtained from 28 patients (14 per group) for visual evidence of improvement. Figure 4(a, b) depicts typical examples of patients' plaque psoriasis at baseline (week 0) and weeks 2, 4, 12 and 24. The percentage PASI improvement from baseline for patients 1–4 was similar to the median for the corresponding treatment group (Table S1; see Supporting Information). Visual improvement for nail psoriasis (week 0 vs. 24) is shown for a patient before and after 24 weeks of ixekizumab treatment (Figure 4c).

Patients in IXORA-R with a prior diagnosis of PsA [24% (122 of 519) on ixekizumab and 20% (103 of 506) on guselkumab] showed significant improvement in PsA as

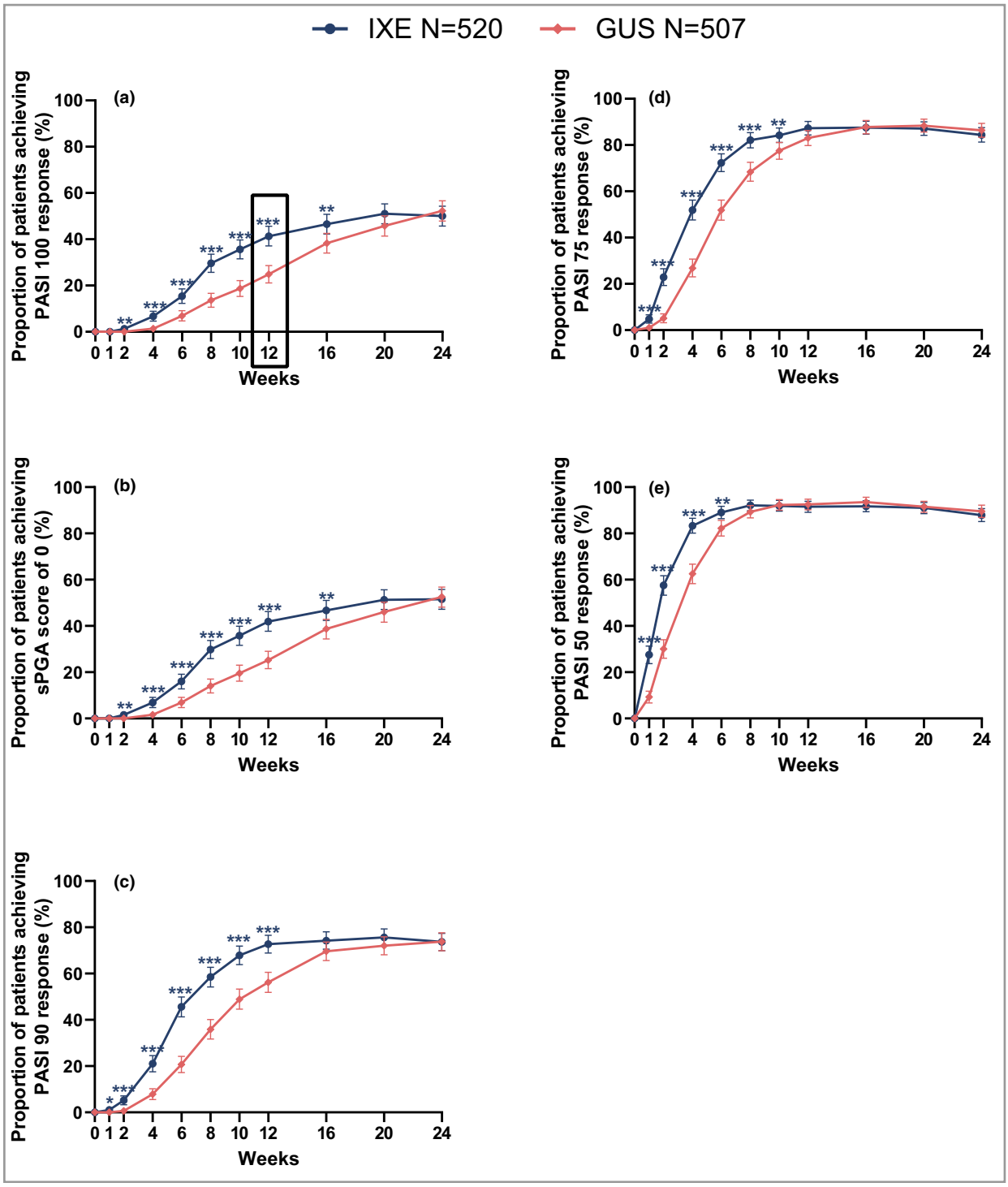

Figure 2 Clinical endpoints through week 24 in the ixekizumab (IXE) and guselkumab (GUS) groups. The data are percentages with 95% confidence intervals (CIs). Proportions of patients achieving (a) 100% improvement in Psoriasis Area and Severity Index (PASI 100), (b) static Physician's Global Assessment (sPGA) score of 0, (c) PASI 90, (d) PASI 75 and (e) PASI 50. The box in panel (a) indicates the primary endpoint (PASI 100 at week 12). Nonresponder imputation was used for missing data. The 95% CIs were constructed using the asymptotic method, without continuity correction (i.e. normal approximation to the binomial distribution). ***$P < 0{\cdot}001$, **$P < 0{\cdot}01$, *$P < 0{\cdot}05$. A prespecified noninferiority test of IXE vs. GUS was performed for the proportion of patients achieving PASI 100 at week 24 (preset noninferiority margin: −11·4%). IXE was noninferior to GUS for PASI 100 at week 24: IXE 50%, GUS 52%, difference −2·3% (95% CI −8·4 to 3·8%). A portion of the data shown here was previously reported, including PASI 100 at weeks 4, 8 and 12; sPGA score of 0 at week 12; PASI 90 at weeks 4 and 8; PASI 75 at week 2 and PASI 50 at week 1.[3]

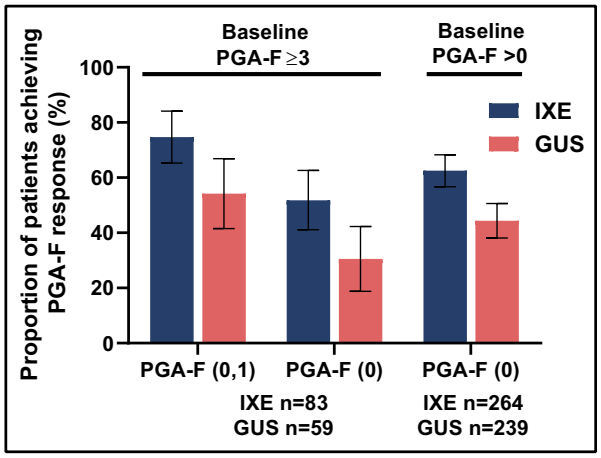

Figure 3 Physician's Global Assessment of Fingernail Psoriasis (PGA-F) response at week 24 in the ixekizumab (IXE) and guselkumab (GUS) groups. Data are percentages with 95% confidence intervals. Nonresponder imputation was used for missing data. The 95% confidence intervals were constructed using the asymptotic method, without continuity correction (i.e. normal approximation to the binomial distribution). n = number of patients with PGA-F ≥ 3 (left and centre columns) or number of patients with PGA-F> 0 (right column).

measured by Physician's Global Assessment of Disease Activity at weeks 12 and 24. However, there were no significant differences between the treatment groups (baseline values in Table S2; change from baseline values in Table S3; see Supporting Information).

Patient-reported outcomes

Of the patients with itch numerical rating scale (NRS) score > 0 at baseline, significantly more patients who received ixekizumab than guselkumab reported complete resolution of itch (itch NRS score of 0) starting at week 4 and continuing through week 16: 41% (210 of 515) vs. 33% (164 of 495); $P < 0{\cdot}05$ (Figure S1c; see Supporting Information). For patients reaching a response of sPGA score of 0 or 1, Patient's Global Assessment score of 0 or 1 and a Dermatology Life Quality Index (DLQI) of 0 or 1, there were no significant differences between the ixekizumab and guselkumab groups from week 16 to week 24 (Figure S1). Patients in IXORA-R with a prior diagnosis of PsA reported significant improvement in their PsA symptoms at weeks 12 and 24; however, there were no significant differences between the ixekizumab and guselkumab treatment groups (Table S3; see Supporting Information).

Speed of onset of treatment effects

To compare further the speed of onset of efficacy for ixekizumab and guselkumab, the median percentage PASI improvement was compared over the 24-week study (Figure 5a). Patients in the ixekizumab group reached the 50%, 75%, 90% and 100% PASI improvement thresholds more rapidly than those on guselkumab (Figure 5a). The median times to first achievement of different PASI levels were significantly shorter for patients on ixekizumab, with patients receiving ixekizumab reaching PASI 50 and 75 a median of 2·0 weeks more rapidly than patients on guselkumab ($P < 0{\cdot}001$; Figure 5b). Median achievement of PASI 90 was 2·1 weeks sooner with ixekizumab ($P < 0{\cdot}001$; Figure 5b; and Figure S2; see Supporting Information). An even greater difference was found for PASI 100: the median time to first PASI 100 was 7·5 weeks earlier for ixekizumab vs. guselkumab (12·6 vs. 20·1 weeks; $P < 0{\cdot}001$; Figure 5b; and Figure S3; see Supporting Information).

The times at which ixekizumab and guselkumab improved quality of life and eliminated itch were also compared. The median time to first achievement of DLQI of 0 or 1 was 5·8 weeks earlier for patients receiving ixekizumab vs. guselkumab (6·3 vs. 12·1 weeks; $P = 0{\cdot}002$; Figure 5b; and Figure S4; see Supporting Information). Similarly, the median time to first achievement of itch NRS of 0 was 4·2 weeks shorter with ixekizumab than with guselkumab (16·1 vs. 20·3 weeks; $P = 0{\cdot}001$; Figure 5b; and Figure S5; see Supporting Information).

Cumulative benefit of ixekizumab vs. guselkumab

To determine the cumulative benefit of ixekizumab vs. guselkumab treatment over 24 weeks, the mean days at response were calculated using measurements of area under the curve from the time-course data in Figure 2 and Figure S1 (see Supporting Information). There were significantly more days of complete clearance (PASI 100: 55·6 vs. 42·2 days; $P < 0{\cdot}001$; Figure 6) and almost complete clearance (PASI 90: 95·2 vs. 78·6 days; $P < 0{\cdot}001$; Figure 6) with ixekizumab than with guselkumab. Patients on ixekizumab also experienced more days without psoriasis impacting their quality of life[10] (DLQI of 0 or 1: 84·9 vs. 77·4 days; $P = 0{\cdot}026$; Figure 6) and days without itch (itch NRS score of 0: 51·2 vs. 41·5 days; $P = 0{\cdot}002$; Figure 6).

To explore the benefit of achieving PASI 100 early vs. late in the study, we divided the 24-week study into four time periods, combined the treatment groups, and evaluated the cumulative days of DLQI of 0 or 1. Patients who first achieved PASI 100 during days 1–42 vs. days 85–126 had significantly more days at DLQI of 0 or 1 (111·1 vs. 95·5 days; $P = 0{\cdot}045$; Figure 7). Patients who first achieved PASI 100 between study days 127 and 184 had fewer days at DLQI of 0 or 1, and those who did not achieve PASI 100 during the 24-week study had the fewest days at DLQI of 0 or 1 (84·8 days and 51·0 days, respectively; Figure 7). Thus, achieving a PASI 100 response earlier was associated with more days at DLQI of 0 or 1, regardless of treatment (Figure 7).

Safety

Similar proportions of patients reported treatment-emergent adverse events (TEAEs) between the treatment groups, with 62% (323 of 519) and 57% (286 of 506) of patients

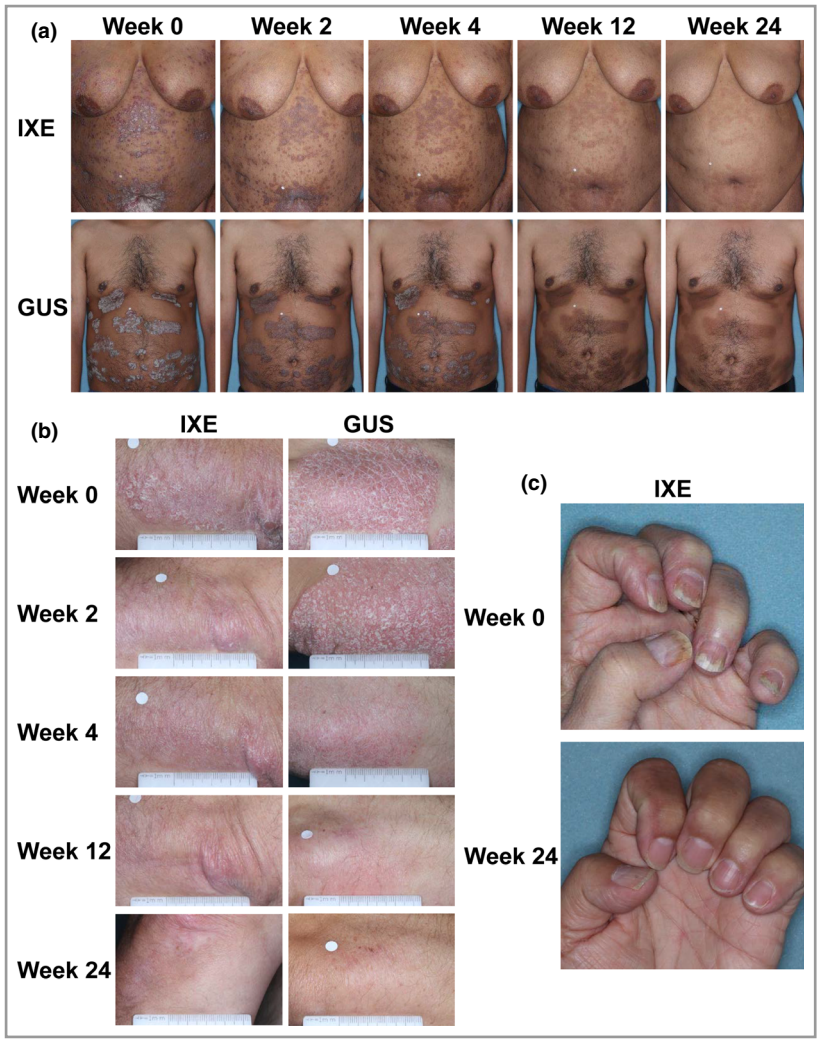

Figure 4 Visual improvement of skin and nails after treatment with ixekizumab (IXE) or guselkumab (GUS). (a) IXE patient 1 had a baseline Psoriasis Area and Severity Index (PASI) of 27·4 and achieved 86% and 98% improvement after 12 and 24 weeks of IXE, respectively. GUS patient 2 had a baseline PASI of 33·8 and achieved 89% and 98% improvement after 12 and 24 weeks of GUS, respectively. (b) IXE patient 3 had a baseline PASI of 13·7 and achieved 93% and 96% improvement after 12 and 24 weeks of IXE, respectively. GUS patient 4 had a baseline PASI of 15·0 and achieved 89% and 100% improvement after 12 and 24 weeks of GUS, respectively. Percentage PASI improvements for patients 1, 2, 3 and 4 are shown in Table S1 (see Supporting Information). (c) Patient scores on the Physician's Global Assessment of Fingernail psoriasis (PGA-F) were 3 at baseline and 1 after 24 weeks of IXE.

reporting at least one TEAE with ixekizumab and guselkumab, respectively (Table 1). Most infections were mild to moderate in severity, and serious AEs were reported by 3% of patients in each group. The proportions of patients discontinuing treatment due to an AE were similar between the ixekizumab and guselkumab groups (3% and 2%, respectively). There were no deaths during the study. Overall, the most common TEAE was upper respiratory tract infection, which occurred in 8% of patients in each group. In total six opportunistic infections were reported; each was a case of either mucocutaneous candidiasis (three in the ixekizumab arm) or herpes zoster (two and one in the ixekizumab and guselkumab arms, respectively), with no deep organ or systemic opportunistic infections reported. More patients who received ixekizumab than guselkumab reported injection-site reactions: 13% (67 of 519) vs. 4% (19 of 506) (Table 1). Most injection-site reactions were mild; none was severe. There was one case of Crohn disease in a patient receiving ixekizumab who had a prior history of IBD.

Discussion

Patient surveys have shown that patients prioritize both complete clearance and speed of improvement for psoriasis treatment.[11–14] In one recent survey, patients indicated that they expect 50% improvement after an average of 2 weeks.[13] In IXORA-R, 58% on ixekizumab vs. 30% on guselkumab achieved PASI 50 at week 2 and met this expectation. Ixekizumab had a faster onset of action than guselkumab. The median times to achieve PASI 50 were 2·1 and 4·1 weeks for

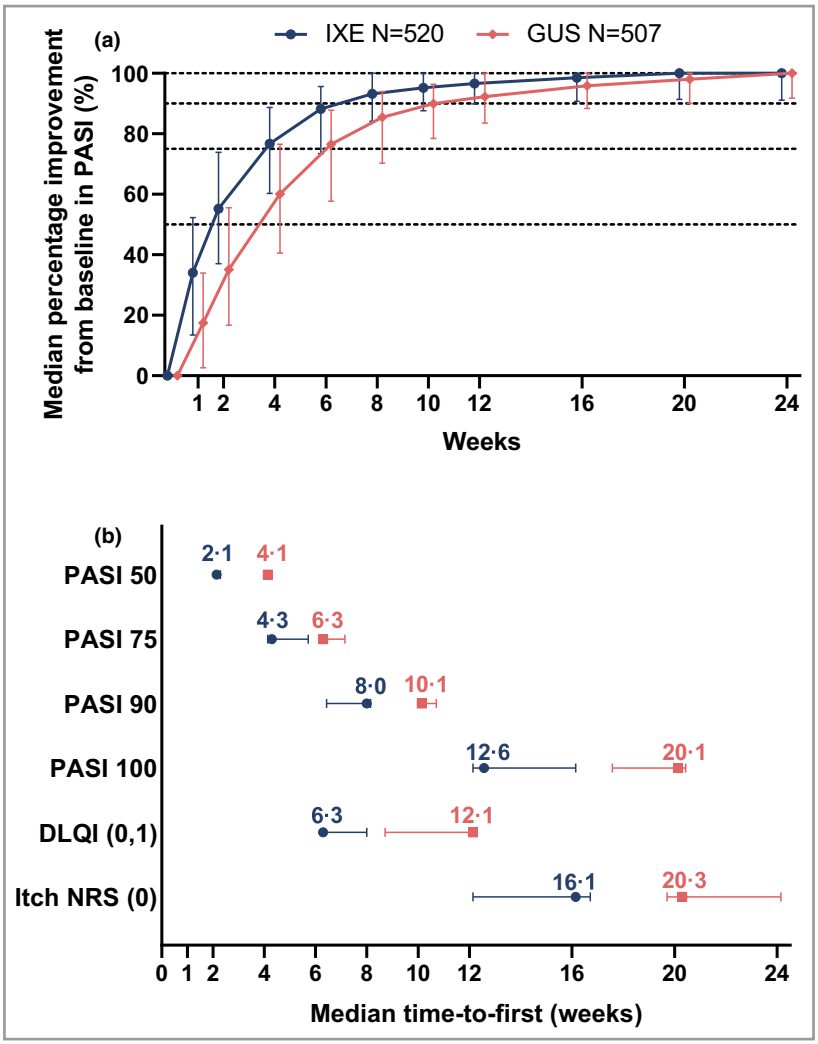

Figure 5 Comparison of the speed of improvement in clinical and patient-reported outcomes. (a) Median percentage improvement from baseline in Psoriasis Area and Severity Index (PASI). Data are shown as the median percentage with interquartile range. Modified baseline observation carried forward was used for missing data. Dashed lines mark 50%, 75%, 90% and 100% thresholds for improvement in PASI. (b) Median time to first achievement of PASI 50/75/90/100, Dermatology Life Quality Index (DLQI) of 0 or 1 and itch numerical rating scale (NRS) score of 0. Data are shown as the median (95% confidence interval) and were determined using Kaplan–Meier analyses. The intention-to-treat population was used for all analyses except for itch NRS score of 0, which used the intention to treat with baseline Itch NRS > 0. $P \leq 0{\cdot}001$ for each pair of medians compared in panel (b) based on adjusted log-rank test stratified by treatment. GUS, guselkumab; IXE, ixekizumab.

patients receiving ixekizumab and guselkumab, respectively (Figure 5b). More than one in five patients experienced even greater improvement after 2 weeks of ixekizumab treatment, achieving PASI 75 at week 2 (Figure 2d). The median times to achieve PASI 75 and PASI 90 were 2 weeks earlier for patients receiving ixekizumab vs. guselkumab (Figure 5b).

More patients on ixekizumab experienced completely clear skin at weeks 4, 8, 12 and 16·[3] Strikingly, 50% of patients receiving ixekizumab achieved PASI 100 by 12·6 weeks, 7·5 weeks sooner than patients receiving guselkumab. The data presented here support the hypothesis that achieving clear skin quickly has a significant effect on a patient's quality of life. Patients who achieved clear skin within the first 6 weeks had significantly more days without psoriasis having an impact on their quality of life than patients who achieved PASI 100 after 12 weeks (Figure 7). The speed of response is not only important for a patient's quality of life and satisfaction but also contributes to treatment persistence. In line with treatment expectations of patients, a lag time between initiation of a therapy and the onset of clinically visible results could be one factor for poor treatment persistence. In fact, a systematic review found that a perceived lack of efficacy was the most common reason for patients with psoriasis not continuing with their treatment.[15] The faster onset of ixekizumab could be associated with better treatment persistence, although this does not seem to be the case for other biologics with rapid onset of improvement. While the IL-17A inhibitor secukinumab also has demonstrated rapid improvement in patients

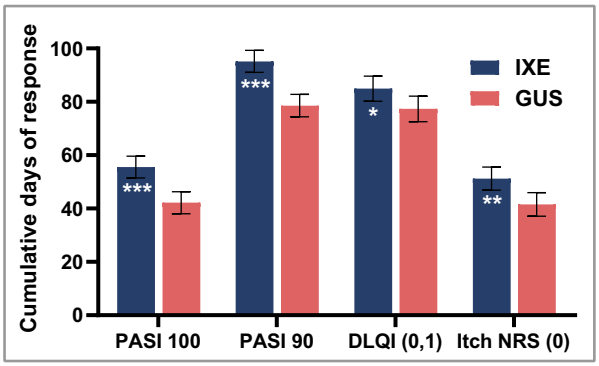

Figure 6 Cumulative benefit of ixekizumab (IXE) vs. guselkumab (GUS) for clinical and patient-reported outcomes. Cumulative days of the indicated response over the 24-week study for 100% and ≥ 90% Psoriasis Area and Severity Index (PASI) improvement, DLQI of 0 or 1, and itch numerical rating scale (NRS) score of 0 for IXE vs. GUS treatments. Data are shown as the least squares mean for normalized area-under-the-curve measurements, with 100% representing the maximum area for each measure, multiplied by the 168-day study duration. Error bars show 95% confidence intervals. ***P < 0·001, **P < 0·01, *P < 0·05 vs. GUS. P-values were calculated using ANCOVA analysis after adjusting for baseline scores and pooled sites.

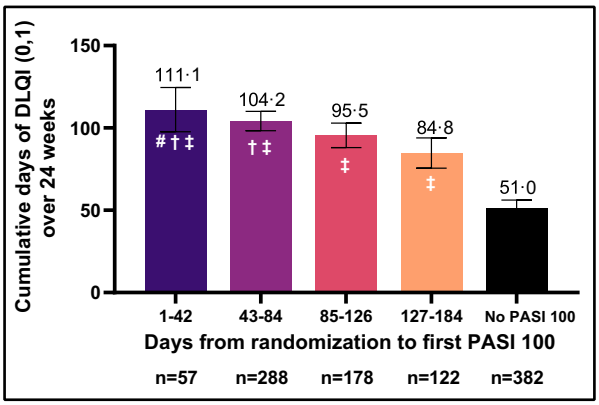

Figure 7 Effect of period (42-day intervals) of achievement of first 100% improvement in Psoriasis Area and Severity Index (PASI 100) on cumulative benefit for Dermatology Life Quality Index (DLQI) of 0 or 1, regardless of drug. Days from randomization to first achieved PASI 100 vs. cumulative days of DLQI score of 0 or 1 over the 24-week study. The data are shown as the least squares mean for normalized area-under-the-curve measurements, with 100% representing the maximum area for each measure, multiplied by the 168-day study duration. Error bars show 95% confidence intervals. #P < 0·05 vs. 85–126 days; †P < 0·01 vs. 127-184 days; ‡P < 0·001 vs. No PASI 100. P-values were calculated using ANCOVA analysis after adjusting for baseline scores and pooled sites.

with psoriasis, secukinumab has lower treatment persistence than ixekizumab in real-world settings.[16]

Achieving clearance of all skin lesions is an important goal for patients. Skin clearance is often associated with resolution of itching.[17,18] A large survey of North American and

Table 1 Safety outcomes

	Ixekizumab, n = 519	Guselkumab, n = 506
TEAEs	323 (62)	286 (57)
Mild	181 (35)	166 (33)
Moderate	124 (24)	99 (20)
Severe[a]	18 (3)	21 (4)
Discontinuation due to an AE	15 (3)	8 (2)
Serious adverse events	18 (3)	16 (3)
Death	0	0
Common TEAEs[b]		
Upper respiratory tract infection	40 (8)	41 (8)
Nasopharyngitis	34 (7)	27 (5)
Injection-site reaction[c]	49 (9)	6 (1)
Headache	22 (4)	15 (3)
Diarrhoea	16 (3)	17 (3)
TEAEs of special interest		
Neutropenias	2 (0·4)	2 (0·4)
Infections	162 (31)	143 (28)
Serious	2 (0·4)	2 (0·4)
Opportunistic infections	5 (1)	1 (0·2)
Mucocutaneous candidiasis	3 (0·6)	0
Herpes zoster	2 (0·4)	1 (0·2)
Reactivated tuberculosis	0	0
Depression	5 (1)	7 (1)
Malignancies	4 (0·8)	3 (0·6)
Allergic reactions	19 (4)	13 (3)
Potential anaphylaxis[d]	0	1 (0·2)
Injection-site reactions[e]	67 (13)	19 (4)
Severe	0	0
MACE[f]	4 (0·8)	2 (0·4)
Cerebrocardiovascular events[f]	7 (1)	4 (0·8)
Inflammatory bowel disease[f]	1 (0·2)	0
Crohn disease[f]	1 (0·2)	0
Ulcerative colitis[g]	0	0
Hepatic events[h]	7 (1)	8 (2)

The data are presented as n (%) of patients in the safety population. AE, adverse event; MACE, major adverse cardiovascular event; TEAE, treatment-emergent adverse event. [a]Patients with multiple occurrences of the same event are counted under the highest severity. [b]Common TEAEs are defined as those that occurred at a frequency of ≥ 3% overall. [c]Numbers reported here include only TEAEs with the Medical Dictionary for Regulatory Activities (MedDRA) low-level term 'injection site reaction'. [d]The potential anaphylaxis was related to the use of amoxicillin. [e]Numbers reported here are for the high-level MedDRA term 'injection site reactions', which includes multiple lower-level MedDRA terms, including, but not limited to, injection site reaction, injection site pain, injection site erythema, injection site swelling, injection site pruritus, injection site discomfort, injection site oedema and injection site warmth. [f]Positively adjudicated by external committee. [g]One case of ulcerative colitis was reported during the follow-up period for a patient who had received ixekizumab. [h]Patients with at least one hepatic-related TEAE.

European patients with psoriasis or PsA indicated that itching was the most bothersome physical symptom.[4] Resolution of itching occurred in more patients receiving ixekizumab at weeks 4–16 (Figure S1c). The combination of signs and symptoms, psychological burden and work restrictions as a result of nail psoriasis makes clearance of nail disease another important treatment goal.[6,19] Complete clearance of nail psoriasis occurred in more patients on ixekizumab than guselkumab, regardless of the baseline level of nail psoriasis (Figure 3). Notably, the percentages of patients achieving complete nail clearance in this study were similar to those seen in the phase III registration studies for ixekizumab, with greater percentages here than seen previously for guselkumab.[20,21]

The data presented here show that ixekizumab was noninferior to guselkumab in skin clearance at week 24. However, more patients who received ixekizumab achieved skin clearance early in the study. This can be illustrated by the significantly greater cumulative benefits experienced by patients on ixekizumab over the 24-week study period. Patients on ixekizumab experienced 13·4 more 'clear skin' days, 9·7 more 'itch-free' days, and 7·6 more days without psoriasis having an impact on their quality of life over the 24-week study.

To our knowledge, this is only the second head-to-head clinical trial comparing IL-17 and IL-23 inhibitors in patients with moderate-to-severe plaque psoriasis. The ECLIPSE trial compared guselkumab with the IL-17 inhibitor secukinumab.[22] While the difference did not reach significance, numerically more patients on secukinumab achieved PASI 90 at week 12.[22] In contrast, significantly more patients on guselkumab achieved PASI 90 response at week 48.[22] While no trials have directly compared the long-term efficacy of ixekizumab and guselkumab, a recent network meta-analysis of 52-week trial data found the efficacy of ixekizumab and guselkumab to be in the same range.[23] Moreover, because the long-term profile displayed by ixekizumab is quite consistent across the phase III programme,[1] it is likely that ixekizumab and guselkumab have similar long-term efficacy in the treatment of psoriasis.

The safety data presented here are consistent with those in previously published studies of ixekizumab and guselkumab for the treatment of psoriasis.[2,24,25] The frequencies of TEAEs (including upper respiratory tract infections, nasopharyngitis and injection-site reactions) and the severity of TEAEs and serious AEs were similar to those in previous clinical trials and consistent with the known safety profile for ixekizumab. Although there was one patient receiving ixekizumab who had a TEAE of Crohn disease, this patient had a history of IBD. The AE occurred on study day 140, 24 days after the patient's last dose of ixekizumab. Patients on ixekizumab should be monitored for new onset or exacerbation of IBD.

The study was conducted only in the USA and Canada, which may limit the general applicability of these results. Another limitation was the length of the trial. However, the primary objective of this study was to compare the rapidity of skin clearance in patients with psoriasis. Previous studies have established the long-term safety and efficacy of both ixekizumab and guselkumab in patients with psoriasis, with ixekizumab reporting 5 years of efficacy and safety data.[1,2,24] This study also sought to understand this hallmark of ixekizumab by linking clinical responses and patient-reported symptoms with microscopic findings and molecular changes in lesional skin. To that end, analyses are underway from a study addendum in which skin biopsies were obtained from patients to compare the early changes in lesion pathology and gene expression associated with ixekizumab and guselkumab.

In conclusion, patients with psoriasis treated with ixekizumab vs. guselkumab demonstrated more rapid resolution of skin and nail lesions over a 24-week period. Quality of life also improved more rapidly for patients treated with ixekizumab vs. guselkumab. Overall, the safety findings were consistent with the known safety profile of ixekizumab for the treatment of adult psoriasis.

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Supporting Information

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

Figure S1 Clinical endpoints and patient-reported outcomes through week 24.

Figure S2 Time to first report of ≥ 90% improvement in Psoriasis Area and Severity Index for patients receiving ixekizumab or guselkumab.

Figure S3 Time to first report of 100% improvement in Psoriasis Area and Severity Index for patients receiving ixekizumab or guselkumab.

Figure S4 Time to first report of Dermatology Life Quality Index score of 0 or 1 for patients receiving ixekizumab or guselkumab.

Figure S5 Time to first itch numerical rating score of 0 for patients receiving ixekizumab or guselkumab.

Table S1 Baseline Psoriasis Area and Severity Index (PASI) and percentage PASI improvement for individual patients whose photographs are shown in Figure 4.

Table S2 Baseline measures of psoriatic arthritis (PsA) disease for patients who had a previous diagnosis of PsA.

Table S3 Change from baseline for clinical and patient-reported outcomes for measures of psoriatic arthritis.

Appendix S1 Supplementary methods: schedule of assessments, outcome measures and statistical analyses.

Powerpoint S1 Journal Club Slide Set.

Video S1 Author video.

Appendix

Conflicts of interest. A.B. has served as a scientific adviser and/or clinical study investigator for AbbVie, Aclaris, Almirall, Arena, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Dermira, Eli Lilly and Company, Forte, Galderma, Incyte, Janssen, LEO, Novartis, Ortho, Pfizer, Rapt, Regeneron, Sandoz, Sanofi Genzyme, Sun Pharma and UCB Pharma; and as a paid speaker for AbbVie. C.L. has been on an advisory board at and/or been a consultant at and/or received speaker's bureaux from and/or is or was an investigator at the following companies: AbbVie, Actavis, Allergan, Amgen, Boehringer Ingelheim, Celgene, Cellceutix, Coherus, Corrona, Dermira, Eli Lilly and Company, Galderma, Glenmark, Janssen, LEO Pharma, Merck, Novartis, Novella, Ortho Dermatologics, Pfizer, Sandoz, Sienna, Stiefel, Sun Pharmaceuticals, UCB, Vitae and Wyeth. B.E. has served as a consultant for Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly and Company, LEO, Menlo, Novartis, Pfizer, Sun, Valeant (Ortho Dermatology) and Verrica; and received clinical research funding from AbbVie, AnaptysBio, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly and Company, Incyte, LEO, Merck, Menlo, Novartis, Pfizer, Regeneron, Sun, Valeant (Ortho Dermatology) and Vanda. J.J.C. has received compensation as a speaker, consultant and investigator for AbbVie, Amgen, Celgene, Eli Lilly and Company, Janssen, Novartis, Regeneron, Sanofi-Aventis, Sun Pharma and UCB; and has been an investigator for Merck, Maruho, Pfizer, Regeneron, Boehringer Ingelheim, MC2, Verrica, Dermira and Sandoz. L.C.G. has been a consultant, investigator and speaker for AbbVie, Amgen, Bausch Health, Boehringer Ingelheim, Celgene, Eli Lilly and

Company, GSK, Janssen, LEO Pharma, Merck, Novartis and Pfizer; has been a speaker and consultant for Actelion; and has been an investigator for UCB and Sun Pharmaceuticals. M.G. reports personal fees from AbbVie, Actelion Pharmaceuticals, Akros Pharma Inc., Amgen Inc., Arcutis Pharmaceuticals Inc., Boehringer Ingelheim International GmbH, Bristol Myers Squibb Company, Celgene Corporation, Dermira Inc., Eli Lilly and Company, Galderma, GlaxoSmithKline, Glenmark, Janssen Inc., LEO Pharma, MedImmune, Merck & Co., Novartis Pharmaceuticals, Pfizer Inc., Regeneron Pharmaceuticals Inc., Roche Laboratories, Sanofi Genzyme, UCB and Valeant Pharmaceuticals Inc. R.G. Langley has served as a principal investigator, speaker and scientific advisory board member for and received compensation in the form of honoraria from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Sun and UCB Pharma. R.V. has been a speaker and/or consultant and/or investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Centocor, Dermira, Eli Lilly and Company, Galderma, GSK, Janssen, LEO, Merck, Novartis, Pfizer, Takeda, UCB and Valeant. A.P. has been an investigator and/or speaker and/or adviser for AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Biontec, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Galderma, GSK, Hexal, Janssen, LEO Pharma, MC2, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pascoe, Pfizer, Tigercat Pharma, Regeneron, Roche, Sandoz Biopharmaceuticals, Sanofi Genzyme, Schering-Plough and UCB Pharma. C.E.M.G. has received honoraria and/or research grants from AbbVie, Almirall, Amgen, BMS, Celgene, Eli Lilly and Company, Galderma, Janssen, LEO Pharma, MSD, Novartis, Pfizer, Sandoz, Stiefel GSK, Sun Pharmaceuticals and UCB Pharma. Y.T. has received grants for research from Maruho, LEO Pharma, Eisai, AbbVie, Kyowa Hakko Kirin, Taiho Pharmaceutical, Celgene, and Eli Lilly and Company; and honoraria for lectures from Torii Pharmaceutical, Maruho, LEO Pharma, Eisai, AbbVie, Kyowa Hakko Kirin, Eli Lilly and Company, Taiho Pharmaceutical, Mitsubishi Tanabe Pharma and Janssen. H.E., R.G. Lima, G.G., L.R., R.B., S.Y.P. and B.Z. are employees and stockholders of Eli Lilly and Company. K.P. has served as a scientific adviser and/or clinical study investigator for AbbVie, Akros, Allergan, Almirall, Amgen, Arcutis, Avillion, Bausch Health, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly and Company, Galderma, Genentech/Roche, GlaxoSmithKline, Janssen, Kyowa Kirin, LEO, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, Takeda, UCB and Valeant; and as a paid speaker for AbbVie, Akros, Allergan, Almirall, Amgen, Bausch Health, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly and Company, Galderma, Genentech/Roche, Janssen, Kyowa Kirin, LEO, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, Takeda, UCB and Valeant.