Dermatol Ther (Heidelb) (2024) 14:1327–1335
https://doi.org/10.1007/s13555-024-01150-y

BRIEF REPORT

Baseline Characteristics and mNAPSI Change from Baseline Scores Through Month 12 for Patients with Moderate-to-Severe Plaque Psoriasis and Concomitant Nail Psoriasis Treated with Biologics from PSoHO

Elisabeth Riedl · Andreas Pinter · Shirin Zaheri · Antonio Costanzo · Alan Brnabic · Bruce Konicek · Robert McKenzie · Anastasia Lampropoulou · Mohamed El Rayes · Natalie Haustrup · Christopher Schuster

Received: February 22, 2024 / Accepted: March 25, 2024 / Published online: April 22, 2024

ABSTRACT

Introduction: Nail psoriasis is highly prevalent among patients with psoriasis yet remains one of the most challenging areas to treat. To better understand the treatment landscape for psoriatic nail disease, more studies are needed that compare the effectiveness of different biologics for patients with nail psoriasis. This study contributes to this objective by directly comparing the effectiveness of approved biologics in improving nail psoriasis for patients up to month 12 in a real-world setting.

Methods: Psoriasis Study of Health Outcomes (PSoHO) is an ongoing 3-year, prospective, non-interventional cohort study of adults with chronic moderate-to-severe plaque psoriasis initiating or switching to a new biologic. This study assessed the change in modified Nail Psoriasis Severity Index (mNAPSI) score from baseline to months 3, 6 and 12 for 763 patients and compared the effectiveness of anti-interleukin (IL)-17A biologics versus other approved biologics, as well as ixekizumab versus secukinumab, guselkumab, risankizumab and adalimumab. Comparative adjusted analyses used frequentist model averaging (FMA). Least square mean difference (LSMD) in mNAPSI scores are presented as observed.

Natalie Haustrup and Christopher Schuster contributed equally to this work.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-024-01150-y.

E. Riedl (✉) · C. Schuster
Department of Dermatology, Medical University of Vienna, Vienna, Austria
e-mail: elisabeth.riedl@meduniwien.ac.at

A. Pinter
University Hospital Frankfurt, Frankfurt Am Main, Germany

S. Zaheri
Department of Dermatology, The Harley Street Clinic, HCA Healthcare UK, London, UK

A. Costanzo
Division of Dermatology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

A. Costanzo
Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy

A. Brnabic · B. Konicek · R. McKenzie · A. Lampropoulou · M. E. Rayes · N. Haustrup · C. Schuster
Eli Lilly and Company, Indianapolis, USA

Results: Irrespective of the severity of nail psoriasis at baseline, the anti-IL-17A cohort had greater mean mNAPSI reductions from baseline compared to the other biologics cohort through month 12, reaching significance at months 3 and 6 in the adjusted analysis. For patients with moderate-to-severe nail psoriasis, ixekizumab showed numerically higher mean reductions in mNAPSI scores compared to all other studied biologics, reaching significance versus guselkumab at all timepoints and risankizumab at month 6.
Conclusion: This real-world study showed that patients with moderate-to-severe psoriasis and any severity of concomitant nail involvement had significantly faster and more substantial improvements in nail psoriasis up to month 6 in the anti-IL-17A cohort compared to the other biologics cohort. Of the individual biologics studied, ixekizumab showed the highest numerical improvements in nail psoriasis at month 12.
Trial registration: EUPAS24207.

Key Summary Points

Why carry out this study?
Nail psoriasis is a chronic, difficult-to-treat condition affecting around half of patients with psoriasis and more studies are needed that compare the effectiveness of different biologics for patients with nail psoriasis.
Psoriasis Study of Health Outcomes (PSoHO) is an ongoing 3-year, prospective, non-interventional cohort study and this analysis compares the effectiveness of approved biologics in improving nail psoriasis for patients up to month 12 in a real-world setting.

What was learned from the study?
The findings of this real-world study showed that patients with moderate-to-severe psoriasis and any severity of concomitant nail psoriasis had significantly faster and more substantial improvements in nail psoriasis up to month 6 in the anti-interleukin (IL)-17A cohort compared to the other biologics cohort.
Of the individual biologics studied, ixekizumab showed the highest numerical improvements in nail psoriasis at month 12.
These results may support physicians in their treatment decisions for patients with psoriasis and concomitant nail psoriasis and may serve as a foundation for further real-world studies of this difficult-to-treat condition.

INTRODUCTION

Nail psoriasis (NP) is a chronic, difficult-to-treat condition affecting around half of patients with psoriasis. It is associated with considerable social stigma and impairment of patients' quality of life [1]. The presence of nail changes not only indicates more severe psoriasis but also serves as a potential predictor of the future development of psoriatic arthritis [2, 3]. This underscores the need for early diagnosis and effective, targeted treatment. In recent years, network meta-analyses (NMAs) of randomized clinical trial data have shown the relative efficacy of different biologics [4, 5]. Yet, there remains a scarcity of comparative data of the real-world effectiveness of these biologics for patients with NP [6].

To address this gap, the Psoriasis Study of Health Outcomes (PSoHO) is an ongoing, international, prospective, non-interventional study that was designed to investigate the comparative effectiveness of biologic treatments for patients with moderate-to-severe psoriasis (PsO) within a real-world setting [7]. This analysis compares the effectiveness of the anti-interleukin (IL)-17A cohort versus the other biologics cohort, as well as ixekizumab versus secukinumab (SEC), guselkumab (GUS), risankizumab (RIS) and adalimumab (ADA) in terms of improvements in NP up to month 12 within a real-world setting.

METHODS

Applying the same methodology as per other recently published PSoHO analyses [7–9], we assessed the change in modified Nail Psoriasis Severity Index (mNAPSI) score from baseline up to month 12 in PSoHO patients with moderate-to-severe PsO.

mNAPSI Assessment

The mNAPSI assessment was developed to enhance the face validity and feasibility of this tool [10]. Based on descriptive criteria, three features (pitting, onycholysis and oil-drop dyschromia, and crumbling) of each fingernail are graded on a scale from 0 to 3. Four features (leukonychia, splinter hemorrhages, hyperkeratosis, and red spots in the lunula) are scored 1 if present and 0 if absent for each fingernail. The range of possible scores using the mNAPSI is 0 to 13 for each fingernail, and 0 to 130 for all 10 fingernails. In PSoHO, only patients' hands were assessed for NP.

Statistical Analyses

This analysis evaluated two patient populations based on the mNAPSI fingernail score at baseline: (1) patients with any degree of NP (mNAPSI $\geq$ 1), and (2) patients with moderate-to-severe NP (mNAPSI $\geq$ 20). The anti-IL-17A cohort was compared to the other biologics cohort, and ixekizumab was compared to individual biologics with sufficiently high sample sizes for comparisons ($n > 50$: SEC, GUS, RIS and ADA). The unadjusted analyses report the mean change from baseline in mNAPSI score at week 12, month 6 and month 12. Adjusted pairwise comparisons use frequentist model averaging (FMA) and report the least square mean difference (LSMD) [7, 8]. Results are statistical significant when the 95% confidence intervals (CIs) do not cross the null hypothesis of LSMD = 0. As a result of the small sample sizes of treatment groups with patients with mNAPSI $\geq$ 20 at baseline, the majority of models did not converge at months 6 and 12. Consequently FMA analyses employed a reduced number of variables to control for baseline differences (see supplementary Table S2). Data are reported as observed. Observed data were also analysed for the population receiving the European Medicines Agency (EMA) on-label dosing of biologics. A sensitivity analysis reports imputed data using last observation carried forward (LOCF).

Study Oversight

All patients provided informed consent for participation in the study. Local ethical review boards approved the protocol, amendments and consent documentation. The study was registered at European Network of Centres for Pharmacoepidemiology and Pharmacovigilance and was conducted according to Good Pharmacoepidemiology Practices guidelines and the Declaration of Helsinki.

RESULTS

Patient Characteristics

From the 1981 patients with moderate-to-severe PsO included in PSoHO, this post hoc analysis focused on 763 patients with any degree of NP (mNAPSI $\geq$ 1), of which 342 patients represented a subset with moderate-to-severe NP (mNAPSI $\geq$ 20). Table 1 provides the baseline demographics and disease characteristics for

Table 1 Demographics and disease characteristics of PSoHO patients with any degree of nail psoriasis at baseline (mNAPSI ≥ 1)

	Overall (n=763)	Anti-IL-17A (n=313)	Other Biologics (n=450)	IXE (n=230)	SEC (n=83)	GUS (n=117)	RIS (n=91)	ADA (n=106)
Age, years	46.1 (12.7)	47.9 (12.6)	44.8 (12.7)**	47.9 (13.3)	47.7 (10.6)	44.7 (12.5)‡	42.8 (12.3)‡	45.5 (12.6)
Sex, n (%)								
Male	519 (68.0)	208 (66.5)	311 (69.1)	158 (68.7)	50 (60.2)	83 (70.9)	71 (78.0)	68 (64.2)
Female	244 (32.0)	105 (33.5)	139 (30.9)	72 (31.3)	33 (39.8)	34 (29.1)	20 (22.0)	38 (35.8)
Weight, kg	87.5 (20.7)	88.6 (20.8)	86.7 (20.7)	89.8 (20.9)	85.3 (20.2)	83.8 (18.5)‡	88.0 (22.5)	89.2 (22.2)
BMI, kg/m^2	29.5 (6.6)	29.9 (6.5)	29.3 (6.7)	30.2 (6.7)	29.1 (5.9)	28.9 (6.3)	29.3 (6.4)	29.9 (7.0)
Race, n (%)								
White	520 (68.2)	222 (70.9)	298 (66.2)	160 (69.6)	62 (74.7)	53 (45.3)†	59 (64.8)	86 (81.1)‡
Asian	142 (18.6)	49 (15.7)	93 (20.7)	38 (16.5)	11 (13.3)	48 (41.0)†	26 (28.6)‡	4 (3.8)†
Disease Duration, median years (Q1, Q3)	15. 8 (8.9, 24.9)	16.3 (8.0, 25.8)	15.4 (9.2, 23.7)	15.9 (7.7, 26.1)	17.1 (8.9, 25.0)	17.4 (10.0. 22.9)	14.1 (9.8, 24.3)	17.7 (8.4, 25.7)
Psoriatic Arthritis[a], n (%)	219 (28.7)	101 (32.3)	118 (26.2)	75 (32.6)	26 (31.3)	41 (35.0)	16 (17.6)‡	26 (24.5)
PASI	16.0 (9.0)	15.7 (8.8)	16.2 (9.2)	15.6 (8.3)	15.7 (10.1)	15.8 (9.0)	18.8 (11.5)‡	14.5 (7.6)
BSA, %	25.6 (20.2)	24.6 (19.2)	26.3 (20.8)	24.1 (18.6)	25.9 (20.9)	25.7 (20.6)	28.7 (24.4)	24.9 (17.7)
sPGA	3.4 (0.83)	3.4 (0.85)	3.4 (0.81)	3.3 (0.79)	3.4 (1.00)	3.4 (0.84)	3.6 (0.76)‡	3.3 (0.7)
DLQI[b]	13.8 (7.8)	14.5 (7.6)	13.3 (7.8)**	14.2 (7.61)	15.2 (7.74)	13.3 (8.26)	12.9 (7.65)	14.2 (7.2)
Prior conventional treatment, n (%)	624 (81.9)	239 (76.6)	385 (85.6)**	174 (76.0)	65 (78.3)	88 (75.2)	81 (89.0)‡	101 (95.3)†
Prior treatment with biologics, n (%)	287 (37.7)	109 (34.9)	178 (39.6)	76 (33.2)	33 (39.8)	86 (73.5)†	40 (44.0)	8 (7.5)†
mNAPSI score for patients with mNAPSI≥1								
Mean (SD)	23.5 (22.2)	25.7 (25.9)	22.0 (19.2)**	26.0 (26.0)	25.1 (25.8)	21.6 (17.9)	23.7 (21.2)	20.8 (16.4)
Median (Q1, Q3)	16.0 (8.0, 33.0)	17.0 (7.0, 36.0)	16.0 (8.0, 31.0)	17.0 (7.0, 37.0)	17.0 (6.0, 32.0)	15.0 (6.0, 33.0)	18.0 (9.0, 33.0)	16.0 (10.0, 30.0)
Presence of Nail PsO features, n (%)								
Onycholysis/ Oil-drop dyschromia	572 (75.0%)	242 (77.3%)	330 (73.3%)	180 (78.3%)	62 (74.7%)	90 (76.9%)	70 (76.9%)	75 (70.8%)
Nail pitting	612 (80.2%)	242 (77.3%)	370 (82.2%)	176 (76.5%)	66 (79.5)	98 (83.8%)	76 (83.5%)	85 (80.2%)
Nail crumbling	327 (42.9%)	149 (47.6%)	178 (39.6%)**	107 (46.5%)	42 (50.6%)	41 (35.0%)	36 (39.6%)	46 (43.4%)
Splinter hemorrhages	260 (34.1%)	108 (34.5%)	152 (33.8%)	88 (38.3%)	20 (24.1%)‡	40 (34.2%)	33 (36.3%)	34 (32.1%)
Hyperkeratosis	285 (37.4%)	118 (37.7%)	167 (37.1%)	92 (40.0%)	26 (31.3%)	37 (31.6%)	33 (36.3%)	36 (34.0%)
Leukonychia	274 (35.9%)	108 (34.5%)	166 (36.9%)	83 (36.1%)	25 (30.1%)	44 (37.6%)	31 (34.1%)	43 (40.6%)
Red spots	92 (12.1%)	48 (15.3%)	44 (9.8%)**	40 (17.4%)	8 (9.6%)	11 (9.4%)	3 (3.3%)†	9 (8.5%)‡
mNAPSI≥20 (mod-to-severe), n (%)	342 (44.8%)	142 (45.4%)	200 (44.4%)	103 (44.8%)	39 (47.0%)	54 (46.2%)	44 (48.4%)	45 (42.5%)
mNAPSI score for patients with mNAPSI≥20								
Mean (SD)	41.8 (21.6)	46.5 (25.7)	38.5 (17.5)*	47.4 (25.4)	44.1 (26.7)	37.5 (13.9)‡	39.5 (20.4)	35.9 (14.3)‡
Median (Q1, Q3)	36.0 (27.0, 49.0)	39.0 (28.0, 60.0)	33.5 (25.5, 45.5)	40.0 (28.0, 60.0)	33.0 (24.0, 57.0)	34.5 (26.0, 48.0)	33.0 (26.0, 48.0)	32.0 (25.0, 42.0)

All results are expressed as mean (standard deviation) of all available data for that measure, unless otherwise indicated. Included patients had a mNAPSI score of 1 or more at baseline. *P* values determined using ANOVA, median test (Monte Carlo estimate) or Fisher's exact test. The anti-IL-17A cohort included IXE and SEC. Other biologics cohort includes all other biologics included in PSoHO

ADA adalimumab, *BMI* body mass index, *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *GUS* guselkumab, *IQR* interquartile range, *IL-17A* interleukin-17A, *IXE* ixekizumab, *mNAPSI* modified Nail Psoriasis Severity Index, *PASI* Psoriasis Area and Severity Index, *sPGA* Static Physician Global Assessment, *Q* quartile, *RIS* risankizumab, *SEC* secukinumab

[a]Psoriatic arthritis diagnosis was recorded by the dermatologists on the basis of the medical history or information provided by the patient, or both

[b]DLQI was measured on a 0–30 scale

**P value < 0.05 vs. the other biologics cohort (shaded in yellow)

*P value < 0.001 vs. the other biologics cohort (shaded in green)

‡P value < 0.05 vs. IXE (shaded in orange)

†P value ≤ 0.001 vs. IXE (shaded in blue)

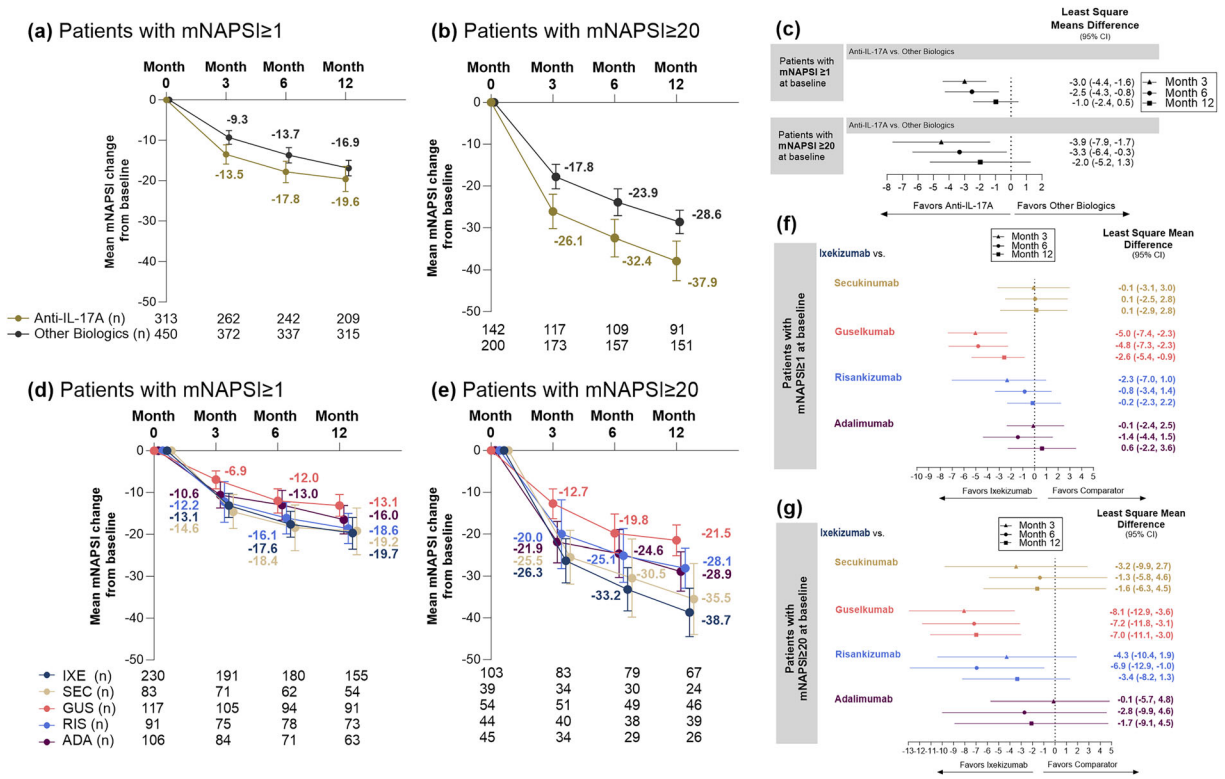

Fig. 1 Mean mNAPSI change from baseline **a** unadjusted analysis of patients with mNAPSI ≥ 1 at baseline in the anti-IL-17A cohort and other biologics cohort; **b** unadjusted analysis of patients with mNAPSI ≥ 20 at baseline in the anti-IL-17A cohort and other biologics cohort; **c** adjusted LSMD comparisons of anti-IL-17A cohort with other biologics cohort for patients with mNAPSI ≥ 1 or mNAPSI ≥ 20 at baseline; **d** unadjusted analysis of patients with mNAPSI ≥ 1 at baseline in IXE, SEC, GUS, RIS and ADA treatment groups; **e** unadjusted analysis of patients with mNAPSI ≥ 20 at baseline in IXE, SEC, GUS, RIS and ADA individual treatment groups; **f** adjusted LSMD comparisons of IXE vs. 4 other individual biologics for patients with mNAPSI ≥ 1 at baseline; **g** adjusted LSMD comparisons of IXE vs. 4 other individual biologics for patients with mNAPSI ≥ 20 at baseline. Data are presented as observed. In adjusted analyses, the result is significant if the confidence intervals do not cross 0. As a result of the small sample sizes of treatment groups with patients with mNAPSI ≥ 20 at baseline, the majority of models did not converge at months 6 and 12 and so Fig. 1g FMA analyses at months 6 and 12 employed a reduced number of variables to control for baseline differences. *ADA* adalimumab, *GUS* guselkumab, *IL-17A* interleukin-17A, *IXE* ixekizumab, *LSMD* least square mean difference, *mNAPSI* modified Nail Psoriasis Severity Index, *n* number of patients, *RIS* risankizumab, *SEC* secukinumab

patients with any degree of NP, as well as the frequency of the NP features captured by the mNAPSI assessment. The patient profiles between the anti-IL-17A cohort ($n = 313$) and other biologics cohort ($n = 450$) are largely comparable, with the few exceptions of age, DLQI score and number of previous conventional treatments. Patient profiles were also similar across individual treatment groups, with differences including age, race and prior treatments (Table 1). At baseline, the anti-IL-17A cohort had higher mNAPSI severity scores compared to the other biologics cohort in both patient populations (mNAPSI ≥ 1 25.7 vs. 22.0; mNAPSI ≥ 20 46.5 vs. 38.5). Nail psoriasis features were generally comparable between the two cohorts except for higher proportions of the anti-IL-17A cohort with nail crumbling and red spots. Table 1 also shows few differences in the prevalence of nail psoriasis features between IXE and the other individual treatments at baseline.

Comparison of Anti-IL-17A Cohort Versus Other Biologics Cohort

Irrespective of the severity of NP, patients in the anti-IL-17A cohort had greater mean mNAPSI reductions from baseline compared to the other biologics cohort through month 12 (Fig. 1a, b). After adjusting for baseline differences, the anti-IL-17A cohort showed significantly greater least square mean reductions in mNAPSI scores compared to the other biologics cohort at months 3 and 6, for both patients with any degree of NP (− 3.0 and − 2.5) and moderate-to-severe NP (− 3.9 and − 3.3; Fig. 1c). No significant results were observed at month 12, however, for the two patient populations (− 1.0 and − 2.0).

Comparisons of Individual Biologics with IXE

Of the biologics studied, IXE-treated patients showed the highest mean mNAPSI change from baseline at month 12 (Fig. 1d, e). Improvements at month 12 for patients with mNAPSI ≥ 1 ranged from − 13.1 with GUS to − 19.7 with IXE (Fig. 1d), and for patients with mNAPSI ≥ 20 ranged from − 21.5 with GUS to − 38.7 with IXE (Fig. 1e). Adjusted pairwise analyses for patients with baseline mNAPSI ≥ 1 revealed comparable mNAPSI results in terms of LSMD between IXE and SEC, RIS and ADA. The exception was versus GUS, where IXE had significantly higher reductions in mNAPSI scores through month 12 (Fig. 1f). For patients with moderate-to-severe NP, Fig. 1g shows IXE-treated patients had numerically higher LSMD reductions in mNAPSI scores compared to the four other studied biologics, which reached significance versus GUS at all timepoints and versus RIS at month 6. Supplementary materials show similar findings in the sensitivity analysis (Fig. S1) and for patients who received the EMA on-label dosing (Fig. S2).

DISCUSSION

Building on recently published long-term data from the PSoHO study [7], these results show that patients with PsO and concomitant NP have significantly better and faster improvements of their NP at months 3 and 6 when prescribed anti-IL-17A biologics compared to other biologics irrespective of baseline NP severity. These results are consistent with an earlier PSoHO study that reported the anti-IL-17A cohort had significantly higher odds of nail clearance at month 3 compared with the other biologics cohort [9]. In comparison to the other biologics, IXE showed a statistically greater improvement in NP than GUS through month 12 for patients with any degree of NP. For patients with moderate-to-severe NP, significant differences were also similarly observed versus GUS at all timepoints, as well as compared to RIS at month 6. Overall, in all treatment groups, patients with moderate-to-severe NP (mNAPSI ≥ 20) at baseline achieved greater numerical improvements in mNAPSI score than patients with any degree of NP (mNAPSI ≥ 1) at baseline.

While a previous comparative study found no statistically significant differences in real-world effectiveness between ADA, etanercept, infliximab and ustekinumab despite having different mechanisms of action [6], this study reports a faster and more pronounced improvement in NP through month 12 with the IL-17A inhibitor, IXE, versus the IL-23 antibody, GUS. These real-world findings confirm and extend results from the IXORA-R trial [11], which demonstrated a comparable effect of IXE and GUS on skin clearance, but superior nail clearance with IXE at week 24. In PSoHO, IXE also showed numerically greater improvements versus another IL-23 inhibitor, RIS, which reached statistical significance for patients with moderate-to-severe NP at month 6. Compared to ADA, a tumour necrosis factor alpha (TNFα) inhibitor, IXE showed numerically greater improvements at all timepoints without reaching statistical significance. These results accompany findings from a previous PSoHO study that used binary questions to ascertain

the presence of NP; the study reported that patients had significantly higher odds of achieving nail clearance at week 12 with IXE than GUS or ADA [9]. Consistent with recent NMAs [4, 5], the improvements shown with IXE also did not differ significantly from the other included IL-17A inhibitor, SEC. PSoHO data also suggests that improvements in NP continue up to month 12 of continuous treatment irrespective of the biologic, although it remains to be seen whether this trend will continue in the longer term.

The results of this study should be interpreted considering certain limitations, especially those associated with the observational study design [8]. In contrast to the routine assessment and capture of PASI scores in everyday clinical practice, the use of dedicated NP assessments may not be as common in real-world settings. Nevertheless, investigators received training on the conduct of mNAPSI assessments as part of this study. At the beginning of PSoHO, IL-23 p19 biologics were not licensed for the treatment of psoriatic arthritis, which, given its association with NP, may have affected the treatment selected for patients with NP. To gain a more complete understanding of the comparative effectiveness of different biologics, data beyond 1 year of treatment, additional NP outcomes and patient perspectives are needed. Small sample sizes of patients with moderate-to-severe NP impacted convergence of statistical models for some treatment comparisons. This analysis has various strengths including its comparative nature, consideration of two levels of baseline NP severity, and the application of a robust, well-established statistical approach for evaluating real-world data that reduces the uncertainty of incorrect model specification.

CONCLUSION

Overall, the findings of this real-world study showed that patients with moderate-to-severe PsO and any severity of concomitant NP had significantly faster and more substantial improvements in NP up to month 6 in the anti-IL-17A cohort compared to the other biologics cohort. Irrespective of NP severity, IXE-treated patients showed the greatest numerical improvements from baseline in mNAPSI scores at month 12. These results may support physicians in their treatment decisions for patients with PsO and concomitant NP and may serve as a foundation for further real-world studies of this difficult-to-treat condition.

ACKNOWLEDGEMENTS

The authors thank the participants, caregivers and investigators of this study.

Medical Writing and Editorial Assistance The authors also appreciate the support from Michaela Gebesmair for help with creating some figures and statistical support from Georgia Martimianaki of Eli Lilly and Company. This medical writing and editorial assistance was funded by Eli Lilly and Company.

Author Contributions. Conceptualization: Elisabeth Riedl, Christopher Schuster, Natalie Haustrup, Alan Brnabic; Statistical analysis: Alan Brnabic, Zbigniew Kadziola; Writing: Natalie Haustrup, Christopher Schuster, Elisabeth Riedl; Interpretation and critical review: Elisabeth Riedl, Andreas Pinter, Shirin Zaheri, Antonio Costanzo, Alan Brnabic, Bruce Konicek, Robert McKenzie, Anastasia Lampropoulou, Mohamed El Rayes, Natalie Haustrup, Christopher Schuster. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Funding. This study and Rapid Service Fee are sponsored by Eli Lilly and Company.

Data Availability. Data are available on reasonable request. Lilly provides access to all individual participant data collected during the study, after anonymization. Data are available to request after primary publication acceptance. No expiration date of data requests is currently

set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

Declarations

Conflict of Interest. Elisabeth Riedl is a former employee, has pending patents with Eli Lilly and Company and has also been a speaker and/or consultant for Eli Lilly and Company, Pelpharma, Novartis, Almirall. Andreas Pinter has served as an investigator, speaker, and/or consultant for AbbVie, Almirall-Hermal, Amgen, Biogen Idec, BioNTech, Boehringer Ingelheim, Celgene, GSK, Eli Lilly and Company, Galderma, Hexal, Janssen, LEO Pharma, MC2, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pascoe, Pfizer, Tigercat Pharma, Regeneron, Roche, Sandoz Biopharmaceuticals, Sanofi Genzyme, Schering-Plough und UCB Pharma. Shirin Zaheri has served as advisory board member or has received fees and speaker's honoraria for AbbVie, Biogen, Eli Lilly and Company, Leo Pharma, L'Oréal and Novartis. Antonio Costanzo served as advisory board member and consultant, and/or has received fees and/or speaker's honoraria and/or has participated to clinical trials for Abbvie, Almirall, Amgen, Eli Lilly and Company, Janssen, Novartis, Sanofi and UCB and is president of European Dermatology Forum and has received payment to participate on the advisory boards for IQVIA. Alan Brnabic, Bruce Konicek, Robert McKenzie, Anastasia Lampropoulou, Mohamed El Rayes, Natalie Haustrup, Christopher Schuster are all employees and minor shareholders of Eli Lilly and Company.

Ethical Approval. The protocol, amendments, and consent documentation were approved by local institutional review boards (IRB). The study was registered at the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCEPP24207) and was conducted according to International Conference on Harmonization, Good Clinical Practice guidelines, and the Declaration of Helsinki. All patients were required to give informed consent for participation in the study. We confirm that the necessary central or local IRB and/or ethics committee approvals have been obtained for this multi-site, international study by United BioSource LLC (UBC). Approvals can be provided on request.

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