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ORIGINAL ARTICLE

# Comparative effectiveness of biologics in clinical practice: week 12 primary outcomes from an international observational *psoriasis study of health outcomes* (PSoHO)

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## Abstract

**Background** Clinical trials study treatment outcomes under stringent conditions, capturing incompletely the heterogeneity of patient populations and treatment complexities encountered in real-world practice.

**Objectives** To compare the effectiveness of anti-interleukin (IL)-17A biologics relative to other approved biologics in patients with moderate-to-severe psoriasis.

**Methods** The Psoriasis Study of Health Outcomes (PSoHO) is an ongoing 3-year observational cohort study in adults with chronic moderate-to-severe plaque psoriasis initiating or switching to a new biologic. Primary study endpoint is the proportion of patients achieving 90% improvement in Psoriasis Area and Severity Index (PASI 90) and/or static Physician Global Assessment (sPGA) 0/1 at Week 12 (W12) in the anti-IL-17A cohort (ixekizumab [IXE], secukinumab) vs. all other approved biologics. Secondary outcomes include the proportion of patients who achieve PASI 75/90/100, absolute PASI scores ≤5, ≤2 and ≤1, Dermatology Life Quality Index (DLQI) score of 0/1 at W12 between the two cohorts and among the individual biologics. Comparative effectiveness analyses were conducted using Frequentist Model Averaging (FMA), a novel causal inference machine learning approach. Missing data for binary outcomes were imputed as non-response.

**Results** Patient profiles in the anti-IL-17A cohort and other biologics cohort were similar, with more frequent comorbid psoriatic arthritis and less frequent exposure to conventional treatments in the patients receiving anti-IL-17A biologics. At W12, 71.4% of patients who received an anti-IL-17A biologic achieved PASI 90 and/or sPGA 0/1 compared to 58.6% of patients who received other biologics (odds ratios [OR], 1.9; 95% confidence intervals [CI], [1.6, 2.4]). Similar findings were observed for secondary outcomes.

**Conclusions** These results reflect the high efficacy and early onset of skin clearance of IL-17A inhibitors observed in randomized clinical trials and confirm the effectiveness of anti-IL-17A biologics in the real-world setting.

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## Conflict of interest

**AP** has served as an investigator, speaker and/or advisor 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. **LP** reports grants to institution from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Janssen, Leo Pharma, Eli Lilly and Company, Novartis, Pfizer, Regeneron, Roche,

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## Introduction

Over the last years, numerous biologics gained approval for moderate-to-severe psoriasis (PsO) following randomized controlled trials.[1] Clinical trials are considered the gold standard for enhancing scientific knowledge on diseases and new therapies. However, they do not necessarily reflect the treatment complexities encountered in real-world practice due to stringent study criteria that prevent the inclusion of a more heterogenous patient population.[2,3]

Postmarketing observational studies and registries help to translate efficacy and safety profiles of drugs that have been evaluated in clinical trials and allow the collection of data in a real-life environment in a more diverse patient population of interest.[4] Several psoriasis-specific registries have been initiated across the globe, most of them focusing on long-term effectiveness and safety.[5] However, comparisons between registries can be impaired by a lack of harmonization across registries, in data collection variables, and registries' funding structures. The Psoriasis Study of Health Outcomes (PSoHO), an international, prospective, multicentre, non-interventional cohort observational study, has been designed to investigate the comparative effectiveness of anti-interleukin (IL)-17A biologics relative to other approved biologics in patients with moderate-to-severe PsO. Here, we report the primary and key secondary endpoints at Week 12 and provide a comprehensive description of demographics and disease characteristics of patients enrolled in PSoHO. These data are further analysed to compare the effectiveness of anti-IL-17A biologics with other biologic therapies, providing comparative data that might prove useful for clinicians who treat patients with varying demographics and comorbidities.

## Methods

### Patients

We enrolled adult patients (age $\geq$ 18) with an established diagnosis (at least 6 months prior to baseline) of moderate-to-severe PsO for whom the treating physician either initiated treatment with a biologic (originator or biosimilar) for the first time (bio-naïve) or who switched (bio-experienced) to another biologic.

Exclusion criteria were contraindication for treatment based on the biologics' label in the participant's country; changes in dose or dosing intervals of an existing biologic treatment (including switching from originators to biosimilars); restart of treatment with a biologic previously received at any time during the patient's treatment history; previous completion or withdrawal from this study; and current participation in any other psoriasis study with any investigational products.

### Study design

PSoHO is an ongoing 36-month prospective, multicentre, international, non-interventional cohort study reflecting treatment with biologics within real-world settings.

Biologics used in this study are the anti-IL-17A antibodies (ixekizumab [IXE] and secukinumab [SEC]) and any other originator or biosimilar biological medication indicated for the treatment of moderate-to-severe PsO (Table S1). Any new biologic treatments that became available during the enrolment period of the study and reimbursed by the country-specific health authorities were included in the other biologics cohort.

Data collection occurred at baseline, first postbaseline visit (12 ± 4 weeks following initiation of or switch to a new biologic), 6-month postbaseline and then at 6-month intervals until study completion. Subjects who discontinued biological treatment could remain in the study.

### Study endpoints

The primary objective was to compare the rates of therapeutic response, defined as achieving at least a 90% improvement in the Psoriasis Area and Severity Index score (PASI 90) and/or a static Physician Global Assessment score of clear or almost clear (sPGA 0/1 on a 6-point scale) at Week 12, between patients treated with anti-IL-17A biologics (IXE and SEC) and those receiving any other biologic. Secondary objective comparisons between the anti-IL-17A cohort and the other biologic treatments include the proportion of patients who achieve PASI 75/90/100, absolute PASI scores ≤5, ≤2 and ≤1, Dermatology Life Quality Index (DLQI) score of 0 or 1, and mean change from baseline in PASI and DLQI scores from baseline to Week 12.

### Study oversight

All patients were required to give informed consent for participation in the study. The protocol, amendments and consent documentation were approved by local ethical review boards. The study was registered at European Network of Centres for Pharmacoepidemiology and Pharmacovigilance[6] and was conducted according to Good Pharmacoepidemiology Practices guidelines and the Declaration of Helsinki.

### Statistical analyses

Descriptive statistics are reported as mean and standard deviation or median and quartiles 1 and 3 (Q1, Q3) for continuous variables and proportions and percentages for categorical variables. Pairwise comparisons of baseline demographics between the anti-IL-17A vs. the other biologics cohort and IXE vs. other individual biologics, respectively, were performed using Fisher's exact test or chi-square for categorical and ANOVA, Mood's median test or exact *P*-value from Median Test (Monte Carlo Estimate) for continuous variables. A *P*-value of less than 0.05 was considered statistically significant.

The comparative effectiveness analyses were performed using a data-driven approach known as Frequentist Model Averaging (FMA).[7] Model averaging is an established methodology; however, application to the causal inference space in a machine learning framework is novel and innovative (Appendix S1).[7] Using this approach, 12 prespecified analysis strategies, including propensity score matching, stratification, inverse weighting and penalized regression approaches, were implemented for each treatment comparison. The treatment effect was calculated from a weighted average of all the models implemented. As a sensitivity analysis, the final treatment effect estimate was selected using the best model that was automatically selected from the strategy with the highest weight (Fig. S1, Table S1). For balancing purposes, 34 covariates were included in the propensity score for all appropriate models (Table S2). These covariates attempted to adjust (balance) for baseline differences between groups. To assess whether the balance was achieved, standardized difference (acceptable ranges are <0.25 or <0.1) and variance ratio (acceptable ranges 0.5–2.0) statistics were calculated.[8] Comparative adjusted results are presented as odds ratios (OR) or least squares mean differences (LSMD) with 95% confidence intervals (CI) formed using the 2.5th and 97.5th percentiles derived from the 100 bootstrap samples. Statistical significance is indicated by the 95% CIs not crossing the null hypotheses (OR = 1; LSMD = 0). Robustness of the treatment effect estimates was assessed using the E-value.[9]

For missing data, the outcomes of interest were imputed using non-responder imputation (NRI) and, as sensitivity analyses, were also reported as observed. For the propensity score logistic regression models and selected outcome models, missing categorical covariates were imputed with the mode and continuous covariates with the mean, if missing was ≤10%. Otherwise, multiple imputation was implemented using SAS PROC MI (SAS Institute, Cary, NC, USA). For gradient boosted tree models (GBTM), the treatment model imputation was implemented *via* the TWANG package in R. Treatment groups with <50 patients at baseline are not reported due to the instability or non-convergence of models within the machine learning comparative framework. All analyses were conducted using SAS 9.4 and R Version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Patients

This study enrolled 1981 eligible patients (Fig. S1) from 240 sites in 23 countries (Table S2). Twenty-eight patients did not

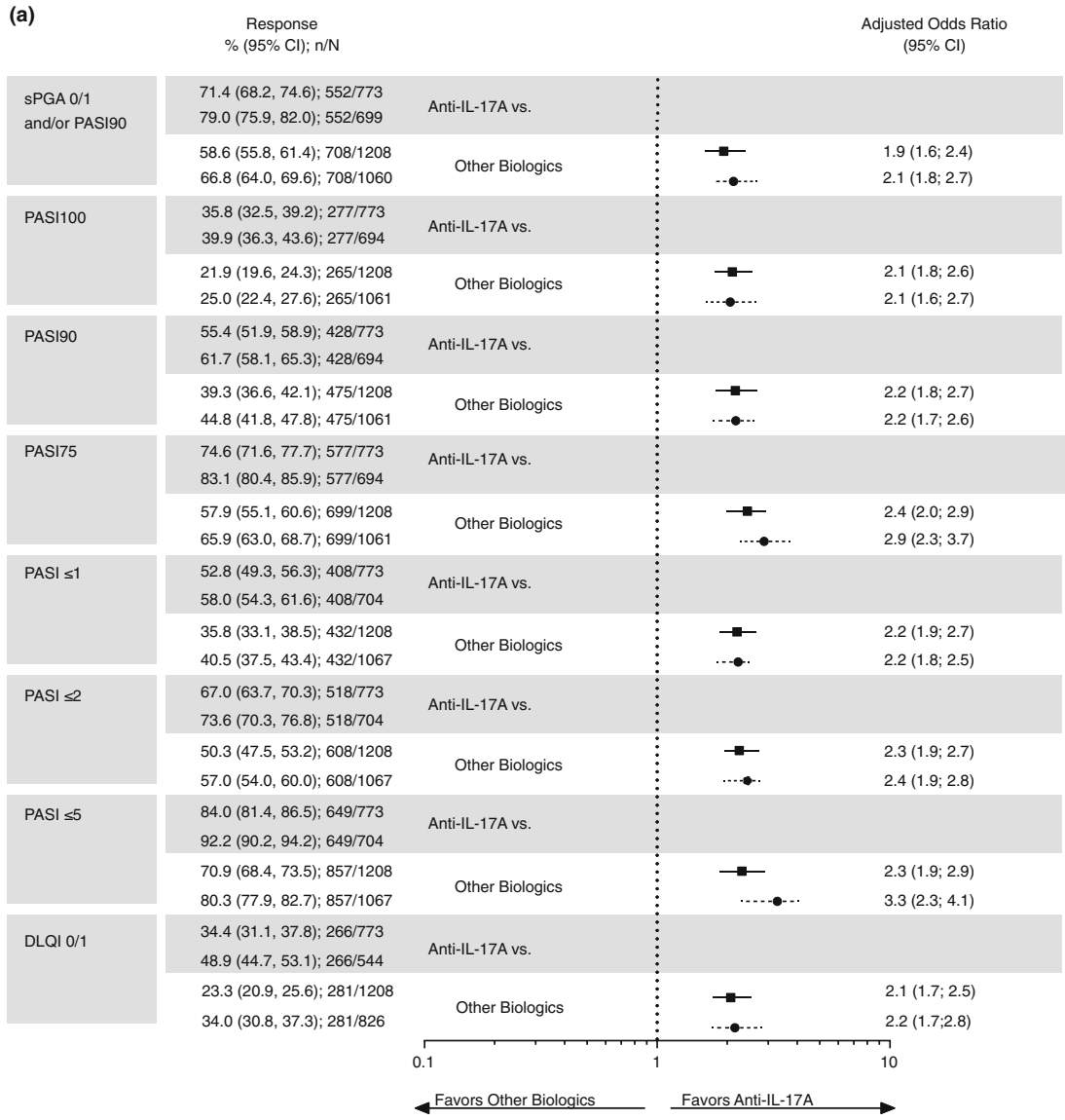
**Table 1** Patients demographics and disease characteristics at baseline

| | Overall (*n* = 1,981) | Anti-IL-17A (*n* = 773) | Other biologics (*n* = 1,208) | IXE (*n* = 532) | SEC *n* = 241) | BROD (*n* = 64) | TILD (*n* = 95) | GUS (*n* = 303) | RIS (*n* = 259) | ADA (*n* = 284) | UST (*n* = 127) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 45.3 (13.6) | 46.8 (13.7)* | 44.4 (13.5) | 47.4 (14.1) | 45.4 (12.8) | 44.1 (14.0) | 45.1 (13.6) | 44.2 (13.2)† | 44.1 (13.7)‡ | 45.1 (13.0)‡ | 46.4 (14.5) |
| Male, *n* (%) | 1,143 (57.7) | 442 (57.2) | 701 (58.0) | 313 (58.8) | 129 (53.5) | 37 (57.8) | 57 (60.0) | 179 (59.1) | 161 (62.2) | 163 (57.4) | 77 (60.6) |
| Weight (kg) | 85.0 (21.1) | 85.6 (20.8) | 84.6 (21.2) | 86.3 (20.4) | 83.9 (21.6) | 85.3 (20.7) | 88.5 (21.8) | 84.0 (21.2) | 83.8 (22.6) | 86.7 (21.3) | 82.9 (17.1) |
| BMI | 29.0 (6.7) | 29.2 (6.6) | 28.9 (6.7) | 29.4 (6.6) | 28.9 (6.5) | 29.5 (7.5) | 29.3 (7.3) | 29.0 (6.7) | 28.6 (6.9) | 29.3 (6.6) | 28.0 (5.6)‡ |
| Race – White, *n* *n* (%) | 1,441 (72.7) | 576 (74.5) | 865 (71.6) | 394 (74.1) | 182 (75.5) | 40 (62.5) | 90 (94.7) | 162 (53.5) | 169 (65.3) | 248 (87.3) | 99 (78.0) |
| Race – Asian, n (%) | 296 (14.9) | 103 (13.3) | 193 (16.0) | 67 (12.6) | 36 (14.9) | 20 (31.3) | 3 (3.2) | 100 (33.0) | 53 (20.5) | 7 (2.5) | 8 (6.3) |
| Other Race/Not Reported, *N* (%) | 238 (12.0) | 90 (11.6) | 148 (12.3) | 68 (12.8) | 22 (9.1) | 5 (7.8) | 1 (1.1) | 40 (13.2) | 37 (14.3) | 29 (10.2) | 19 (15.0) |
| Median Disease Duration, Years (Q1, Q3) | 14.0 (6.8, 23.8) | 14.3 (6.4, 24.2) | 13.8 (7.1, 23.6) | 13.9 (6.7, 25.3) | 14.9 (6.0,21.8) | 12.9 (6.5, 20.9) | 15.4 (6.5, 25.7) | 14.9 (7.8, 24.4) | 13.7 (8.2, 23.5) | 14.2 (6.3,25.0) | 12.1 (6.3,23.7) |
| PASI | 14.5 (8.6) | 14.6 (8.5) | 14.5 (8.6) | 14.4 (8.5) | 15.0 (8.7) | 16.3 (8.5) | 14.1 (8.5) | 14.6 (9.3) | 15.4 (9.8) | 13.3 (7.1) | 14.4 (7.9) |
| % of Body Surface Area (BSA) | 21.3 (17.7) | 21.1 (17.5) | 21.5 (17.9) | 20.6 (17.2) | 22.3 (18.1) | 24.2 (18.3) | 20.3 (16.7) | 21.7 (18.5) | 20.6 (18.9) | 20.6 (16.6) | 22.6 (17.7) |
| sPGA, *n* (%) Moderate | 988 (50.7) | 387 (50.7) | 601 (50.8) | 267 (50.6) | 120 (50.8) | 37 (59.7) | 42 (44.7) | 143 (47.7) | 102 (40.8) | 170 (60.5) | 68 (54.8) |
| Severe | 610 (31.3) | 242 (31.7) | 368 (31.1) | 176 (33.3) | 66 (28.0) | 18 (29.0) | 27 (28.7) | 101 (33.7) | 93 (37.2) | 69 (24.6) | 37 (29.8) |
| Very Severe | 76 (3.9) | 34 (4.5) | 42 (3.5) | 16 (3.0) | 18 (7.6) | 3 (4.8) | 2 (2.1) | 14 (4.7) | 15 (6.0) | 5 (1.8) | 2 (1.6) |
| DLQI [a] | 12.6 (7.8) | 12.9 (7.9) | 12.4 (7.8) | 12.6 (7.9) | 13.5 (7.7) | 13.6 (7.8) | 10.8 (7.6) | 12.3 (8.1) | 11.8 (7.3) | 12.9 (7.6) | 12.3 (8.0) |
| ≥1 Current Comorbidity, *n* (%) | 1157 (58.4) | 476 (61.6)** | 681 (56.4) | 327 (61.5) | 149 (61.8) | 37 (57.8) | 57 (60.0) | 169 (55.8) | 143 (55.2) | 157 (55.3) | 78 (61.4) |
| Number of Current Comorbidities Reported [b] | 1.5 (1.8) | 1.6 (1.8) | 1.4 (1.8) | 1.6 (1.8) | 1.6 (1.9) | 1.5 (1.8) | 1.6 (1.9) | 1.5 (1.7) | 1.4 (1.8) | 1.4 (1.7) | 1.7 (2.1) |
| Psoriatic Arthritis, *n* (%) [c] | 461 (23.3) | 227 (29.4)* | 234 (19.4) | 161 (30.3) | 66 (27.4) | 16 (25.0) | 18 (18.9)‡ | 71 (23.4)‡ | 32 (12.4)† | 64 (22.5)‡ | 19 (15.0)† |
| Nail Psoriasis, *n* (%) [d] | 750 (37.9) | 305 (39.5) | 445 (36.9) | 221 (41.5) | 84 (34.9) | 19 (29.7) | 50 (52.6) | 115 (38.1) | 88 (34.1) | 105 (37.0) | 45 (35.7) |
| Any Previous Conventional Therapy, *n* (%) | 1565 (79.0) | 573 (74.2)* | 992 (82.1) | 393 (74.0) | 180 (74.7) | 54 (84.4) | 83 (87.4) | 225 (74.3) | 199 (76.8) | 265 (93.3)† | 106 (83.5)† |
| Prior treatment with biologics, *n* (%) [e] | 706 (35.7) | 291 (37.7) | 415 (34.4) | 204 (38.4) | 87 (36.1) | 23 (35.9) | 30 (31.6) | 178 (58.7)† | 111 (42.9) | 25 (8.8)† | 35 (27.6)‡ |

All results are expressed as mean (standard deviation) of all available data for that measure, unless otherwise indicated.
ADA, adalimumab; BMI, body mass index; BROD, brodalumab; BSA, body surface area; DLQI, Dermatology Life Quality Index; GUS, guselkumab; IQR, interquartile range; IL-17A, interleukin-17A; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index; sPGA, Static Physician Global Assessment; PASI, Psoriasis Area and Severity Index; Q, quartile; RIS, risankizumab; SEC, secukinumab; TILD, tildrakizumab; UST, ustekinumab.
***P*-value $< 0.05$ vs. the other biologics cohort (shaded in grey).
**P*-value $< 0.001$ vs. the other biologics cohort (shaded in green).
‡*P*-value $< 0.05$ vs. IXE (shaded in blue).
†*P*-value $\leq 0.001$ vs. IXE (shaded in yellow).
[a]DLQI was measured on a 0–30 scale.
[b]Comorbidities were captured based on a predefined list.
[c]PsA diagnosis was recorded by the dermatologists based on the medical history and/or information provided by the patient.
[d]Recorded as a simple y/n question (investigator assessed).
[e]Information about prior biologic use missing in 1 patient.

complete the Week 12 visit. The overall patient population was 57.7% male, with a mean age of 45.3 years, mean body mass index of 29.0 kg/m$^2$ and a median disease duration of 14.0 years. Baseline mean scores for PASI, sPGA and DLQI for the overall study cohort were 14.5, 3.2 and 12.6, respectively. Concomitant nail PsO and psoriatic arthritis (PsA) were reported in 37.9% and 23.3% of the patients, respectively. The study participants were 64.3% ($n$ = 1274) bio-naïve and 35.7%

**Figure 1** Comparative adjusted analysis of primary and secondary outcomes actual responses rates and adjusted odds ratios (1a) and LSMD PASI and DLQI change from baseline (1b) at Week 12 for the anti-IL-17A cohort vs. the other biologics cohort. NRI results are depicted by top/solid lines, and as-observed results are depicted by bottom/dashed lines. Results are statistically significant if 1 is not covered by the 95% CI for the odds ratios (a) and if 0 is not covered by the 95% CI for the LSMD (b). Unadjusted CIs (a) were calculated using the normal approximation. BL, baseline; CI, confidence interval; IL, interleukin; LSMD, least squares mean difference; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; sPGA, Static Physician Global Assessment; DLQI, Dermatology Life Quality Index.



($n$ = 706) bio-experienced. At baseline, 39.0% ($n$ = 773) initiated an anti-IL-17A biologic (532 patients received IXE, 241 SEC), and 61.0% ($n$ = 1208) received other biologics (Table 1).

The patient profiles were comparable between the anti-IL-17A cohort and other biologics cohort with few exceptions. In the anti-IL-17A cohort, the average age was higher, as was the proportion of patients with at least one current comorbidity than in the other biologics cohort, as exemplified by the frequency of comorbid PsA (29.4% vs. 19.4%, respectively). Conversely, more patients in the other biologics cohort had received prior conventional treatments (74.2% vs. 82.1%), while no statistical difference in the prior use of biologics was found. At the individual biologic level, numerical differences were observed in disease activity markers, such as the PASI, sPGA or DLQI. IXE-treated patients had the highest numerical frequency of comorbid PsA and, along with tildrakizumab (TILD), nail PsO, whereas patients treated with adalimumab (ADA) and guselkumab (GUS) had the highest prior use of conventional or biologic treatments, respectively.

### Comparison of the anti-IL-17A cohort vs. the other biologics cohort

At Week 12, 71.4% of patients who received anti-IL-17A biologics achieved PASI 90 and/or sPGA 0/1 compared to 58.6% of patients who received other biologics, with 1.9 times higher odds for the anti-IL-17A vs. the other biologics cohort of reaching this outcome (OR, 1.9; 95% CIs, 1.6, 2.4, NRI) (Fig. 1a). PASI 75/90/100, absolute PASI scores ≤5/≤2/≤1, and DLQI (0,1) were reached by higher proportions of patients in the anti-IL-17A cohort compared with patients who received other biologics; OR were consistently greater than 2 for achieving any of these outcomes (NRI and as observed) (Fig. 1a). Accordingly, the anti-IL-17A cohort showed a greater reduction in mean PASI scores compared with the other biologics cohort at Week 12 (−13.1 and −11.4, Fig. 1b); after adjustment for baseline differences, the LSMD between the two cohorts was −1.6 (95% CI [−1.9, −1.2]). Similarly, a higher reduction in DLQI total scores was observed in anti-IL-17A-treated patients (−9.4 vs. −7.3 in the other biologics cohort) with an adjusted LSMD of −2.1 (95% CI [−2.6, −1.5], Fig. 1b). In patients who received the EMA-approved on-label dosing (1767/1981; 89.2%), results in those outcomes studied were comparable (Table S3).

### Pairwise comparisons of biologics vs. IXE

Secondary objectives aimed to compare the effectiveness of IXE to other biologics. Of all the biologics studied, IXE-treated patients showed the highest response rate for achieving PASI 90 and/or sPGA 0/1 at Week 12 (NRI: 74.2%; as observed: 82.1%). IXE's response rate was approximately 7% to 9% higher than that of risankizumab (RIS) (65.6%; 95% CI [59.9, 71.4]), brodalumab (BROD) (67.2%; 95% CI [55.7, 78.7]) and SEC (65.1%; 95% CI [59.1, 71.2]), and up to 20% higher than that of ustekinumab (UST) (52.8%; 95% CI [44.1, 61.4]), ADA (55.3%; 95% CI [49.5, 61.1]) and GUS (57.1%; 95% CI [51.5, 62.7]) (NRI). IXE had 60% greater odds of response vs. RIS (OR, 1.6; 95% CI [1.1, 2.2]), BROD (OR, 1.7; 95% CI [0.9, 2.7]) and SEC (OR, 1.7; 95% CI [1.2, 2.3]). In addition, the adjusted FMA OR of IXE vs. ADA, UST, TILD and GUS were all greater than 2.0 (NRI and as observed) (Fig. 2a).

PASI 75 response rates were highest in the IXE group (NRI and as observed), though comparative effectiveness relative to SEC and BROD did not reach statistical significance in the as-observed analysis. In the unadjusted analysis, patients treated with BROD had the highest PASI 100 and PASI 90 response rates, though the adjusted comparison between IXE and BROD in attaining PASI 100 or PASI 90 did not reach statistical significance (Fig. 2b,d). This was also observed in the subgroup of patients with on-label treatment (Table S3). IXE had the highest response rates for reaching absolute PASI ≤5 and ≤2 (NRI and as observed), while IXE and BROD had the highest proportions of patients achieving absolute PASI ≤1 at Week 12 (Fig. 3a–c). For DLQI (0, 1) responses at Week 12, BROD, IXE and SEC showed up to 15% higher response rates than GUS, RIS, TILD, UST and ADA (NRI and as observed) (Fig. 3d). The highest mean reduction in PASI and DLQI scores from baseline was observed in IXE-treated patients at Week 12, followed by SEC (Fig. 4a,b).

## Discussion

PSoHO is a prospective, multi-country observational study evaluating the effectiveness of biologics in adults with moderate-to-severe PsO in the real-world setting over 3 years.

At Week 12, this study demonstrated that the anti-IL-17A biologics achieved significantly higher PASI 90 and/or sPGA 0/1 scores compared with the other included biologics in real-world clinical practice.

Clear or almost clear skin, as measured by PASI 90 and PASI 100 responses, is generally regarded as a clinically meaningful outcome and is associated with the highest reduction in DLQI score and gain in quality of life.[10,11] Indirect comparison approaches, such as network meta-analyses, have been applied on clinical trial data to estimate the comparative efficacy of biologics for the treatment of moderate-to-severe plaque PsO.[12] In general, and regardless of the short-term outcome studied, newer drug classes inhibiting IL-17 or IL-23 cytokines rank more highly overall compared with older biologics blocking TNF or IL-12/23.[13,14] In PSoHO, the anti-IL-17A cohort outperformed the other biologics cohort on all clinical outcome measures at Week 12, confirming their general short-term efficacy and rapid onset of action in the real-world setting.[13,15] The effectiveness analyses, however, also illustrate the importance of considering treatments individually, rather than only grouped together by class. In the absence of a head-to-head randomized clinical trial

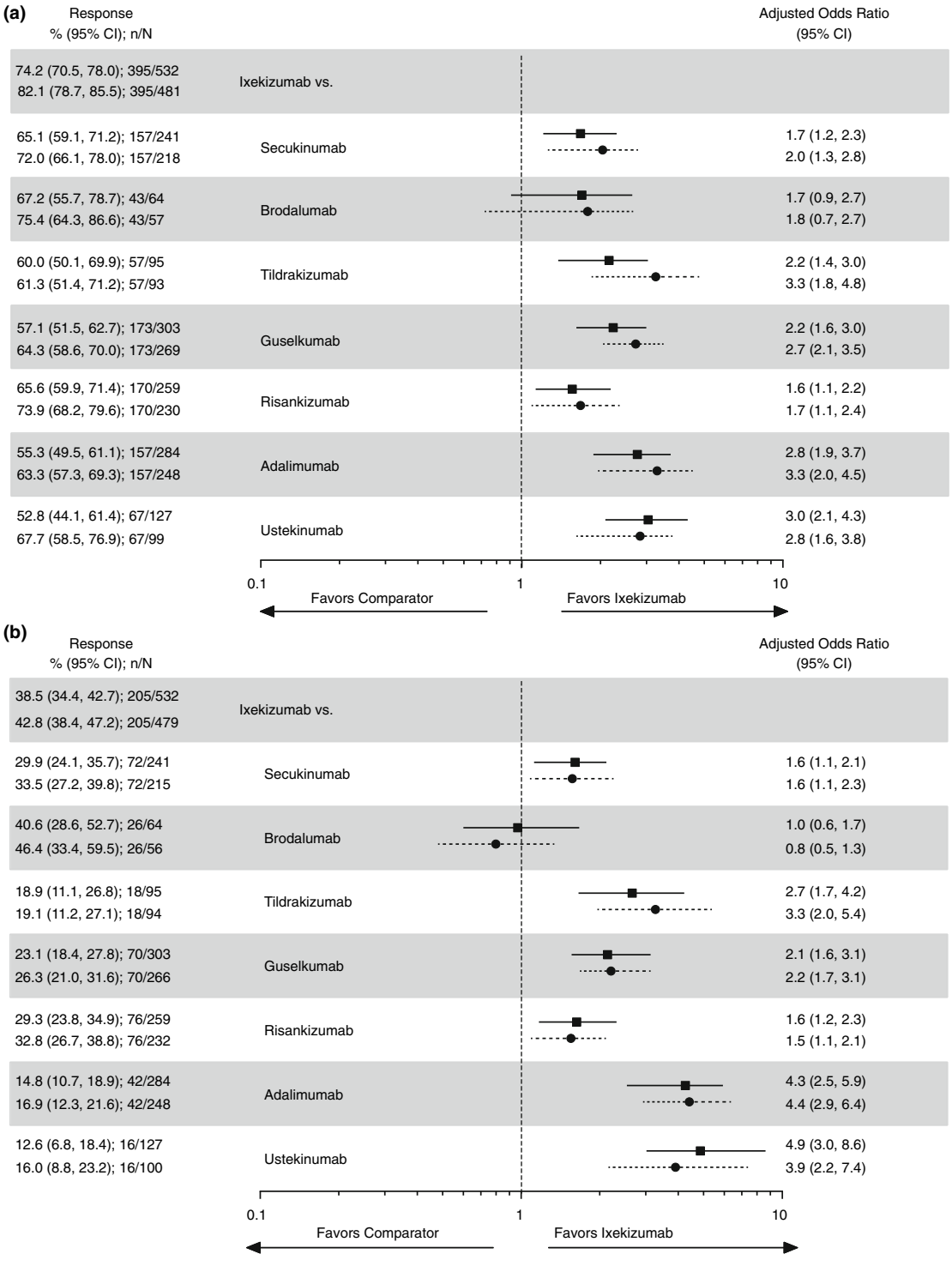



**Figure 2** Comparative adjusted analysis of PASI 90 and/or sPGA 0/1 (a), PASI 100 (b), PASI 90 (c) and PASI 75 (d) actual responses rates and adjusted odds ratios at Week 12 for ixekizumab vs. individual treatments. NRI results are depicted by top/solid lines, and as-observed results are depicted by bottom/dashed lines. Results are statistically significant if 1 is not covered by the 95% CI. Unadjusted CIs were calculated using the normal approximation. CI, confidence interval; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; sPGA, Static Physician Global Assessment.

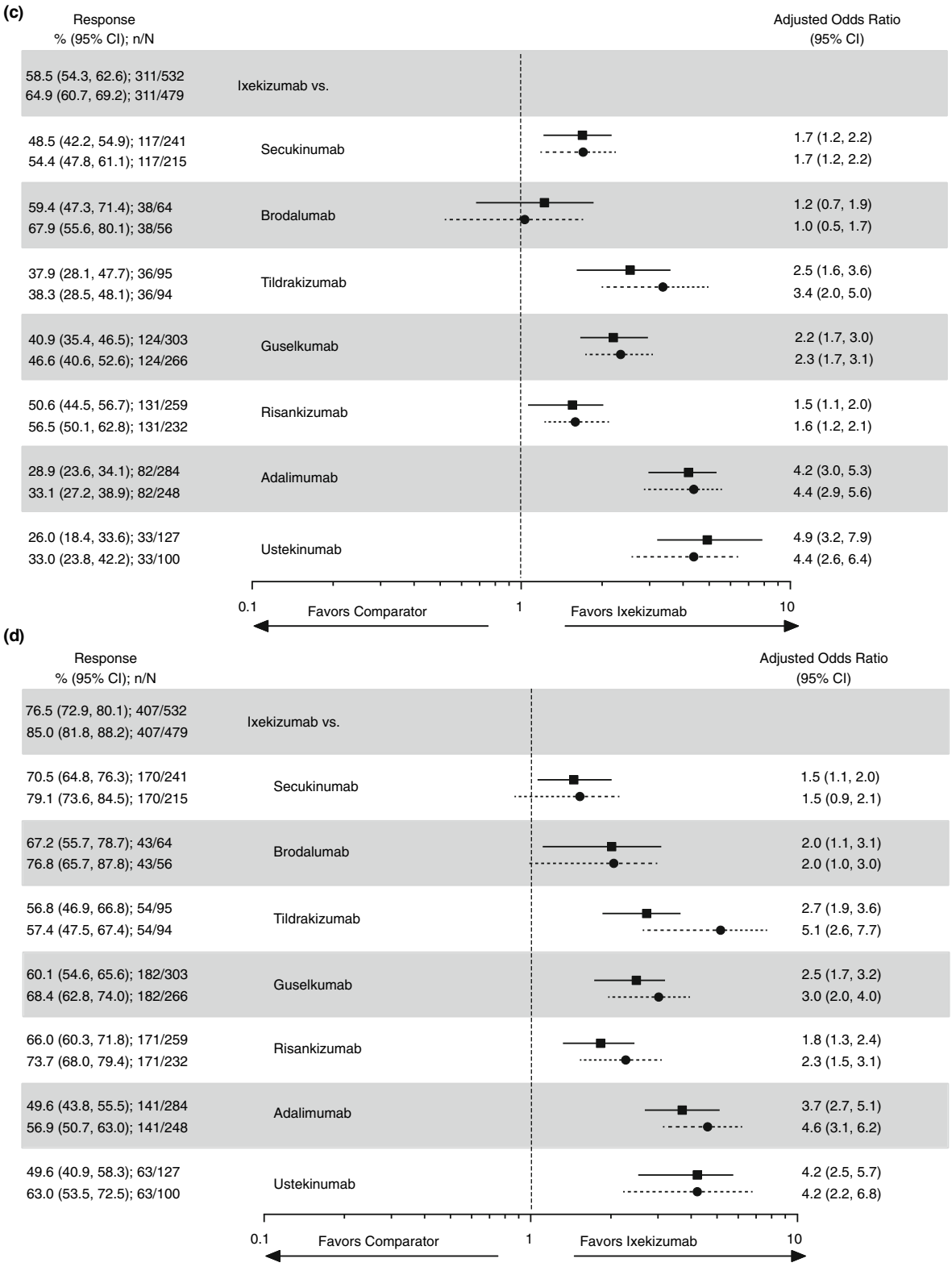



**Figure 2** *Continued*

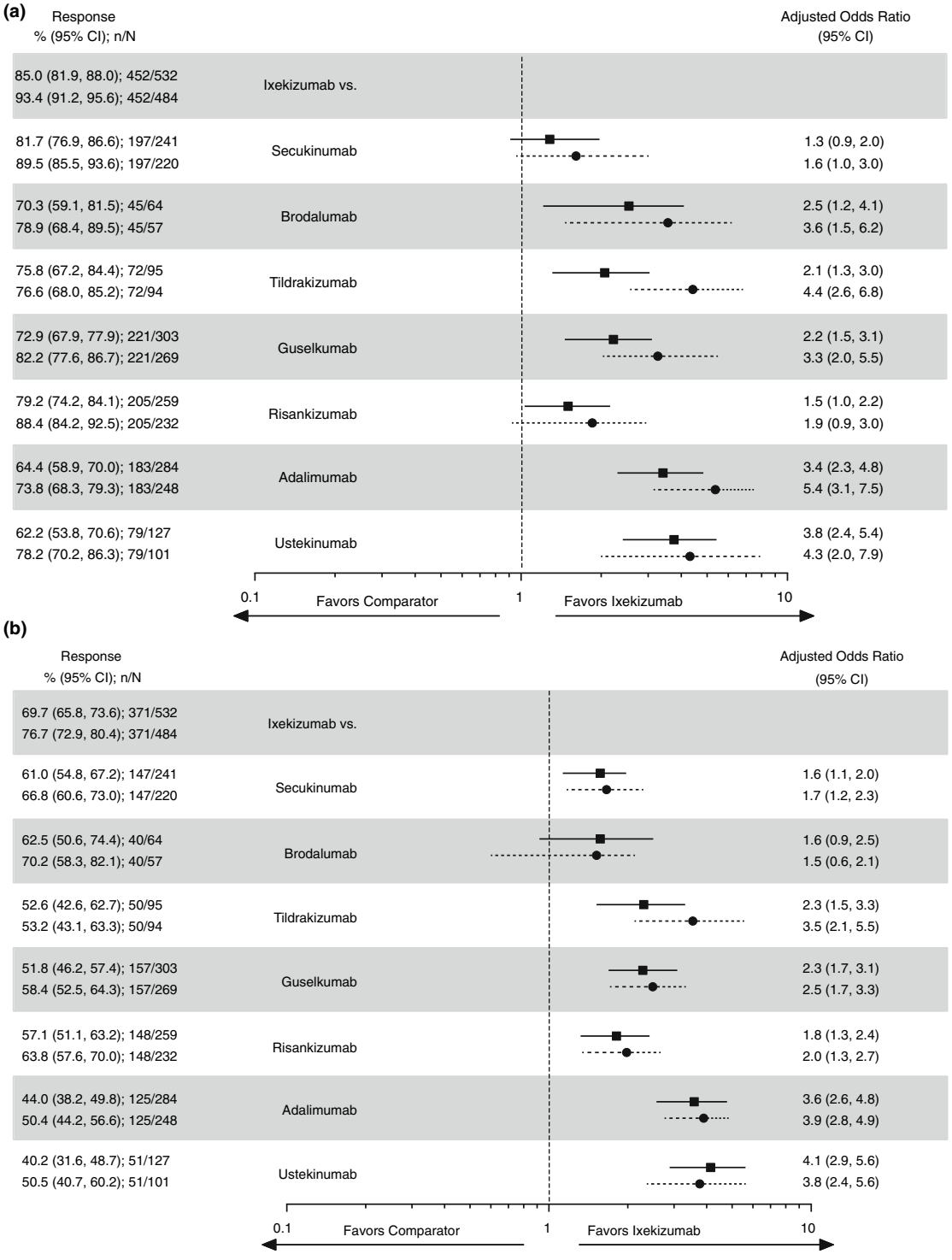



**Figure 3** Comparative adjusted analysis of absolute PASI ≤5 (a), absolute PASI ≤2 (b), absolute PASI ≤1 (c) and DLQI (0, 1), indicating no effect on patient quality of life (d), actual response rates and adjusted odds ratios at Week 12 for ixekizumab vs. individual treatments. NRI results are depicted by top/solid line, and as-observed results are depicted by bottom/dashed lines. Results are statistically significant if 1 is not covered by the 95% CI for the odds ratios. Unadjusted CIs (1a) were calculated using the normal approximation. CI, confidence interval; DLQI, Dermatology Life Quality Index; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index.

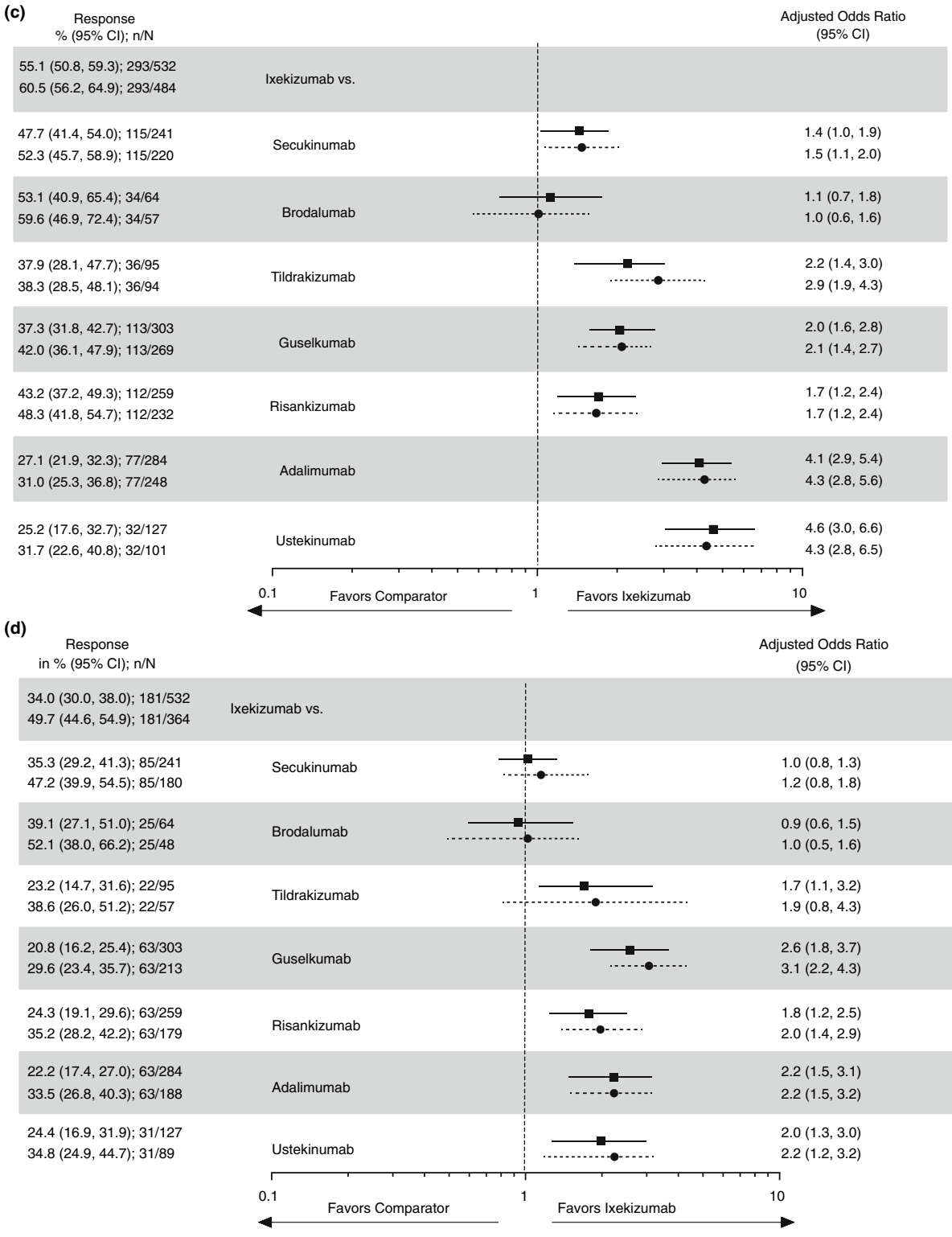



**Figure 3** *Continued*

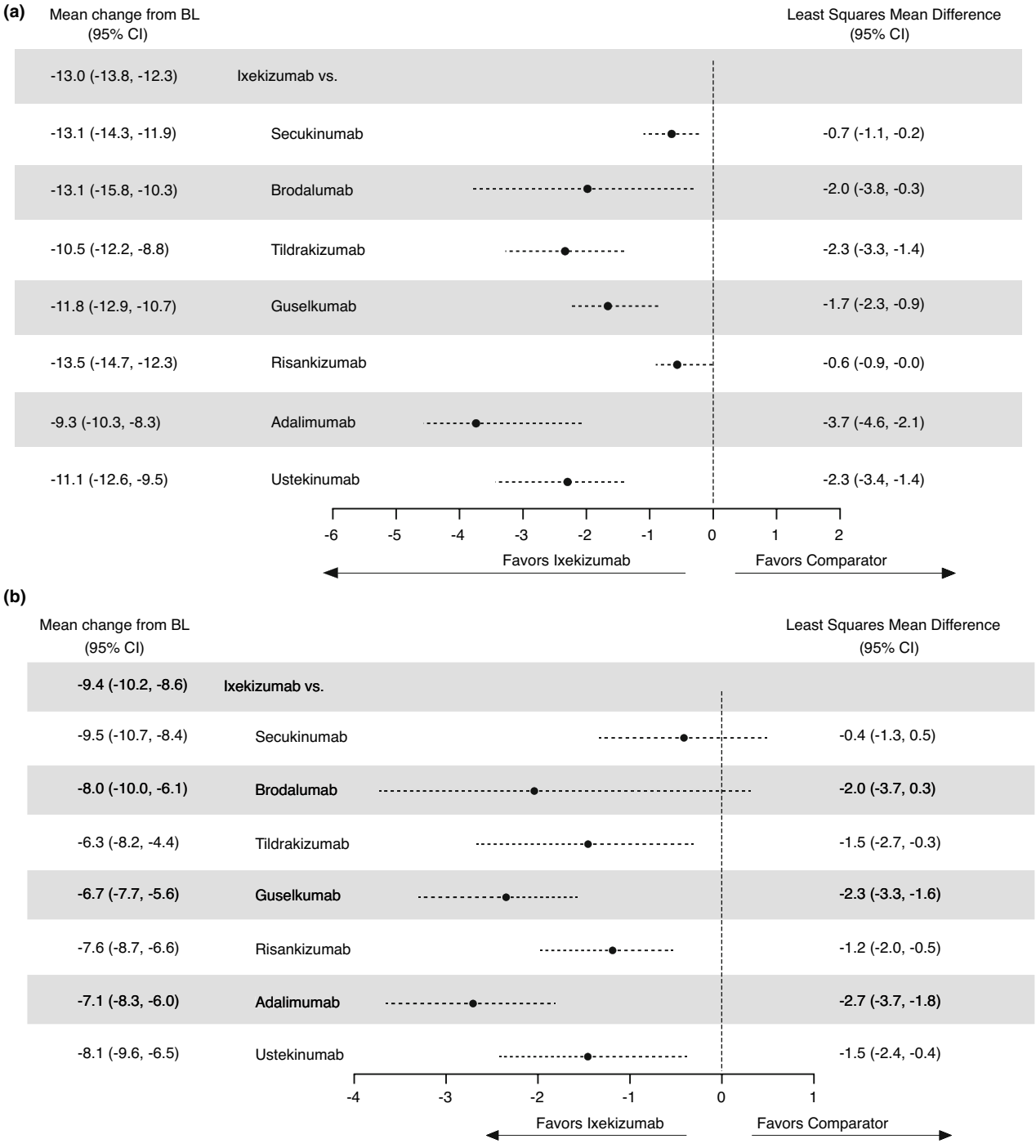



**Figure 4** Mean PASI change from baseline (a), and mean DLQI (0, 1) change from baseline (b) at Week 12 for ixekizumab vs. individual treatments. Results are statistically significant if 0 is not covered by the 95% CI for the LSMD (b). BL, baseline; CI, confidence interval; DLQI, Dermatology Life Quality Index; LSMD, least squares mean difference; PASI, Psoriasis Area and Severity Index.

of SEC vs. IXE, PSoHO provides a direct comparison of the two anti-IL-17A biologics for the first time, showing higher response rates for IXE vs. SEC for the primary endpoint, PASI 75/90/100, as well as absolute PASI ≤5, ≤2, ≤1.[16,17] Conversely, BROD, a biologic blocking the subunit A of the IL-17 receptor (IL-17RA) and thus preventing the activity of numerous IL-17 cytokines

apart from IL-17A, shows numerically, but not significantly higher PASI 90 and PASI 100 response rates than IXE at Week 12. Interestingly, the response rates for the primary endpoint, PASI 75, and all absolute PASI outcomes are lower (NRI), implying that while BROD treatment leads to a faster high-level response in some patients,[15] more BROD-treated than IXE-treated patients are primary-PASI 75 non-responders at Week 12. Among the IL-23 inhibitors, RIS had the highest PASI response rates, but was consistently lower than IXE at Week 12, as were those for TILD, GUS, UST and ADA.[18]

Owing to their mechanism of action, biologics targeting IL-17 cytokines, particularly IXE and BROD, have been shown in various head-to-head studies and network meta-analyses to provide the most rapid response and the earliest clinical benefit.[15,19,20,21] Rapid improvement of cutaneous signs and resolution of symptoms are among the most important treatment expectations to many patients, contributing to alleviating the burden of disease.[22] In this study, BROD, IXE and SEC achieved the highest DLQI (0, 1) responses at Week 12, indicating no impact of PsO on the patient's quality of life; IXE was more effective compared with biologics with other mechanisms of action, including those inhibiting IL-23. These results confirm clinical trial data and extend them to the real-world setting. Whether early clinical response and overall higher response rates at Week 12 associated with some biologics translate into better overall long-term clinical outcomes and/or increased adherence is currently not known, but will be further investigated within PSoHO.

The severity of PsO in the PSoHO study population was substantial, as observed in other observational studies,[23-25] but generally lower than reported in randomized clinical trials.[26] Minor differences in PASI, sPGA and DLQI baseline scores reported for the different treatments most likely resulted from the observational study design (i.e. the lack of randomization), different reimbursement requirements associated with a multi-country study and the possibility that in real-life patients might be switched to a new biologic before losing response completely. Of note, apart from their slightly younger age, patients receiving IXE or SEC more often had comorbid PsA, not only compared with patients treated with UST and all IL-23 inhibitors, but also to ADA. Both IXE and SEC have shown higher response rates than ADA for the resolution of skin and nail manifestations of PsO and comparable response rates regarding improvement in joint symptoms.[27,28] A speculative explanation for the higher prescription by dermatologists of IL-17A inhibitors compared with ADA in those patients with comorbid PsA is their well-recognized efficacy on both skin and joint outcomes. GUS-treated patients had the highest frequency of prior exposure to biologics, a previously reported finding requiring further investigation.[23]

Unique to PSoHO is its prospective, comparative study design. All recently approved biologics are represented, with the majority in sufficiently high numbers to perform comparisons of the physician- and patient-reported outcomes collected. While a recently published retrospective multi-country study already provides insights into the drug survival of IL-12/23, IL-17 and IL-23 inhibitors,[23] PSoHO yields additional real-world data on the patient's profile, as well as the comparative effectiveness of well-studied, older biologics, such as ADA or UST, alongside more recently approved biologics targeting IL-23 or IL-17A. We observed that within the first 3 months after treatment initiation and irrespective of the biologic used, most patients were treated according to the label. Long-term follow-up is necessary to monitor these treatment patterns.[29]

Strengths of the prospective PSoHO study include its large sample size of 1981 patients from various healthcare settings and the evaluation of 11 treatments, including recently approved biologics. Moreover, PSoHO allows for the assessment of clinical outcomes in patients who are receiving biologic agents in clinical practice settings, with consistent and continuous data collection processes across different geographies. An important strength includes the application of a robust, innovative statistical methodology using a machine learning approach. The results were consistent across many different statistical models per outcome, for both as-observed and imputed analyses. As an observational study, PSoHO is subject to confounding factors and various forms of bias, including selection bias or participation bias or measurement error. The potential effect of unmeasured confounding was evaluated using the E-value, which confirmed the robustness of the reported treatment estimates (see Appendix S1).[9] While generalizability is increased by having multiple centres across many countries, different countries may have various levels of access to treatment and not all treatments are registered or reimbursed in different countries, increasing the variability within some treatment groups.[30,31]

The highest proportion of patients were prescribed IXE, translating to higher statistical precision, whereas some of the treatment groups contained low patient numbers (infliximab, etanercept, certolizumab and BROD), leading to less stability of models and non-convergence, especially in the machine learning framework. Per protocol, BROD was not part of the anti-IL-17A cohort as it binds the subunit A of the IL-17 receptor (IL-17RA) compared with SEC and IXE, which inhibit the IL-17A molecule itself.[32] Limitations of this study include the grouping of non-anti-IL-17A biologics into a single category, and pairwise comparisons of individual treatment effectiveness were only completed relative to IXE. Also, as safety is not in the scope of PSoHO per protocol, detailed safety information was not collected, preventing comparisons of adverse events between treatments.

The results reported here, along with similar findings from other studies, reflect the high short-term efficacy of IL-17A inhibitors and early onset of skin clearance observed in randomized clinical trials and confirm the effectiveness of anti-IL-17A biologics in the real-life setting.

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## Data availability statement

Data are available on reasonable request. Lilly provides access to all individual participant data collected during the trial, 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.

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## Supporting information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1** Statistical analysis.

**Figure S1** Study Flow Diagram.
**Figure S2** Best model PASI 90 and/or sPGA 0/1 at Week 12

**Table S1** Biologics Included in PSoHO.
**Table S2** Participating Countries and Biologics Prescription Pattern.
**Table S3** Subgroup of patients who received the EMA-approved on-label dosing.