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ORIGINAL RESEARCH

Comparing Achievement of National Psoriasis Foundation Treatment Targets among Patients with Plaque Psoriasis Treated with Ixekizumab versus Other Biologics in Clinical and Real-World Studies

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ABSTRACT

Introduction: The National Psoriasis Foundation (NPF) recommends evaluating patient response to treatment at week 12, with a target response of ≤ 1% body surface area (BSA) affected by plaque psoriasis and an acceptable response of BSA ≤ 3% or ≥ 75% improvement. This post hoc analysis compared the achievement of NPF target and acceptable responses for ixekizumab (IXE) versus other biologics.

Methods: Outcomes were evaluated at week 12 for patients with moderate-to-severe plaque psoriasis from four head-to-head randomized clinical trials (RCTs; UNCOVER-2, UNCOVER-3, IXORA-R, and IXORA-S) and one real-world prospective observational study (Psoriasis Study of Health Outcomes; PSoHO). RCT patients were treated with IXE or etanercept (ETN; UNCOVER-2/3), guselkumab (GUS; IXORA-R), or ustekinumab (UST; IXORA-S). PSoHO patients were treated with anti-interleukin (IL)-17A biologics (IXE, secukinumab, SEC) and

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other approved biologics for the treatment of plaque psoriasis. Patients with missing outcomes were imputed as non-responder imputation. For RCT data, statistical comparisons between treatment groups were performed using Fisher's exact test with no multiplicity adjustments. For real-world data, adjusted comparative analyses were performed using frequentist model averaging (FMA) and reported as odds ratio (OR).

Results: Across the four head-to-head clinical trials analyzed, significantly higher proportions of patients achieved target and acceptable responses at week 12 with IXE versus ETN, GUS, or UST. Likewise, the proportion of PSoHO patients achieving target and acceptable response at week 12 was higher with IXE compared with other individual biologics. Adjusted comparative analyses showed that IXE had significantly greater odds of target and acceptable response at week 12 versus SEC, GUS, risankizumab (RIS), adalimumab (ADA), UST, and tildrakizumab (TILD) and numerically greater odds of target and acceptable response at week 12 versus brodalumab (BROD).

Conclusion: Across both clinical studies and real-world settings, more patients treated with IXE achieved NPF target and acceptable responses at week 12 compared with those treated with other biologics.

Trial Registration: UNCOVER-2 (NCT01597245); UNCOVER-3 (NCT01646177); IXORA-R (NCT03573323); IXORA-S (NCT02561806); PSoHO (EUPAS24207).

Keywords: Biologics; Body surface area; Head-to-head; Ixekizumab; National Psoriasis Foundation; Plaque psoriasis; Real world; Systemic therapies; Treat-to-target; Treatment goals

Key Summary Points

Why carry out this study?

Very brief background leading to the study.

The NPF recommends evaluating patient response to treatment at week 12, with a target response of BSA $\leq$ 1% and an acceptable response of BSA $\leq$ 3% or a $\geq$ 75% improvement in BSA.

Numbers of patients achieving NPF week 12 target and acceptable responses for ixekizumab (IXE) versus other biologics have not been demonstrated across clinical trials or real-world studies of plaque psoriasis.

What did the study ask?

This post hoc analysis aimed to compare the achievement of NPF target and acceptable responses at week 12 for IXE versus other biologics across four head-to-head clinical trials and the real-world PSoHO observational study.

What was learned from the study?

What were the study outcomes/conclusions?

Greater proportions of patients with plaque psoriasis treated with IXE achieved NPF target and acceptable responses at week 12 compared with those treated with other biologics.

What has been learned from the study?

IXE demonstrated therapeutic benefit in providing patients with NPF-defined target or acceptable responses at week 12 across clinical trial and real-world settings and in both biologic (bio)-naïve and bio-experienced patients.

INTRODUCTION

The NPF's treatment targets for plaque psoriasis provide a comprehensive treat-to-target (T2T) strategy to guide therapeutic approaches for clinical practice in the USA, with the goal of reducing disease burden and improving patient outcomes [1]. The aim of the development of the guidelines was to establish defined treatment targets toward which clinicians and patients with psoriasis can strive to inform treatment decisions, reduce disease burden, and improve outcomes in practice. T2T recommendations have also been developed for Canadian, British, and Italian clinical practice [2–4]. The primary treatment objective for plaque psoriasis is clear or almost clear skin, and a key goal for patients is to achieve rapid skin improvements [5, 6]. Skin improvement can be measured by several methods, including Psoriasis Area and Severity Index, Physician's Global Assessment, and the percent change in BSA affected by plaque psoriasis. T2T strategies for plaque psoriasis define specific target disease activity endpoints and the recommended timeframes to achieve them. The NPF T2T strategy recommends assessing treatment response 12 weeks after starting a new therapy [1]. The NPF-defined target response at week 12 is BSA $\leq$ 1% [1]. The NPF additionally defines an acceptable response at week 12 as BSA $\leq$ 3%, or an improvement in BSA of $\geq$ 75% [1].

The proinflammatory cytokine IL-17A is a key regulator of plaque psoriasis pathogenesis. Ixekizumab (IXE) is a high-affinity monoclonal antibody that selectively targets IL-17A and is approved to treat moderate-to-severe plaque psoriasis [7]. The therapeutic efficacy of IXE compared with other psoriasis biologics has been demonstrated across numerous head-to-head clinical trials [8–12]. In addition to these clinical data, real-world effectiveness of IXE has been proven through real-world studies [13], including PSoHO—an international, prospective, observational study comparing the effectiveness of anti-IL-17A biologics (IXE and SEC) with other approved biologics for the treatment of moderate-to-severe plaque psoriasis [14–17].

Here, we assessed head-to-head clinical trial and real-world data to compare the achievement of NPF target and acceptable responses at week 12 in patients with plaque psoriasis treated with IXE versus other biologics.

METHODS

Study Design, Participants, and Treatment

This post hoc analysis includes data from four head-to-head clinical trials (UNCOVER-2, UNCOVER-3, IXORA-R, and IXORA-S) and one real-world prospective observational study (PSoHO). Each study included patients with moderate-to-severe plaque psoriasis who were treated with IXE by subcutaneous injection. The US Food and Drug Administration (FDA) approved on-label IXE dosing for adults with moderate-to-severe plaque psoriasis is 160 mg at week 0, followed by 80 mg every 2 weeks (Q2W) from weeks 2–12, then 80 mg every 4 weeks (Q4W) thereafter.

UNCOVER-2–3

UNCOVER-2 and UNCOVER-3 were two phase 3, randomized, double-blinded, placebo (PBO)-controlled studies comparing the efficacy and safety of IXE with ETN in adult patients with moderate-to-severe plaque psoriasis. Study design and patient eligibility criteria have previously been published [8]. This post hoc analysis integrated patients from the intent-to-treat (ITT) populations of UNCOVER-2 and UNCOVER-3. Patients were randomly assigned in a 1:2:2:2 ratio to receive PBO, 50 mg ETN twice weekly, 80 mg IXE Q2W, or 80 mg IXE Q4W. Only patients who received IXE Q2W or ETN were included in this analysis; patients who received PBO or IXE Q4W were not included.

IXORA-R

IXORA-R was a phase 4, 24-week, randomized, double-blinded, parallel-group study comparing the efficacy and safety of IXE with GUS in adult patients with moderate-to-severe plaque psoriasis. Study design and patient eligibility criteria

have previously been published [11, 12]. This post hoc analysis included patients from the ITT population of IXORA-R. Patients were randomly assigned in a 1:1 ratio to receive IXE or GUS at the approved dosing; the approved dosing for GUS is 100 mg at weeks 0 and 4, followed by 100 mg Q8W thereafter.

IXORA-S

IXORA-S was a phase 3b, 52-week, randomized, double-blinded, parallel-group study comparing the efficacy and safety of IXE with ustekinumab (UST) in adult patients with moderate-to-severe plaque psoriasis. Study design and patient eligibility criteria have previously been published [9]. This post hoc analysis included patients from the ITT population of IXORA-S. Patients were randomly assigned in a 1:1 ratio to receive IXE or UST. IXE was administered per approved label dosing. UST-treated patients were dosed at weeks 0, 4, 16, 28, and 40 according to their weight; patients weighing $\leq$ 100 kg received 45 mg, and patients weighing $>$ 100 kg received 90 mg.

PSoHO

PSoHO is an ongoing 3-year, prospective, international, observational study reflecting treatment with biologics within real-world settings. A detailed description of the study design has previously been published [14–16]. PSoHO includes adult patients from 23 countries who had a confirmed diagnosis of moderate-to-severe plaque psoriasis at least 6 months prior to baseline and who initiated or switched biologic treatment during routine medical care. Biologics used in this study are the anti-IL-17A biologics (IXE and SEC) and other approved biologics for the treatment of moderate-to-severe plaque psoriasis. The other approved biologics target IL-17 receptor A (BROD), tumor necrosis factor α [ADA, certolizumab (CZP), ETN, infliximab (INF)], IL-23 p19 (GUS, RIS, and TILD), or IL-12/23 p40 (UST). This post hoc analysis included 1773 patients receiving the US FDA-approved on-label (US OL) dosing.

Ethics Statement

All study protocols, amendments, and consent documentation were approved by the necessary central or local institutional review boards (IRB) and/or ethics committees. All patients were required to give written informed consent prior to participation in UNCOVER-2, UNCOVER-3, IXORA-R, IXORA-S, or PSoHO. Each study was conducted in compliance with local laws and regulations and according to International Conference on Harmonization, Good Clinical Practice guidelines, and the Declaration of Helsinki of 1964 and its later amendments. We confirm that the necessary central or local IRB and/or ethics committee approvals have been obtained for each study. Approvals can be provided on request.

Outcome Measures

The two primary outcomes of the present analysis are the proportions of patients achieving (i) NFP-defined target responses of BSA $\leq$ 1% and (ii) NFP-defined acceptable responses of BSA $\leq$ 3% or a BSA improvement of 75% or more at week 12.

Statistical Analyses

Head-to-Head Clinical Trial Data

The post hoc analysis of RCT data report proportions with 95% confidence intervals (CI) of patients achieving NPF target and acceptable responses at week 12 among the ITT (overall) populations of UNCOVER-2 and UNCOVER-3 (IXEQ2W, N = 736; ETN, N = 740), IXORA-R (IXE, N = 520; GUS, N = 507), and IXORA-S (IXE, N = 136; UST, N = 166), as well as the respective biologic (bio)-naïve and bio-experienced subpopulations of each trial. Post hoc statistical comparisons between treatment groups were performed using Fisher's exact test with no multiplicity adjustments, where patients with missing outcomes were imputed as non-responder imputation (NRI).

Real-World Data (PSoHO)

This post hoc analysis used real-world data from PSoHO to measure achievement of NPF target and acceptable responses among the US OL (overall) population ($N = 1773$), as well as its bio-naïve and bio-experienced subpopulations. The target response analysis included 1697 (96%) patients who had greater than 1% BSA baseline involvement. The acceptable response analysis included 1635 (92%) patients who had greater than 3% BSA baseline involvement. Proportions with 95% CI were calculated for patients achieving NPF target and acceptable responses at week 12. The adjusted comparative effectiveness of the anti-IL-17A biologics versus other approved biologics cohort, and of IXE versus each individual biologic, was evaluated using FMA and reported as OR with 95% CI; an overview of this data-driven methodology has been described previously [15]. FMA is an advanced data-driven modeling approach that combines machine learning approach with model averaging technique to decrease the chance of model misspecification; this approach aims to adjust confounding factors on model outcome in real-world settings [18]. In the current analysis, the statistical models could not converge for certolizumab, etanercept, or infliximab due to their small sample sizes, so these individual treatments were excluded from the analysis. The main analysis of all patient data applied NRI for patients with missing binary outcomes.

RESULTS

Clinical Data from Head-to-Head Trials

Patients

For the overall populations of UNCOVER-2 and UNCOVER-3 ($N = 2570$), IXORA-R ($N = 1027$), and IXORA-S ($N = 302$), the mean (standard deviation) BSA involvement at baseline was 27.2% (16.8), 23.9% (15.8), and 27.1% (16.6), respectively. The majority of study participants were bio-naïve: UNCOVER-2 and UNCOVER-3, 80.7%; IXORA-R, 73.4%; IXORA-S, 85.8%. Overall patient demographics and disease characteristics have been published previously for each of these clinical trials [8, 9, 11, 12]. Table 1 provides the baseline demographics and disease characteristics of the treatment arms included in the present analysis, from the overall patient population as well as two subpopulations who achieved either NPF target or acceptable responses at week 12. Baseline patient profiles were similar between treatment groups across each population.

Achievement of NPF Target Responses at Week 12

Across the four head-to-head clinical trials analyzed, significantly higher proportions of patients achieved BSA $\leq$ 1% at week 12 with IXE versus other biologics (Fig. 1A). In UNCOVER-2 and UNCOVER-3, 52.2% (CI 48.6–55.8) of IXE-treated patients achieved target responses at week 12 compared with 14.9% (CI 13.1–16.7) of ETN-treated patients ($p < 0.001$). In IXORA-R, 61.0% (CI 56.8–65.2) of IXE-treated patients achieved target responses at week 12 compared with 44.8% (CI 40.4–49.1) of GUS-treated patients ($p < 0.001$). In IXORA-S, 50.7% (CI 42.3–59.1) of IXE-treated patients achieved target responses at week 12 compared with 24.1% (CI 17.6–30.6) of UST-treated patients ($p < 0.001$).

These findings were consistent across the bio-naïve and bio-experienced subpopulations of each trial (Fig. 1B–C).

Achievement of NPF Acceptable Responses at Week 12

Across the four head-to-head clinical trials analyzed, significantly higher proportions of patients achieved BSA $\leq$ 3% or a $\geq$ 75% improvement in BSA at week 12 with IXE versus other biologics (Fig. 2A). In UNCOVER-2 and UNCOVER-3, 73.6% (CI 70.5–76.8) of IXE-treated patients achieved acceptable responses at week 12 compared with 35.7% (CI 33.2–38.1) of ETN-treated patients ($p < 0.001$). In IXORA-R, 81.3% (CI 78.0–84.7) of IXE-treated patients

Table 1 Baseline patient demographics and disease characteristics across the analyzed head-to-head clinical trials

UNCOVER-2 AND UNCOVER-3

	All enrolled patients		**Patients with NPF target responses at week 12[a]**		**Patients with NPF acceptable responses at week 12[b]**	
	IXE Q2W (*N* = 736)	**ETN (*N* = 740)**	**IXE Q2W (*N* = 384)**	**ETN (*N* = 110)**	**IXE Q2W (*N* = 542)**	**ETN (*N* = 264)**
Age, years	45.1 (13.2)	45.5 (13.3)	44.7 (13.8)	45.6 (14.7)	44.9 (13.4)	45.2 (14.3)
Male, *n* (%)	475 (64.5)	505 (68.2)	233 (60.7)	69 (62.7)	334 (61.6)	177 (67.0)
BMI	30.1 (7.1)	31.0 (7.4)*	29.3 (6.8)	28.2 (5.8)	29.7 (6.9)	29.3 (6.4)
Duration since PsO symptom onset or diagnosis, years, *median (min, max)*	16.2 (0.5, 63.0)	16.4 (0.6, 56.9)	16.9 (0.5, 61.4)	18.1 (0.7, 51.6)	15.3 (0.5, 63.0)	17.3 (0.7, 51.6)
Previous conventional therapy, *n* (%)	386 (52.4)	388 (52.4)	198 (51.6)	57 (51.8)	276 (50.9)	142 (53.8)
Previous biologic therapy, *n* (%)	142 (19.3)	136 (18.4)	87 (22.7)	16 (14.5)	119 (22.0)	38 (14.4)*
Used 1 therapy, *n* (%)	94 (12.8)	102 (13.8)	59 (15.4)	14 (12.7)	80 (14.8)	29 (11.0)
Used 2 therapies, *n* (%)	32 (4.3)	22 (3.0)	19 (4.9)	0 (0)	26 (4.8)	5 (1.9)
Used $\geq$ 3 therapies, *n* (%)	16 (2.2)	12 (1.6)	9 (2.3)	2 (1.8)	13 (2.4)	4 (1.5)
PASI	20.1 (7.8)	19.9 (7.5)	19.3 (7.2)	17.8 (5.2)*	19.9 (7.5)	20.0 (7.1)
BSA % involvement	26.6 (16.7)	26.8 (16.6)	25.0 (15.7)	22.1 (12.3)	26.3 (16.2)	27.8 (16.2)
sPGA	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)	3.3 (0.5)*	3.5 (0.6)	3.5 (0.6)
Moderate, *n* (%)	385 (52.3)	376 (50.8)	212 (55.2)	74 (67.3)	292 (53.9)	144 (54.5)
Severe, *n* (%)	308 (41.8)	330 (44.6)	158 (41.1)	35 (31.8)	226 (41.7)	110 (41.7)
Very severe, *n* (%)	43 (5.8)	34 (4.6)	14 (3.6)	1 (0.9)	24 (4.4)	10 (3.8)

Table 1 continued

IXORA-R	All enrolled patients		Patients with NPF target responses at week 12[a]		Patients with NPF acceptable responses at week 12[b]	
	IXEQ2W (*N* = 520)	**GUS (*N* = 507)**	**IXEQ2W (*N* = 317)**	**GUS (*N* = 227)**	**IXEQ2W (*N* = 423)**	**GUS (*N* = 358)**
Age, years	49.0 (13.9)	49.0 (14.9)	48.4 (14.0)	47.5 (15.1)	48.6 (14.0)	48.4 (15.2)
Male, *n* (%)	338 (65.0)	314 (61.9)	212 (66.9)	134 (59.0)	278 (65.7)	217 (60.6)
BMI	32.9 (7.9)	32.8 (8.0)	32.0 (7.7)	31.6 (7.1)	32.7 (7.9)	31.9 (7.4)
Duration since PsO symptom onset or diagnosis, years, *median (min, max)*	14.1 (0.5, 70.3)	12.1 (0.5, 67.2)	14.2 (0.5, 70.3)	11.3 (0.5, 55.2)*	14.2 (0.5, 70.3)	12.1(0.5, 67.2)
Previous conventional therapy, *n* (%)	170 (32.7)	141 (27.8)	96 (30.3)	75 (33.0)	136 (32.2)	106 (29.6)
Previous biologic therapy, *n* (%)	139 (26.7)	134 (26.4)	86 (27.1)	57 (25.1)	113 (26.7)	93 (26.0)
Used 1 therapy, *n* (%)	97 (18.7)	97 (19.1)	68 (21.5)	45 (19.8)	81 (19.1)	69 (19.3)
Used 2 therapies, *n* (%)	28 (5.4)	27 (5.3)	15 (4.7)	11 (4.8)	22 (5.2)	19 (5.3)
Used ≥ 3 therapies, *n* (%)	14 (2.7)	10 (2.0)	3 (0.9)	1 (0.4)	10 (2.4)	5 (1.4)
PASI	19.5 (7.9)	19.3 (7.1)	18.9 (7.9)	19.3 (7.5)	19.5 (8.1)	19.6 (7.2)
BSA % involvement	24.1 (16.1)	23.8 (15.4)	22.4 (15.0)	23.9 (16.2)	23.9 (16.0)	24.6 (15.7)
sPGA	n/a	n/a	n/a	n/a	n/a	n/a
Moderate, *n* (%)	266 (51.3)	252 (49.7)	169 (53.3)	123 (54.2)	217 (51.3)	179 (50.0)
Severe, *n* (%)	224 (43.2)	232 (45.8)	132 (41.6)	100 (44.1)	182 (43.0)	166 (46.4)
Very severe, *n* (%)	29 (5.6)	23 (4.5)	16 (5.0)	4 (1.8)	24 (5.7)	13 (3.6)

Table 1 continued

IXORA-S	All enrolled patients		Patients with NPF target responses at week 12[a]		Patients with NPF acceptable responses at week 12[b]	
	IXEQ2W (*N* = 136)	UST (*N* = 166)	IXEQ2W (*N* = 40)	UST (*N* = 69)	IXEQ2W (*N* = 87)	UST (*N* = 111)
Age, years	42.7 (12.7)	44.0 (13.3)	42.2 (12.1)	43.0 (12.7)	41.7 (11.9)	42.6 (12.4)
Male, *n* (%)	90 (66.2)	112 (67.5)	15 (37.5)	25 (36.2)	35 (40.2)	38 (34.2)
BMI	28.8 (5.6)	29.7 (7.0)	28.9 (6.6)	28.4 (5.5)	28.6 (6.2)	28.7 (5.4)
Duration since PsO symptom onset or diagnosis, years, *median (min, max)*	16.0 (1, 50)	16.5 (0, 59)	14.5 (1.0, 52.0)	16.0 (1.0, 43.0)	15.0 (0, 52.0)	15.0 (1.0, 43.0)
Previous conventional therapy, *n* (%)	74 (54.4)	107 (64.5)	n/a	n/a	n/a	n/a
Previous biologic therapy, *n* (%)	18 (13.2)	25 (15.1)	6 (15.0)	7 (10.1)	12 (13.8)	15 (13.5)
1 therapy, *n* (%)	12 (8.8)	18 (10.8)	n/a	n/a	n/a	n/a
2 therapies, *n* (%)	5 (3.7)	7 (4.2)	n/a	n/a	n/a	n/a
≥ 3 therapies, *n* (%)	1 (0.7)	0 (0)	n/a	n/a	n/a	n/a
PASI	19.9 (8.2)	19.8 (9.0)	19.6 (9.5)	19.2 (7.4)	19.8 (8.9)	20.0 (7.8)
BSA % involvement	26.7 (16.5)	27.5 (16.7)	29.1 (16.7)	25.6 (15.9)	29.1 (17.4)	27.1 (16.7)
sPGA	3.6 (0.7)	3.6 (0.6)	3.5 (0.6)	3.4 (0.6)	3.5 (0.6)	3.5 (0.6)
Moderate, *n* (%)	61 (44.9)	71 (42.8)	n/a	n/a	n/a	n/a
Severe, *n* (%)	63 (46.3)	83 (50.0)	n/a	n/a	n/a	n/a
Very severe, *n* (%)	10 (7.4)	12 (7.2)	n/a	n/a	n/a	n/a

Data are mean (standard deviation) unless otherwise indicated. Values are rounded to one decimal place where applicable

Percentages were calculated on the basis of the number of patients with non-missing values

BMI body mass index, *BSA* body surface area, *ETN* etanercept, *GUS* guselkumab, *IXE* ixekizumab, *max* maximum, *min* minimum, *n/a* data not available, *NPF* National Psoriasis Foundation, *PASI* Psoriasis Area and Severity Index, *PsO* psoriasis, *Q2W* every 2 weeks, *sPGA* static Physician Global Assessment, *UST* ustekinumab

[*] *p*-Value < 0.05 versus IXE

[a] NPF target response: BSA ≤ 1%

[b] NPF acceptable response: BSA ≤ 3% or BSA improvement from baseline ≥ 75%

achieved acceptable responses at week 12 compared with 70.6% (CI 66.6–74.6) of GUS-treated patients ($p < 0.001$). In IXORA-S, 81.6% (CI 75.1–88.1) of IXE-treated patients achieved acceptable responses at week 12 compared with 52.4% (CI 44.8–60.0) of UST-treated patients ($p < 0.001$).

These findings were consistent across the bio-naïve and bio-experienced subpopulations of each trial (Fig. 2B–C).

Real-World Data (PSoHO) Patients

For the 1773 PSoHO patients who received US OL dosing, the mean (standard deviation) BSA involvement at baseline was 21.7% (17.9). The majority ($n = 1127$, 63.6%) of these patients were bio-naïve. Table 2 provides the baseline demographics and disease characteristics for the overall US OL population as well as the anti-IL-17A, other biologics, and individual treatment groups. At baseline, 40.6% ($n = 720$) initiated an anti-IL-17A biologic (IXE or SEC) and 59.4% ($n = 1053$) received other biologics. The US OL patient profiles were comparable between the anti-IL-17A cohort and other biologics cohort with few exceptions, similar to what has been described for the total PSoHO study population [15]. The average age in the anti-IL-17A cohort was higher than that in the other biologics cohort (47 years versus 44 years). Conversely, more patients in the other biologics cohort had received prior conventional treatments (82.1% versus 74.4%), while no statistical difference was found in the prior use of biologics.

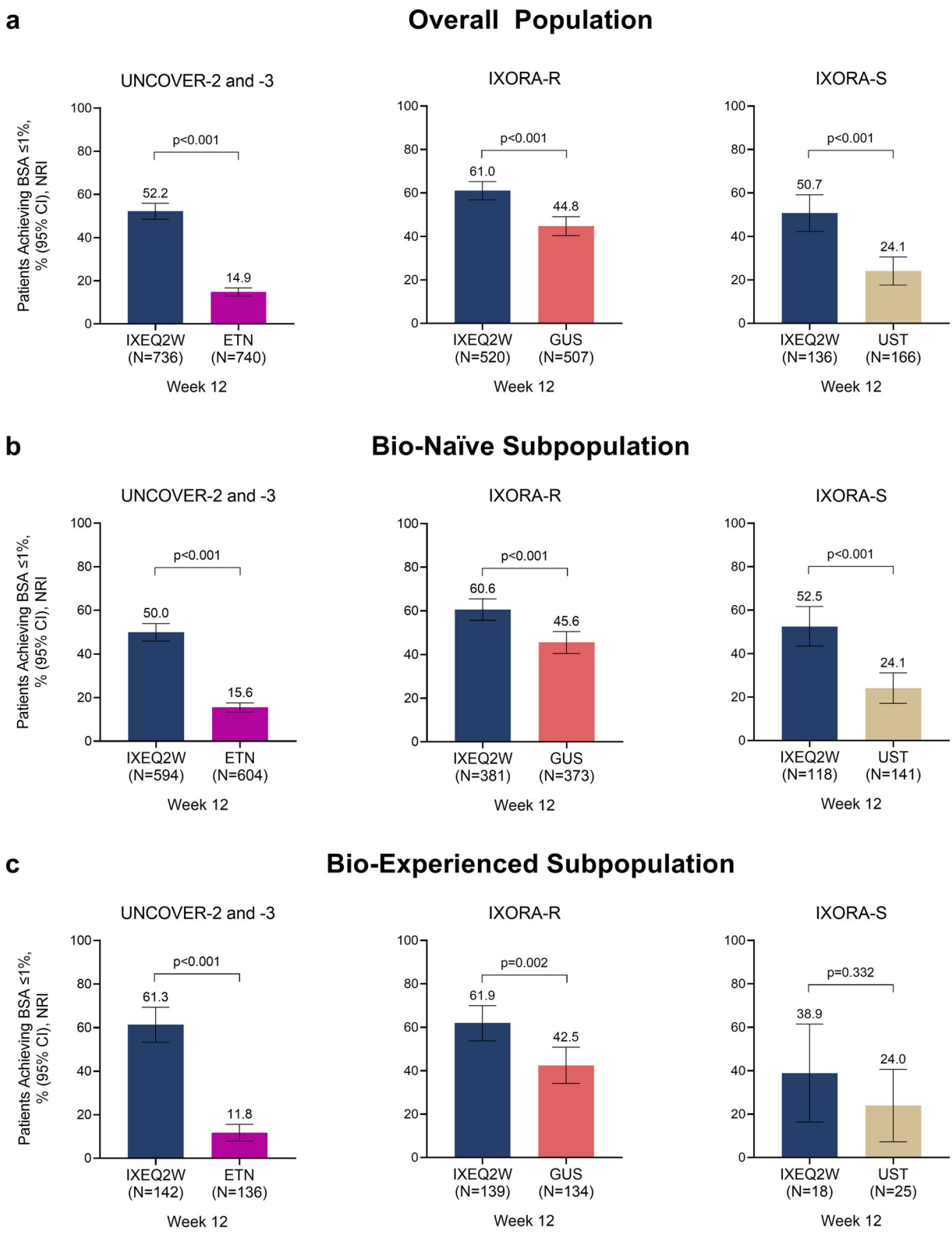
Table S1 in the electronic supplementary material details the use of concomitant medications, prior non-biologic systemic therapies, and prior biologic therapies for the overall US OL population as well as the anti-IL-17A, other biologics, and individual treatment groups.

Achievement of NPF Target Responses at Week 12

Proportions of PSoHO patients who achieved BSA ≤ 1 at week 12 for the anti-IL-17A cohort and other biologics cohort were 52.0% and 39.4%, respectively (Fig. S1 in the electronic supplementary material). Significantly, the anti-IL-17A cohort had approximately two times greater odds (OR 1.8) of achieving target responses compared with the other biologics cohort. Similarly, in the bio-naïve and bio-experienced subpopulations, unadjusted response rates and adjusted ORs for target responses were greater for the anti-IL-17A cohort compared with the other biologics cohort (Supplementary Fig. S1).

Proportions of patients achieving BSA ≤ 1 at week 12 were numerically higher with IXE compared with other individual biologics (Fig. 3). A total of 54.2% of patients treated with IXE achieved target response at week 12 compared with 47.1% with SEC, 40.5% with GUS, 47.1% with RIS, 32.6% with ADA, 26.9% with UST, 33.3% with TILD, and 53.6% with BROD (Fig. 3). Adjusted comparative analyses showed that IXE had significantly greater odds of target response versus SEC (OR 1.4), GUS (OR 1.6), RIS (OR 1.4), ADA (OR 2.9), UST (OR 3.6), and TILD (OR 2.7) (Fig. 3). Notably, IXE-treated patients had approximately three times greater odds of achieving target responses compared with those who received ADA, UST, or TILD (Fig. 3). IXE also had numerically greater odds of target response versus BROD (OR 1.1) (Fig. 3).

Across both the bio-naïve and bio-experienced subpopulations, the adjusted ORs for target response and the proportions of patients achieving BSA $\leq 1\%$ were numerically higher with IXE compared with other individual biologics, except for BROD in bio-naïve patients (Fig. 4). With all biologics apart from UST, proportions of patients achieving BSA $\leq 1\%$ were lower among bio-experienced patients compared with bio-naïve patients. Among bio-naïve patients, IXE had significantly greater odds of achieving target response versus SEC (OR 1.6), GUS (OR 1.6), ADA (OR 2.9), UST (OR 4.6), and TILD (OR 2.8); numerically greater odds of achieving target response versus RIS (OR 1.5); and equivalent odds of achieving target response versus BROD (OR 1.0) (Fig. 4a). Notably, the odds of bio-naïve patients achieving


a
Overall Population
UNCOVER-2 and -3
IXORA-R
IXORA-S
Patients Achieving BSA ≤1%, % (95% CI), NRI
p<0.001
52.2
14.9
IXEQ2W (N=736)
ETN (N=740)
61.0
44.8
IXEQ2W (N=520)
GUS (N=507)
50.7
24.1
IXEQ2W (N=136)
UST (N=166)
Week 12
b
Bio-Naïve Subpopulation
50.0
15.6
IXEQ2W (N=594)
ETN (N=604)
60.6
45.6
IXEQ2W (N=381)
GUS (N=373)
52.5
24.1
IXEQ2W (N=118)
UST (N=141)
c
Bio-Experienced Subpopulation
61.3
11.8
IXEQ2W (N=142)
ETN (N=136)
p=0.002
61.9
42.5
IXEQ2W (N=139)
GUS (N=134)
p=0.332
38.9
24.0
IXEQ2W (N=18)
UST (N=25)

◀**Fig. 1** NPF target treatment responses in head-to-head clinical trials. Proportions (%) of patients who achieved BSA ≤ 1% at week 12 among the **a** overall population, **b** bio-naïve subpopulation, and **c** bio-experienced subpopulation of the UNCOVER-2 and UNCOVER-3, IXORA-R, and IXORA-S head-to-head clinical trials. Percentages are shown with 95% CI. Missing data were imputed by the NRI method. *bio* biologic, *BSA* body surface area, *CI* confidence interval, *ETN* etanercept, *GUS* guselkumab, *IXE Q2W* ixekizumab every 2 weeks, *NPF* National Psoriasis Foundation, *NRI* non-response imputation, *UST* ustekinumab

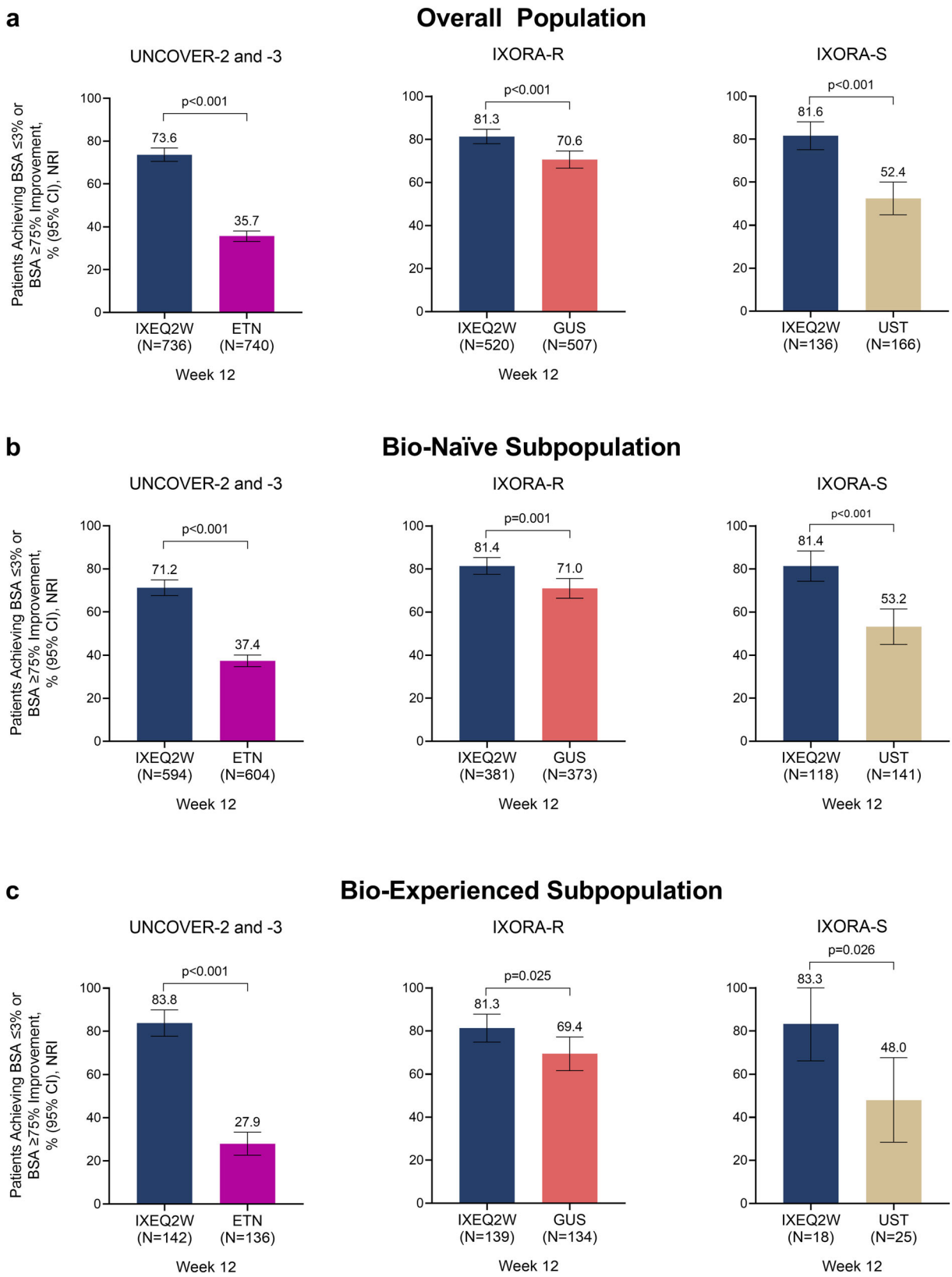
target response with IXE were almost five times greater versus UST and approximately three times greater versus ADA and TILD (Fig. 4a). Among bio-experienced patients, IXE had significantly greater odds of achieving target response versus the IL-23 p19 inhibitors GUS (OR 1.8) and TILD (OR 2.3) and numerically greater odds of achieving target response versus RIS (OR 1.4) (Fig. 4b). In bio-experienced patients, the odds of achieving target response also reached statistical significance for IXE versus ADA (OR 3.0) and were numerically greater for IXE versus SEC (OR 1.3), UST (OR 2.4), and BROD (OR 2.0) (Fig. 4b).

Achievement of NPF Acceptable Responses at Week 12

Proportions of PSoHO patients who achieved BSA ≤ 3% or a ≥ 75% improvement in BSA at week 12 for the anti-IL-17A cohort and other biologics cohort were 74.1% and 61.4%, respectively (Fig. S2 in the electronic supplementary material). Significantly, the anti-IL-17A cohort had two times greater odds (OR 2.0) of achieving acceptable responses compared with the other biologics cohort. In the bio-naïve and bio-experienced subpopulations, unadjusted response rates and adjusted ORs for acceptable response were also greater for the anti-IL-17A cohort compared with the other biologics cohort (Supplementary Fig. S2).

Proportions of patients achieving BSA ≤ 3% or a ≥ 75% improvement in BSA at week 12 was numerically higher with IXE compared with other individual biologics (Fig. 5). A total of 77.0% of patients treated with IXE achieved acceptable response at week 12 compared with 67.2% with SEC, 62.7% with GUS, 70.6% with RIS, 55.2% with ADA, 51.0% with UST, 60.3% with TILD, and 67.9% with BROD. Adjusted comparative analyses showed that IXE-treated patients had significantly greater odds of achieving acceptable responses compared with SEC (OR 1.8), GUS (OR 1.6), RIS (OR 1.5), ADA (OR 3.2), UST (OR 3.4), and TILD (OR 2.4) (Fig. 5). Notably, IXE had more than two times greater odds of acceptable responses versus TILD and more than three times greater odds of acceptable responses versus ADA and UST. IXE also had numerically greater odds of acceptable response compared with BROD (OR 1.9) (Fig. 5).

Across both the bio-naïve and bio-experienced subpopulations, the adjusted ORs for acceptable response and the proportions of patients achieving BSA ≤ 3% or a ≥ 75% improvement were numerically higher with IXE compared with all other individual biologics (Fig. 6). With all biologics apart from ADA, proportions of patients achieving BSA ≤ 3% or a ≥ 75% improvement were lower among bio-experienced patients compared with bio-naïve patients. Among bio-naïve patients, IXE had significantly greater odds of achieving acceptable response versus SEC (OR 2.0), ADA (OR 3.1), UST (OR 3.8), and TILD (OR 2.0) and numerically greater odds of achieving acceptable response versus GUS (OR 1.6), RIS (OR 1.6), and BROD (OR 1.8) (Fig. 6a). Among bio-experienced patients, IXE had significantly greater odds of achieving acceptable response versus the IL-23 inhibitors GUS (OR 2.2) and TILD (OR 3.3) and numerically greater odds of achieving acceptable response versus RIS (OR 1.4) (Fig. 6b). Bio-experienced patients treated with IXE also had numerically greater odds of achieving acceptable response versus SEC (OR 1.5), ADA (OR 3.0), UST (OR 3.1), and BROD (OR 2.7) (Fig. 6b).


a
Overall Population
UNCOVER-2 and -3
IXORA-R
IXORA-S
Patients Achieving BSA ≤3% or BSA ≥75% Improvement, % (95% CI), NRI
p<0.001
73.6
35.7
IXEQ2W (N=736)
ETN (N=740)
Week 12
p<0.001
81.3
70.6
IXEQ2W (N=520)
GUS (N=507)
Week 12
p<0.001
81.6
52.4
IXEQ2W (N=136)
UST (N=166)
b
Bio-Naïve Subpopulation
UNCOVER-2 and -3
IXORA-R
IXORA-S
p<0.001
71.2
37.4
IXEQ2W (N=594)
ETN (N=604)
Week 12
p=0.001
81.4
71.0
IXEQ2W (N=381)
GUS (N=373)
Week 12
p<0.001
81.4
53.2
IXEQ2W (N=118)
UST (N=141)
Week 12
c
Bio-Experienced Subpopulation
UNCOVER-2 and -3
IXORA-R
IXORA-S
p<0.001
83.8
27.9
IXEQ2W (N=142)
ETN (N=136)
Week 12
p=0.025
81.3
69.4
IXEQ2W (N=139)
GUS (N=134)
Week 12
p=0.026
83.3
48.0
IXEQ2W (N=18)
UST (N=25)
Week 12

◀**Fig. 2** NPF acceptable treatment responses in head-to-head clinical trials. Proportions (%) of patients who achieved BSA $\leq$ 3% or a $\geq$ 75% improvement in BSA at week 12 among the **a** overall population, **b** bio-naïve subpopulation, and **c** bio-experienced subpopulation of the UNCOVER-2 and UNCOVER-3, IXORA-R, and IXORA-S head-to-head clinical trials. Percentages are shown with 95% CI. Missing data were imputed by the NRI method. *bio* biologic, *BSA* body surface area, *CI* confidence interval, *ETN* etanercept, *GUS* guselkumab, *IXE Q2W* ixekizumab every 2 weeks, *NPF* National Psoriasis Foundation, *NRI* non-response imputation, *UST* ustekinumab

DISCUSSION

The T2T strategy for plaque psoriasis that was established by the NPF recommends evaluating patient response to treatment at week 12, with a target response of BSA $\leq$ 1% and an acceptable response of BSA $\leq$ 3% or a $\geq$ 75% improvement in BSA [1]. Across all studies included in the present analysis, more than half of IXE-treated patients achieved NPF target (Figs. 1A, 3) and acceptable (Figs. 2A, 5) responses at week 12. Rapid skin improvement is one of the most important treatment goals targeted by patients with plaque psoriasis [5, 6]. Skin improvements have been associated with a lower Dermatology Life Quality Index (corresponding to less impaired health-related quality of life) in patients with plaque psoriasis from RCTs [11, 19] and real-world observational studies [16]. Clinical improvements in ixekizumab-treated patients were accompanied by rapid improvements in health-related quality-of-life measures in the UNCOVER 2 and 3 trials [20]. Additionally, a study from the CorEvitas Psoriasis Registry showed that real-world patients not meeting the NPF target or acceptable treatment responses at 6 months post-treatment initiation had higher odds for worse quality of life compared with patients who had achieved these respective targets [21]. The results of the present analysis demonstrate the rapid skin resolution achieved with IXE compared with other biologics and reinforce its therapeutic benefits [15, 22] from a patient perspective.

A strength of the current study is that it assessed the achievement of NPF target and acceptable responses at week 12 using both clinical and real-world data. The results showed that numerically higher proportions of patients with plaque psoriasis treated with IXE achieved NPF target and acceptable responses at week 12 compared with those treated with other biologics across both clinical (Figs. 1a, 2a) and real-world (Figs. 3, 5) settings. Adjusted comparative analyses of real-world data also showed that IXE had greater overall odds of target (Fig. 3) and acceptable (Fig. 5) responses versus other biologics. These real-world data additionally established that patients treated with anti-IL-17A biologics had significantly greater target and acceptable response rates compared with those who received other biologic classes.

Another strength of the present analysis is that it considered treatment responses among the bio-naïve and bio-experienced subpopulations of each study. In psoriasis, bio-experienced patients treated with biologics are reported to have lower response rates and lower drug survival compared with bio-naïve patients [14, 23–25]. Here, the real-world proportions achieving target and acceptable responses tended to be lower among bio-experienced patients compared with bio-naïve patients. Nevertheless, IXE demonstrated a numerically greater, and in some cases statistically significant, benefit versus other biologics in both the bio-naïve and bio-experienced subpopulations, except for target response versus BROD in the real-world bio-naïve subpopulation. Notably, the adjusted analyses of real-world bio-naïve and bio-experienced subpopulations showed that the odds of target response for IXE versus UST in the bio-naïve subpopulation were almost double that of IXE versus UST in the bio-experienced subpopulation (OR 4.6 versus 2.4). Conversely, IXE had numerically greater odds of achieving target response versus BROD in the bio-experienced

Table 2 Baseline demographics and disease characteristics of patients receiving US OL dosing in the PSoHO observational study

	Overall US OL (*N* = 1773)	**Anti-IL-17A (*N* = 720)**	**Other biologics (*N* = 1053)**	**IXE (*N* = 501)**	**SEC (*N* = 219)**	**GUS (*N* = 272)**	**RIS (*N* = 230)**	**ADA (*N* = 225)**	**UST (*N* = 112)**	**TILD (*N* = 83)**	**BROD (*N* = 60)**
Age, years	45.3 (13.6)	46.8 (13.7)‡	44.3 (13.3)	47.3 (14.0)	45.6 (13.0)	44.2 (12.9)	44.0 (13.6)	45.0 (12.7)	46.1 (14.5)	45.4 (13.1)	44.4 (14.1)
Male, *n* (%)	1014 (57.2)	407 (56.5)	607 (57.6)	290 (57.9)	117 (53.4)	158 (58.1)	145 (63.0)	131 (58.2)	65 (58.0)	49 (59.0)	34 (56.7)
BMI	29.2 (6.8)	29.4 (6.6)	29.1 (6.9)	29.5 (6.7)	29.1 (6.5)	29.2 (6.7)	28.9 (7.1)	29.7 (6.7)	28.2 (5.6)	29.6 (7.6)	29.3 (7.6)
Duration since onset of PsO, years, *median (Q1, Q3)*	14.1 (7.1, 23.8)	14.6 (6.5, 24.6)	14.0 (7.4, 23.1)	14.1 (6.6, 25.5)	15.0 (6.3, 22.2)	15.7 (8.2, 24.6)	13.7 (8.0, 23.0)	14.0 (6.5, 23.0)	12.1 (6.3, 23.3)	16.0 (8.1, 25.8)	15.0 (7.7, 21.0)
Previous conventional therapy, *n* (%)	1400 (79.0)	535 (74.4)‡	865 (82.1)	374 (74.8)	161 (73.5)	200 (73.5)	177 (77.0)	211 (93.8)	95 (84.8)	73 (88.0)	50 (83.3)
Previous biologic therapy, *n* (%)	645 (36.4)	275 (38.2)	370 (35.1)	193 (38.6)	82 (37.4)	165 (60.7)	97 (42.2)	18 (8.0)	31 (27.7)	26 (31.3)	22 (36.7)
1 therapy, *n* (%)	437 (24.7)	190 (26.4)	247 (23.5)	130 (26.0)	60 (27.4)	100 (36.8)	68 (29.6)	12 (5.3)	24 (21.4)	20 (24.1)	13 (21.7)
2 therapies, *n* (%)	105 (5.9)	48 (6.7)	57 (5.4)	33 (6.6)	15 (6.8)	31 (11.4)	14 (6.1)	3 (1.3)	5 (4.5)	2 (2.4)	1 (1.7)
≥ 3 therapies, *n* (%)	103 (5.8)	37 (5.1)	66 (6.3)	30 (6.0)	7 (3.2)	34 (12.5)	15 (6.5)	3 (1.3)	2 (1.8)	4 (4.8)	8 (13.3)
PASI	14.7 (8.7)	14.6 (8.6)	14.7 (8.8)	14.4 (8.5)	15.0 (8.9)	14.9 (9.5)	15.7 (10.1)	13.5 (7.4)	14.6 (8.1)	14.2 (8.0)	16.2 (8.6)
BSA % involvement	21.7 (17.9)	21.4 (17.7)	21.8 (18.1)	20.8 (17.2)	22.9 (18.6)	22.2 (18.7)	21.1 (19.0)	20.9 (17.3)	23.2 (18.1)	19.9 (15.1)	23.9 (18.5)
sPGA	3.2 (0.9)	3.2 (0.9)	3.2 (0.9)	3.2 (0.9)	3.3 (0.9)	3.3 (0.8)	3.3 (1.0)	3.1 (0.8)	3.1 (0.9)	3.0 (1.0)	3.2 (0.9)
Moderate, *n* (%)	885 (50.7)	364 (51.2)	521 (50.4)	254 (51.1)	110 (51.4)	129 (48.0)	87 (39.0)	134 (60.1)	62 (56.4)	37 (45.1)	35 (60.3)
Severe, *n* (%)	546 (31.3)	220 (30.9)	326 (31.6)	163 (32.8)	57 (26.6)	91 (33.8)	85 (38.1)	57 (25.6)	30 (27.3)	24 (29.3)	16 (27.6)

Table 2 continued

OL(N = 1773)	Overall US Anti-IL-17A (N = 720)	Other biologics (N = 1053)	IXE (N = 501)	SEC (N = 219)	GUS (N = 272)	RIS (N = 230)	ADA (N = 225)	UST (N = 112)	TILD (N = 83)	BROD (N = 60)
Very severe, n (%)	74 (4.2)	33 (4.6)	41 (4.0)	16 (3.2)	17 (7.9)	14 (5.2)	15 (6.7)	5 (2.2)	2 (1.8)	2 (2.4)	3 (5.2)

All results are expressed as mean (standard deviation) of all available data for that measure, unless otherwise indicated
Percentages were calculated on the basis of the number of patients with non-missing values. Values are rounded to one decimal place where applicable
The other biologics cohort (N = 1053) includes GUS (N = 272), RIS (N = 230), ADA (N = 225), UST (N = 112), TILD (N = 83), BROD (N = 60), CZP (N = 35), ETN (N = 30), and INF (N = 6). Individual data not shown for CZP, ETN, or INF due to low number of patients
ADA adalimumab, *BMI* body mass index, *BROD* brodalumab, *BSA* body surface area, *CZP* certolizumab, *ETN* etanercept, *GUS* guselkumab, *IL-17A* interleukin-17A, *INF* infliximab, *IXE* ixekizumab, *PASI* Psoriasis Area Severity Index, *P3O* psoriasis, *Q* quartile, *RIS* risankizumab, *SEC* secukinumab, *sPGA* static Physician Global Assessment, *TILD* tildrakizumab, *US OL* US FDA-approved on-label, *UST* ustekinumab
‡p-Value < 0.001 versus the other biologics cohort

Fig. 3 Actual response rates and comparative adjusted odds ratios for NPF target treatment responses in the real-world Psoriasis Study of Health Outcomes. Missing data were imputed using the NRI method for proportions (%) of patients who achieved BSA $\leq$ 1% at week 12. Adjusted odds ratios calculated using FMA. Results are statistically significant if 1 is not covered by the 95% CI for the odds ratio. For lower CIs presented as 1.0, * denotes that the lower CI is greater than 1. *BSA* body surface area, *CI* confidence interval, *FMA* frequentist model averaging, *NPF* National Psoriasis Foundation, *NRI* non-response imputation

subpopulation (OR 2.0) but equal odds among bio-naïve patients (OR 1.0).

There are several limitations to the current study, including the small sample size in some subpopulations, which limit the generalizability of results. The execution and statistical precision of the comparative analyses were constrained by the number of representative patients in each treatment cohort; larger sample sizes translate to higher statistical precision, whereas smaller sample sizes result in lower stability models and broader confidence intervals. This post hoc analysis excluded the results of certolizumab, etanercept, and infliximab from the individual biologics due to the small sample, which prevented convergence of the statistical models. Regarding the clinical trials included in the present analysis, the predominantly white study population of UNCOVER-2–3 [8] and the fact that IXORA-R was conducted only in the USA and Canada [11, 12] limit the general applicability of these results.

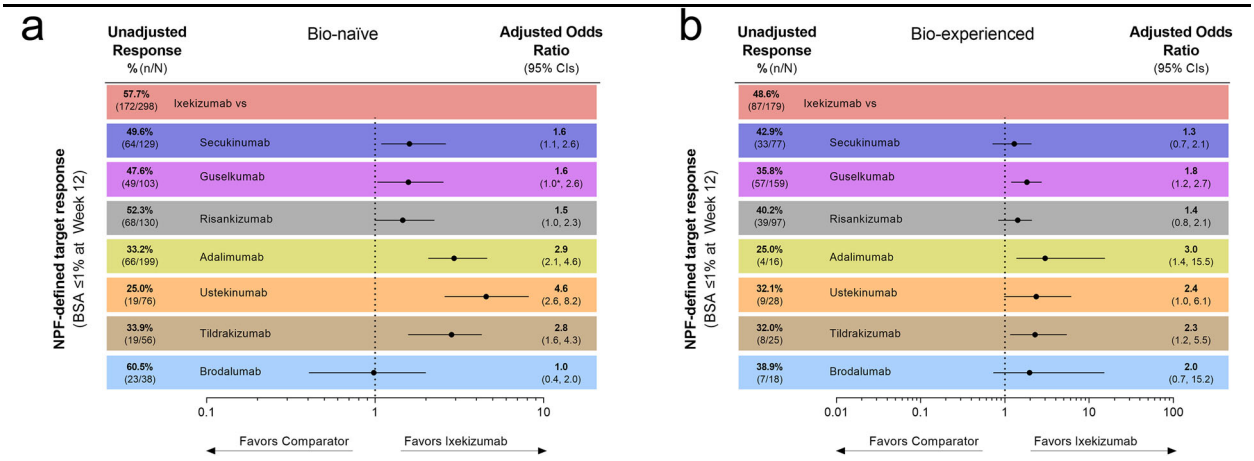


Fig. 4 Actual response rates and comparative adjusted odds ratios for NPF target treatment responses in **a** bio-naïve and **b** bio-experienced subpopulations from the real-world Psoriasis Study of Health Outcomes. Missing data were imputed using the NRI method for proportions (%) of patients who achieved BSA $\leq$ 1% at week 12. Adjusted odds ratios calculated using FMA. Results are statistically significant if 1 is not covered by the 95% CI for the odds ratio. For lower CIs presented as 1.0, * denotes that the lower CI is greater than 1. *bio* biologic, *BSA* body surface area, *CI* confidence interval, *FMA* frequentist model averaging, *NPF* National Psoriasis Foundation, *NRI* non-response imputation

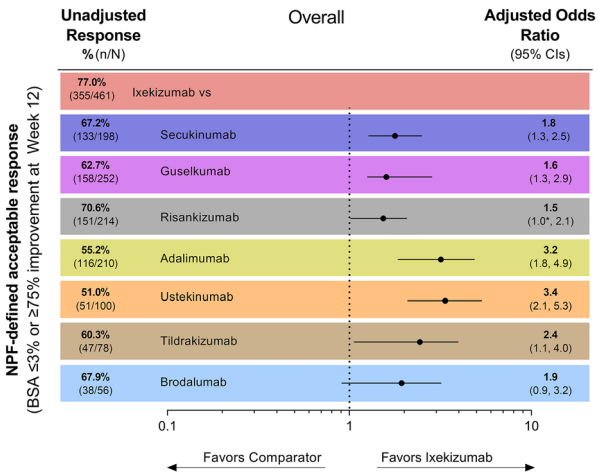


Fig. 5 Actual response rates and comparative adjusted odds ratios for NPF acceptable treatment responses in the real-world Psoriasis Study of Health Outcomes. Missing data were imputed using the NRI method for proportions (%) of patients who achieved BSA $\leq$ 3% or a $\geq$ 75% improvement in BSA at week 12. Adjusted odds ratios calculated using FMA. Results are statistically significant if 1 is not covered by the 95% CI for the odds ratio. For lower CIs presented as 1.0, * denotes that the lower CI is greater than 1. *BSA* body surface area, *CI* confidence interval, *FMA* frequentist model averaging, *NPF* National Psoriasis Foundation, *NRI* non-response imputation

However, inclusion of real-world data from the PSoHO observational study, which was conducted across 23 countries, may offset some of these limitations. Detailed descriptions of the limitations of PSoHO have previously been published [14–16, 26]. Additionally, as an observational study, PSoHO has inherent limitations, including measured and unmeasured confounding and other bias compared with RCTs. The application of FMA can accommodate for some of these uncertainties in model choice through the machine learning framework [18].

CONCLUSION

This analysis demonstrates the therapeutic benefit of IXE compared with other biologics in providing patients with NPF-defined target or acceptable responses at week 12. The complementary clinical trial and real-world data presented here provide additional evidence supporting the rapid skin resolution achieved with IXE treatment, which has previously been proven to improve health-related quality of life in patients [11, 16, 19].

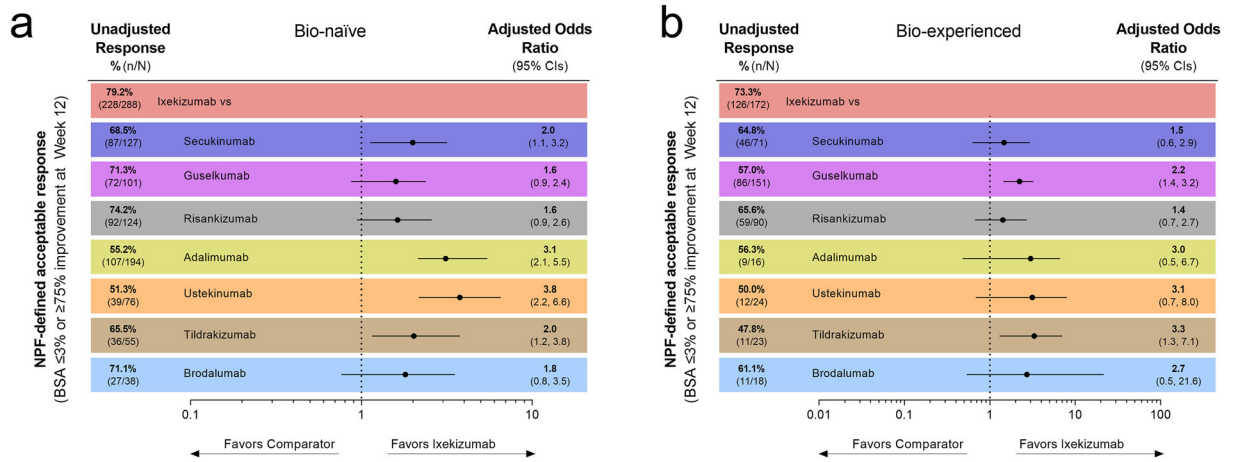


Fig. 6 Actual response rates and comparative adjusted odds ratios for NPF acceptable treatment responses in **a** bio-naïve and **b** bio-experienced subpopulations from the real-world Psoriasis Study of Health Outcomes. Missing data were imputed using the NRI method for proportions (%) of patients who achieved BSA $\leq$ 3% or a $\geq$ 75% improvement in BSA at week 12. Adjusted odds ratios calculated using FMA. Results are statistically significant if 1 is not covered by the 95% CI for the odds ratio. *bio* biologic, *BSA* body surface area, *CI* confidence interval, *FMA* frequentist model averaging, *NPF* National Psoriasis Foundation, *NRI* non-response imputation

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Data Availability. Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available for request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. 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, and 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. April Armstrong has received grants or contracts from, and served as a consultant, speaker and/or investigator for: AbbVie, Almirall, Arcutis, ASLAN, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Dermira, Eli Lilly and Company, EPI Health, Incyte, LEO Pharma, UCB, Janssen, Nimbus, Novartis, Ortho Dermatologics, Pfizer, Sun, Sanofi, and Regeneron; has participated on data safety monitoring or advisory boards for: Boehringer Ingelheim and Parexel; and has been elected to the Board of Directors for the American Academy of Dermatology. Alvaro González-Cantero has served as a consultant and speaker for: AbbVie, Almirall, Celgene, Eli Lilly and Company, Janssen, LEO Pharma, L'Oreal, MSD, Novartis, and UCB Pharma; and has received grants or contracts from: Almirall, Celgene, and LEO Pharma. Saakshi Khattri has received grants or contracts from, and/or served as a consultant and/or speaker for: AbbVie, Bristol Myers Squibb, Eli Lilly and Company, Incyte, Janssen, LEO Pharma, Pfizer, Regeneron, Sanofi, and UCB Pharma. Guilherme Muzy has received honoraria and/or consulting fees from: AbbVie, Eli Lilly and Company, Sanofi, Novartis, Janssen, and Pfizer; has been a speaker for: AbbVie, Eli Lilly, Sanofi, Novartis, Janssen and Pfizer; and has participated on data safety monitoring or advisory boards for: Abbvie, Eli Lilly, Sanofi, Janssen, and Pfizer. William N. Malatestinic, Anastasia Lampropoulou, and Sophia Kyoungah See are employees and shareholders of Eli Lilly and Company. Meghan Feely is associate staff at Mount Sinai Hospital, Mount Sinai West, and Mount Sinai Morningside; a current employee and shareholder of Eli Lilly and Company; and has received consulting, travel, or speaker fees from: American Academy of Dermatology, Aerolase, Castle Biosciences, CeraVe—L'Oréal, DREAM USA, Galderma Aesthetics, Glow Recipe, La Roche-Posay—L'Oréal, Revian, Sonoma Pharmaceuticals, Sun Pharma, and Suneva Medical. Can Mert is a contractor of HaaPACs GmbH and conducted statistical analysis for this project on behalf of Eli Lilly and Company. Andrew Blauvelt has served as a speaker (received honoraria) for: Eli Lilly and Company, Pfizer, and UCB Pharma; served as a scientific adviser (received honoraria) for: AbbVie, Abcentra, Aclaris, Affibody, Aligos, Almirall, Alumis, Amgen, Anaptysbio, Apogee, Arcutis, Arena, ASLAN Pharmaceuticals, Athenex, Bluefin Biomedicine, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, CTI BioPharma, Dermavant, EcoR1, Eli Lilly and Company, Escient, Evelo, Evommune, Forte, Galderma, HighlightII Pharma, Incyte, InnoventBio, Janssen, Landos, LEO pharma, Lipidio, Microbion, Merck, Monte Rosa Therapeutics, Nektar, Novartis, Overtone Therapeutics, Paragon, Pfizer, Q32 Bio, Rani, Rapt, Regeneron, Sanofi Genzyme, Spherix Global Insights, Sun Pharma, Takeda, TLL Pharmaceutical, TrialSpark, UCB Pharma, Union, Ventyx, Vibliome, and Xencor; and has acted as a clinical study investigator (institution has received clinical study funds) for: AbbVie, Acelyrin, Allakos, Almirall, Alumis, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Concert, Dermavant, DermBiont, Eli Lilly and Company, Evelo, Evommune, Galderma, Incyte, Janssen, Leo, Merck, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, Takeda, UCB Pharma, and Ventyx.

Ethical Approval. All study protocols, amendments, and consent documentation were approved by the necessary central or local institutional review boards (IRB) and/or ethics committees. All patients were required to give written informed consent prior to participation in UNCOVER-2, UNCOVER-3, IXORA-R, IXORA-S, or PSoHO. Each study was conducted in compliance with local laws and regulations and according to International Conference on Harmonization, Good Clinical Practice guidelines, and the Helsinki Declaration of 1964, and its later amendments. We confirm that the necessary central or local IRB and/or ethics

committee approvals have been obtained for each study. Approvals can be provided on request.

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