

Efficacy and Safety of Switching to Ixekizumab in Etanercept Non-Responders: A Subanalysis from Two Phase III Randomized Clinical Trials in Moderate-to-Severe Plaque Psoriasis (UNCOVER-2 and -3)

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Abstract

Background Patients with psoriasis who have an inadequate response to one biologic may benefit from switching to a new biologic, such as ixekizumab, a high affinity monoclonal antibody that selectively targets interleukin (IL)-17A.

Objective Our aim was to assess the response to ixekizumab in patients with moderate-to-severe plaque psoriasis who did not respond adequately to etanercept using a post-hoc analysis in two phase III studies.

Methods For the subanalyses in two phase III trials (UNCOVER-2 and -3), non-response was defined by either failure to have a static physician global assessment (sPGA) of 0/1 in UNCOVER-2 or failure to have at least 75% improvement in psoriasis area and severity index (PASI 75) in UNCOVER-3 at Week 12 of each study. Non-responders treated with twice-weekly etanercept 50 mg in the first 12 weeks received two injections of placebo at Week 12 (4-week wash-out period), followed by ixekizumab every 4 weeks (Q4W) for Weeks 16–60. Non-responders to placebo in the first 12 weeks were administered ixekizumab 160 mg at Week 12, followed by ixekizumab Q4W for Weeks 16–60.

Results After switching to ixekizumab Q4W, a substantial proportion of patients with moderate-to-severe psoriasis who did not respond to etanercept experienced rapid and durable improvement in all efficacy evaluations. Among sPGA 0/1 (UNCOVER-2) and PASI 75 (UNCOVER-3) non-responders to etanercept, 73.0% achieved sPGA 0/1 and 78.2% achieved PASI 75, respectively, after 12 weeks of ixekizumab treatment. Safety profiles in patients switched from etanercept to ixekizumab were similar to those in patients switched from placebo to ixekizumab.

Conclusion Patients who were non-responders to etanercept after 12 weeks, as defined by failure to meet sPGA 0/1 (UNCOVER-2) or PASI 75 (UNCOVER-3), achieved high levels of response 12 weeks after switching to ixekizumab. Studies are registered with ClinicalTrials.gov (NCT01597245 and NCT01646177).

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Key Points

Alternative therapies are needed for patients with psoriasis who must discontinue a tumor necrosis factor alpha (TNF- α) inhibitor due to limited efficacy, loss of efficacy, or adverse reactions.

In patients switched to ixekizumab following non-response to etanercept, a TNF- α inhibitor, we observed a favorable response in the majority of patients.

In both UNCOVER-2 and -3, safety profiles were comparable in placebo non-responders and etanercept non-responders after switching to ixekizumab.

1 Introduction

There are several emerging biologic therapies for the treatment of psoriasis, providing patients with more options for the management of this chronic and at times debilitating disease [1–4]. Availability of new agents raises the question of how prior treatment might affect future therapies. Patients who do not respond optimally to one biologic therapy may benefit from switching to a biologic that acts through a different mechanism. Indeed, in the ACCEPT trial, psoriasis area and severity index (PASI) response rates of patients who were non-responders to etanercept during the induction period improved after switching to ustekinumab, even though response rates after 12 weeks were lower among these patients compared with those given ustekinumab during the induction period [5]. On the other hand, a Danish observational study found no association between prior treatment with tumor necrosis factor alpha (TNF- α) inhibitors and response to subsequent therapy with ustekinumab [6].

Ixekizumab is a high affinity monoclonal antibody that selectively targets interleukin (IL)-17A. This drug has previously been reported to have rapid and lasting efficacy in the treatment of moderate-to-severe plaque psoriasis in three phase III clinical trials (UNCOVER-1, -2, and -3) [1, 2]. Two of these trials (UNCOVER-2 and -3) included an etanercept treatment arm during the induction period (Weeks 0–12). In this post-hoc subanalysis of UNCOVER-2 and -3 trials, we examined the safety and efficacy of ixekizumab in patients switched to ixekizumab every 4 weeks (Q4W) following non-response (NR) to 12 weeks of treatment with etanercept or placebo. For completeness of the analysis in trials with differing study designs, we looked at two different criteria for defining non-responders:

failure to reach the static physician global assessment (sPGA) 0/1 (UNCOVER-2) or failure to reach 75% improvement in PASI (PASI 75; UNCOVER-3).

2 Methods

2.1 Patients

An investigational review board at each site approved study protocols and informed consent forms, and all patients signed informed consent prior to undergoing study-related procedures. UNCOVER-2 (NCT01597245) was registered on May 10, 2012 and UNCOVER-3 (NCT01646177) was registered on July 18, 2012 with ClinicalTrials.gov. Complete patient eligibility criteria for the UNCOVER-2 and -3 trials have been previously described [1]. Briefly, patients aged 18 years or older were eligible with a confirmed diagnosis of chronic plaque psoriasis at least 6 months prior to baseline (randomization), at least a moderate disease severity as measured by clinician-rated measure of sPGA score ≥ 3 , at least 10% body surface area (BSA) involvement, and PASI score ≥ 12 at both screening and baseline visits. Patients with prior exposure to etanercept were excluded from these studies.

2.2 Study Design and Treatment Regimens

2.2.1 Induction Period (UNCOVER-2 and -3): Weeks 0–12

During the 12-week placebo- and active-controlled period in each of these phase III trials, patients were randomized at a 2:2:2:1 ratio stratified by center to one of the following treatment groups: ixekizumab 80 mg every 2 weeks (Q2W) or Q4W following a starting dose of 160 mg, etanercept 50 mg twice weekly, or placebo.

2.2.2 Weeks 12–60 (UNCOVER-2)

In UNCOVER-2, failure to meet sPGA 0/1 at Week 12 was the pre-specified criterion defining non-response to treatment. All sPGA 0/1 non-responders, regardless of induction treatment group, were switched to ixekizumab 80 mg Q4W. Therefore, UNCOVER-2 data support the analysis of patients who were non-responders to etanercept based on sPGA definition. All patients who received etanercept in the induction period and did not achieve sPGA 0/1 at Week 12 underwent a 4-week washout period where placebo injections were given at Week 12, and patients were started on ixekizumab 80 mg Q4W at Week 16. All patients who received placebo in the induction period who did not achieve sPGA 0/1 at Week 12 were given ixekizumab

160 mg at Week 12, and ixekizumab 80 mg Q4W starting at Week 16.

2.2.3 Weeks 12–60 (UNCOVER-3)

In UNCOVER-3, all patients, regardless of induction treatment group and sPGA response at Week 12, were switched to ixekizumab 80 mg Q4W. Therefore, UNCOVER-3 data support the analysis of patients who were non-responders to etanercept based on PASI 75 definition. All patients who received etanercept in the induction period (regardless of response at Week 12) underwent a 4-week washout period where placebo injections were given at Week 12, followed by ixekizumab Q4W starting at Week 16. All patients who received placebo in the induction period were given ixekizumab 160 mg at Week 12 and ixekizumab 80 mg Q4W starting at Week 16. Safety data for UNCOVER-3 is based on the data reported at the time of the Week 60 interim database lock; therefore, some events occurred beyond 60 weeks.

2.3 Statistical Analyses

For the analyses described here, we looked at two definitions of NR. In UNCOVER-2, the pre-specified definition of NR based on FDA guidance was failure to meet sPGA 0/1 at Week 12. In a post-hoc subanalysis of UNCOVER-3, NR was defined as failure to achieve PASI 75 by Week 12.

Non-responder imputation (NRI) was used for categorical variables for missing data. Change from baseline PASI and percent improvement in PASI used last observation carried forward (LOCF), and treatment comparisons in the induction period for these variables were done using an analysis of covariance model, including treatment, pooled center, and baseline (Week 0) PASI value in the model.

Safety analyses were conducted on all patients who received at least one dose of assigned study treatment during the study period. An adverse event is considered a treatment-emergent adverse event if it first occurs or worsens following the start of treatment during a study period. Incidence rates (IRs) were based on the number of events per 100 person-years of exposure, with entire time on treatment considered the exposure time rather than time until the first event. If a patient had multiple events, all events were counted.

3 Results

In both UNCOVER-2 and -3, baseline characteristics of etanercept responders were generally comparable to those of non-responders, except for weight, which was

numerically higher in the non-responder (as defined by either sPGA 0/1 or PASI 75) versus responder groups (Table 1).

At Week 12 in UNCOVER-2, 64% of etanercept-treated patients, 27.1% of ixekizumab Q4W-treated patients, and 16.8% of ixekizumab Q2W-treated patients were sPGA 0/1 non-responders. Among the etanercept-treated patients who did not reach sPGA 0/1 at Week 12 and switched to ixekizumab Q4W ($n = 200$), 73.0% had an sPGA 0/1, 83.5% had a PASI 75, 57.0% had a PASI 90, and 22.0% had a PASI 100 after 12 weeks of treatment with ixekizumab Q4W (Week 28) (Fig. 1a). After 44 weeks (Week 60) of treatment with ixekizumab Q4W, among induction-period sPGA 0/1 non-responders to etanercept, 71.0% achieved an sPGA 0/1, 82.5% achieved a PASI 75, 68.5% achieved a PASI 90, and 43.5% achieved a PASI 100 (Fig. 1a; Table 2). sPGA 0/1, PASI 75, 90, and 100 responses for placebo-treated patients who were sPGA 0/1 non-responders at Week 12 and treated with ixekizumab from Weeks 12–60 (48 weeks of treatment with ixekizumab Q4W) are presented in Fig. 1b and Table 2. At Week 60, the percent improvement in PASI and percentages of patients achieving nail psoriasis area and severity index (NAPSI) and psoriasis scalp severity index (PSSI) scores of 0 were also similarly high in non-responders to both placebo and etanercept after switching to ixekizumab (Table 2).

At Week 12 in UNCOVER-3, 46.6% of etanercept-treated patients, 15.8% of ixekizumab Q4W-treated patients, and 12.7% of ixekizumab Q2W-treated patients were PASI 75 non-responders. Among the etanercept-treated patients who were PASI 75 non-responders at Week 12 and switched to ixekizumab Q4W ($n = 165$), 78.2% had a PASI 75, 58.8% had a PASI 90, and 27.3% had a PASI 100 after 12 weeks of treatment with ixekizumab Q4W (Week 28) (Fig. 2a). As described previously with UNCOVER-2, long-term efficacy was also observed in UNCOVER-3, with 77.6% of etanercept PASI 75 non-responders achieving a PASI 75, 67.9% achieving a PASI 90, and 43.0% achieving a PASI 100 after 44 weeks (Week 60) of treatment with ixekizumab Q4W (Fig. 2a; Table 2). PASI 75, 90, and 100 responses for placebo-treated patients who were PASI 75 non-responders at Week 12 and treated with ixekizumab from Weeks 12 to 60 (48 weeks of treatment with ixekizumab Q4W) are also presented in Fig. 2b and Table 2. As in UNCOVER-2, in UNCOVER-3 the percent improvement in PASI, and percentages of patients achieving NAPSI and PSSI scores of 0 for patients who switched to ixekizumab after non-response to etanercept or placebo were similarly high at Week 60 (Table 2).

Overall, safety profiles, represented as incidence rates of treatment-emergent adverse events (TEAEs) of any severity, serious adverse events (AEs), or AEs leading to

Table 1 Baseline characteristics of responders and nonresponders to etanercept at Week 12

	UNCOVER-2		UNCOVER-3	
	sPGA 0/1 responders (N = 132)	sPGA 0/1 NR (N = 200)	PASI 75 responders (N = 204)	PASI 75 NR (N = 165)
Age, years	42.9 (12.6)	46.7 (12.6)	45.3 (14.0)	46.5 (13.8)
Male, n (%)	89 (67.4)	126 (63.0)	139 (68.1)	121 (73.3)
Weight, kg	87.6 (17.6)	96.7 (24.1)	86.0 (20.7)	100.0 (25.7)
Psoriasis duration, years	19.4 (12.4)	18.6 (12.3)	17.6 (11.4)	18.9 (12.5)
Percentage of BSA involved	26.7 (14.9)	23.4 (14.8)	28.4 (16.6)	28.2 (18.8)
sPGA	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)	3.6 (0.6)
PASI	19.1 (6.2)	18.7 (6.4)	20.6 (7.8)	20.9 (8.7)
PSSI	21.3 (16.5)	18.9 (14.3)	19.7 (13.6)	20.1 (13.2)
NAPSI	28.5 (18.7)	31.7 (21.5)	25.3 (21.2)	25.5 (18.5)

All data presented as mean (SD) unless otherwise stated

BSA body surface area, NAPSI nail psoriasis severity index, NR non-responder, PASI psoriasis area and severity index, PSSI psoriasis scalp severity index, SD standard deviation, sPGA static physician global assessment

Among patients who had at least one dose of ixekizumab or placebo in the Week 12-60 period of each study

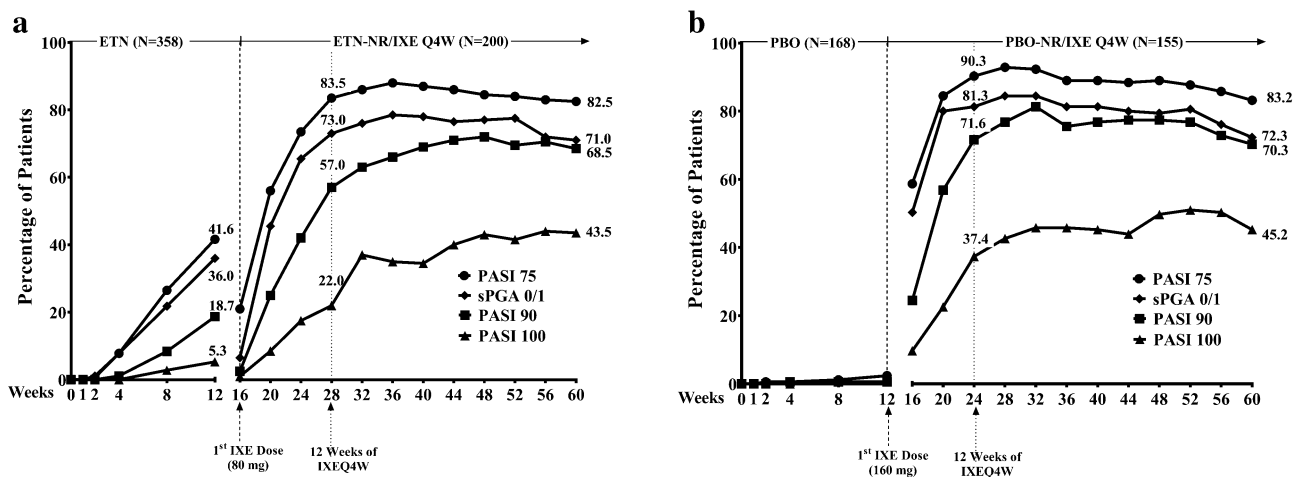


Fig. 1 UNCOVER-2: sPGA and PASI response rates through Week 60 in Week 12 sPGA 0/1 non-responders. sPGA 0/1, PASI 75, PASI 90, and PASI 100 response rates among patients in UNCOVER-2 who were switched to ixekizumab Q4W if they were Week 12 sPGA 0/1 non-responders to etanercept (a) or placebo (b). Response rates for all patients treated with etanercept (a) or placebo (b) during the first 12 weeks have been previously reported and are

provided for reference [1]. ETN etanercept, ETN-NR/IXEQ4W etanercept Weeks 0–12, placebo at Week 12, and 80 mg ixekizumab every 4 weeks for Weeks 16–60, NR sPGA 0/1 non-responder at Week 12, PASI psoriasis area and severity index, PBO placebo, PBO-NR/IXEQ4W placebo Weeks 0–12 and 80 mg ixekizumab every 4 weeks for Weeks 16–60 after a starting dose of 160 mg at Week 12, sPGA static physician global assessment

discontinuation in the two subgroups of non-responders to placebo or etanercept in UNCOVER-2 or -3 were generally comparable after switching to ixekizumab (Table 3). Furthermore, there were also no outstanding differences in incidence rates of adverse events of special interest, including injection-site reactions, infections, *Candida* infections, and inflammatory bowel disease in either subgroup in either trial after switching to ixekizumab (Table 3).

4 Discussion

In both trials, high percentages of patients who were sPGA 0/1 (UNCOVER-2) or PASI 75 (UNCOVER-3) etanercept non-responders during the induction period achieved sPGA 0/1, PASI 75, 90, and 100 after 12 weeks and maintained this response through 44 weeks following the switch to ixekizumab Q4W, demonstrating a potential long-term benefit in switching to ixekizumab following non-response

Table 2 Psoriasis outcomes after 12 and 60 weeks in each study

	Induction period, Week 12				Open-label ixekizumab treatment, Week 60			
	UNCOVER-2		UNCOVER-3		UNCOVER-2 (sPGA 0/1 NR)		UNCOVER-3 (PASI 75 NR)	
	PBO (N = 168)	ETN (N = 358)	PBO (N = 193)	ETN (N = 382)	PBO/ IXEQ4W (N = 155)	ETN/ IXEQ4W (N = 200)	PBO/ IXEQ4W (N = 169)	ETN/ IXEQ4W (N = 165)
sPGA 0/1 (NRI), n (%)	4 (2.4)	129 (36.0)	13 (6.7)	159 (41.6)	112 (72.3)	142 (71.0)	132 (78.1)	114 (69.1)
PASI 75 (NRI), n (%)	4 (2.4)	149 (41.6)	14 (7.3)	204 (53.4)	129 (83.2)	165 (82.5)	147 (87.0)	128 (77.6)
PASI 90 (NRI), n (%)	1 (0.6)	67 (18.7)	6 (3.1)	98 (25.7)	109 (70.3)	137 (68.5)	133 (78.7)	112 (67.9)
PASI 100 (NRI), n (%)	1 (0.6)	19 (5.3)	0	28 (7.3)	70 (45.2)	87 (43.5)	93 (55.0)	71 (43.0)
NAPSI = 0 (NRI), n (%) ^a	10 (8.8)	24 (10.5)	5 (4.3)	24 (10.2)	57 (53.3)	58 (45.0)	65 (60.7)	50 (49.5)
PSSI = 0 (NRI), n (%) ^b	11 (7.3)	144 (44.7)	16 (9.1)	178 (51.1)	103 (73.0)	130 (71.4)	130 (83.9)	111 (74.5)
Change from baseline PASI (LOCF) ^c	-0.9 (0.5)	-11.6 (0.3)	-3.1 (0.4)	-14.5 (0.3)	-19.1 (8.5)	-16.4 (8.1)	-19.6 (8.9)	-18.2 (9.1)
% Improvement from baseline PASI (LOCF) ^c	6.8 (2.1)	58.9 (1.5)	14.1 (1.8)	68.8 (1.3)	92.5 (17.2)	88.2 (37.9)	93.0 (17.1)	87.2 (23.4)

ETN etanercept, ETN-NR/IXEQ4W etanercept Weeks 0–12, placebo at Week 12, and ixekizumab every 4 weeks for Weeks 16–60, LOCF last observation carried forward, NAPSI nail psoriasis severity index, NR non-responder, NRI non-responder imputation, PASI psoriasis area and severity index, PBO placebo, PBO-NR/IXEQ4W placebo Weeks 0-12 and ixekizumab every 4 weeks for Weeks 16–60 after a starting dose of 160 mg at Week 12, PSSI psoriasis scalp severity index, sPGA static physician global assessment

^a Only patients with NAPSI >0 at baseline were included in this analysis

^b Only patients with PSSI >0 at baseline were included in this analysis

^c Week 12 results are reported as least squares (LS) mean (standard error) and Week 60 results are reported as LS mean (standard deviation)

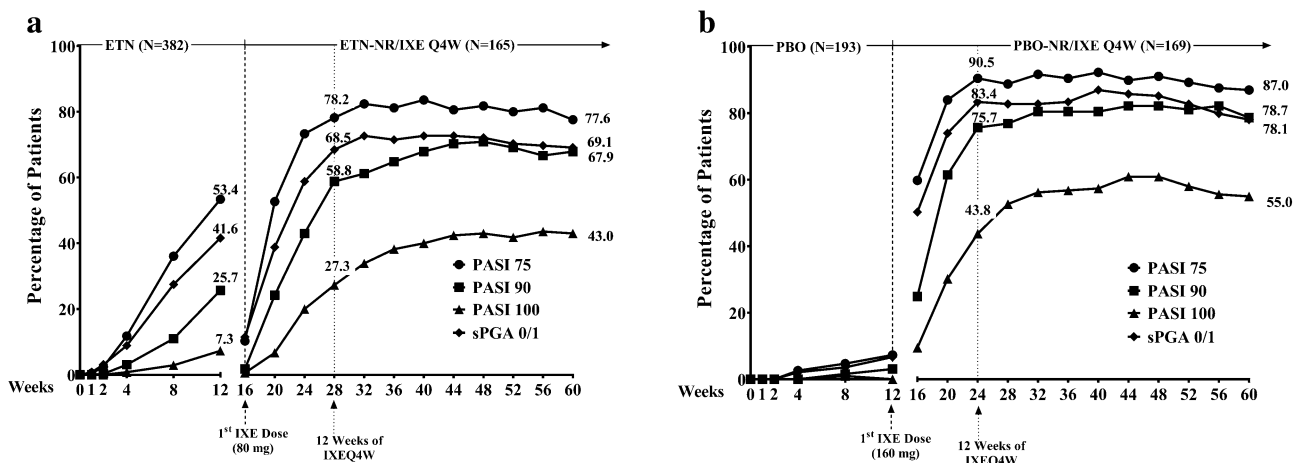


Fig. 2 UNCOVER-3: sPGA and PASI response rates through Week 60 in Week 12 PASI 75 non-responders. sPGA 0/1, PASI 75, PASI 90, and PASI 100 response rates among patients in UNCOVER-3 who were switched to ixekizumab 4W if they were Week 12 PASI 75 non-responders to etanercept (a) or placebo (b). Response rates for all patients treated with etanercept (a) or placebo (b) during the first 12 weeks have been previously reported and are

provided for reference [1]. ETN etanercept, ETN-NR/IXEQ4W etanercept Weeks 0–12, placebo at Week 12, and 80 mg ixekizumab every 4 weeks for Weeks 16–60, NR PASI 75 non-responder at Week 12, PASI psoriasis area and severity index, PBO placebo, PBO-NR/IXEQ4W placebo Weeks 0-12 and 80 mg ixekizumab every 4 weeks for Weeks 16–60 after a starting dose of 160 mg at Week 12, sPGA static physician global assessment

Table 3 Adverse events Weeks 12–60^a of UNCOVER-2 and -3

	UNCOVER-2 (sPGA 0/1 NR)		UNCOVER-3 (PASI 75 NR)	
	PBO/IXEQ4W (N = 155) (PY = 134.3) n (IR)	ETN/IXEQ4W (N = 200) (PY = 174.4) n (IR)	PBO/IXEQ4W (N = 169) (PY = 233.0) n (IR)	ETN/IXEQ4W (N = 165) (PY = 217.0) n (IR)
TEAE	125 (93.0)	158 (90.6)	137 (58.8)	125 (57.6)
Mild	42 (31.3)	56 (32.1)	50 (21.5)	40 (18.4)
Moderate	65 (48.4)	85 (48.8)	68 (29.2)	71 (32.7)
Severe	18 (13.4)	17 (9.8)	19 (8.2)	14 (6.5)
SAE	12 (8.9)	9 (5.2)	20 (8.6)	13 (6.0)
AE leading to discontinuation	8 (6.0)	8 (4.6)	8 (3.4)	7 (3.2)
Injection site reactions	17 (12.7)	24 (13.8)	16 (6.9)	11 (5.1)
Infections	86 (64.0)	111 (63.7)	93 (39.9)	85 (39.2)
<i>Candida</i>	1 (0.7)	3 (1.7)	0	0
Crohn's disease	1 (0.7)	0	1 (0.4)	0
Ulcerative colitis	0	0	0	0

AE adverse event, ETN etanercept, ETN-NR/IXEQ4W etanercept Weeks 0–12, placebo at Week 12, and ixekizumab every 4 weeks for Weeks 16–60, IR incidence rate/100 patient years, NR non-responder, PBO placebo, PBO-NR/IXEQ4W placebo Weeks 0–12 and ixekizumab every 4 weeks for Weeks 16–60 after a starting dose of 160 mg at Week 12, PY patient years, SAE serious AE, TEAE treatment-emergent AE

^a Safety data for UNCOVER-3 are based on the data reported at the time of the Week 60 interim database lock; therefore, some events occurred beyond 60 weeks

to etanercept. Responses to etanercept did not appear to be impacted substantially by differences in baseline characteristics, with the potential exception of weight. This is generally consistent with previously established findings, where greater percentages of patients in lower weight (or body mass index [BMI]) categories had higher responses than patients in higher weight (or BMI) categories, although weight category cut points varied by study [7, 8].

There is currently variability in guidance regarding what defines a non-response that warrants change in treatment. sPGA 0/1 or PASI 75 has frequently been the treatment goal in phase III clinical trials; however, non-response has often been defined as failure to achieve PASI 50. Furthermore, current guidelines by the European Consensus Program [9] recommend remaining on the same treatment regimen unless the following conditions apply: reduction in PASI of <50%, or a reduction in PASI of at least 50% and <75% combined with a DLQI (Dermatology Life Quality Index) score >5. The results of the present analysis suggest that PASI 75 or sPGA 0/1 non-responders may indeed benefit from switching, although neither of these trials had a comparator group that continued receiving etanercept to determine the full level of benefit from switching over time.

Of note, it has been recommended that clinicians should wait four times the terminal biologic half-life to ensure that the first biologic has been cleared from the body before starting a second biologic [10]. Interestingly, a recent consensus report from the Transitioning Therapies

program, created by dermatologists from 33 countries, suggests using a washout period when patients are switching biologic therapies for safety concerns but not when switching due to lack of efficacy [11]. In UNCOVER-2 and -3, five times the terminal half-life was deemed appropriate for a drug under development. Hence, the response to ixekizumab without a washout in etanercept-treated patients was not assessed.

There are several limitations to these analyses. These studies were not designed to directly compare outcomes in etanercept non-responders versus placebo non-responders switched to ixekizumab Q4W. Additionally, while patients and investigators in UNCOVER-2 remained blinded through Week 60, patients and investigators in UNCOVER-3 were not blinded after the first 12 weeks of treatment, potentially resulting in higher responses after Week 12 in that trial. Another potential limitation is that some patients may require more than 12 weeks to achieve sPGA 0/1 or PASI 75 in response to etanercept; therefore, it is conceivable that with longer exposure to etanercept, some of the non-responders might have become responders. The ixekizumab dosing regimen currently approved in several markets for the treatment of moderate-to-severe plaque psoriasis includes a 160-mg starting dose at Week 0 followed by 12 weeks of 80 mg ixekizumab every 2 weeks [9]. It is possible that responses following the switch to ixekizumab may have been higher if this induction dosing regimen had been used in the etanercept non-responders at Week 16.

Like the results found in the present analyses, the ACCEPT study showed that many patients who were non-responders to etanercept experienced a PASI 75 response after switching to ustekinumab [5]. However, in contrast to the ACCEPT study, in both UNCOVER-2 and -3, patients who switched to ixekizumab Q4W after non-response to etanercept had similarly high responses (84 and 78% had a PASI 75; 57% and 59% had a PASI 90) as patients treated with ixekizumab Q4W as induction therapy (78 and 84% had a PASI 75; 60 and 65% had a PASI 90) following 12 weeks of treatment [1, 5]. This supports the notion that switching an etanercept non-responder to a biologic that inhibits IL-17A may be a clinically beneficial strategy. Of note, there are currently no guideline recommendations regarding optimal sequence of therapies for patients with psoriasis and whether patients would benefit from a faster/higher level of clearance at early stages of treatment.

5 Conclusions

Patients with moderate-to-severe plaque psoriasis who were non-responders to etanercept therapy after 12 weeks, as defined by different criteria (i.e., sPGA 0/1 and PASI 75), had high levels of clinical responses after being switched to 80 mg ixekizumab Q4W. This response was attained quickly and maintained through Week 60 in two phase III trials, with similar safety profiles for both placebo non-responders and etanercept non-responders who switched to ixekizumab.

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Compliance with Ethical Standards

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Ethics Approval and Consent to Participate This report contains post hoc analyses of previously published studies (Griffiths CE, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet*. 2015;386:541-51 and Gordon KB, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med*. 2016;375:345-56). Study protocols and informed consent forms for NCT01597245 and NCT01646177 were approved by an investigational review board at each site, all patients signed informed consent before undergoing study-related procedures, and the trials were conducted in accordance with the ethical principles of the Declaration of Helsinki.

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