Journal of Dermatological Treatment

ISSN: 0954-6634 (Print) 1471-1753 (Online) Journal homepage: https://www.tandfonline.com/loi/ijdt20

A subset analysis of efficacy and safety outcomes from phase 3 clinical studies of ixekizumab for the treatment of patients with severe plaque psoriasis

Lynda Spelman, Diana Rubel, Alan Brnabic, Nicole Burkhardt, Elisabeth Riedl & Peter Foley

To cite this article: Lynda Spelman, Diana Rubel, Alan Brnabic, Nicole Burkhardt, Elisabeth Riedl & Peter Foley (2020): A subset analysis of efficacy and safety outcomes from phase 3 clinical studies of ixekizumab for the treatment of patients with severe plaque psoriasis, Journal of Dermatological Treatment, DOI: 10.1080/09546634.2020.1752888

To link to this article: https://doi.org/10.1080/09546634.2020.1752888

JOURNAL OF DERMATOLOGICAL TREATMENT
https://doi.org/10.1080/09546634.2020.1752888

Taylor & Francis
Taylor & Francis Group

ARTICLE

OPEN ACCESS Check for updates

A subset analysis of efficacy and safety outcomes from phase 3 clinical studies of ixekizumab for the treatment of patients with severe plaque psoriasis

Lynda Spelman[a], Diana Rubel[b], Alan Brnabic[c], Nicole Burkhardt[c]*, Elisabeth Riedl[d,e] and Peter Foley[f,g]

[a]Veracity Clinical Research, Brisbane, Australia; [b]Woden Dermatology, ACT, Australia; [c]Eli Lilly Australia Pty Limited, West Ryde, Australia; [d]Eli Lilly Ges.m.b.H, Vienna, Austria; [e]Department of Dermatology, Medical University of Vienna, Vienna, Austria; [f]Skin Health Institute, Carlton, Australia; [g]The University of Melbourne, St Vincent's Hospital Melbourne, Fitzroy, Australia

ABSTRACT

Background: Factors beyond the Psoriasis Area and Severity Index (PASI) contribute to disease severity in psoriasis and potentially affect treatment responses.

Objective: This subset analysis of data from two phase 3 clinical studies assessed baseline parameters in patients with different degrees of psoriasis severity in order to determine treatment responses to ixekizumab and safety outcomes.

Methods: This study used integrated data from the UNCOVER-2 and -3 trials involving 2709 patients with chronic plaque psoriasis to assess the efficacy and safety of ixekizumab in three subgroups of patients, defined by PASI $>$ 15 (group 1), PASI $>$ 15 and history of $\geq$3 non-biologic systemic therapies (group 2), or PASI $=$ 12-15 (group 3).

Results: In groups 1 and 2, additional baseline features were identified that could influence treatment responses, including age at disease onset, Dermatology Life Quality Index, and work productivity. Irrespective of subgroup, ixekizumab demonstrated high PASI responses at weeks 12 and 60, which were evident as early as week 2. Adverse events did not differ across subgroups.

Conclusion: Our data support the efficacy, early onset of action, and maintained response of ixekizumab as observed in previous trials, and highlight the complexity of comprehensively defining disease severity in psoriasis.

ARTICLE HISTORY
Received 16 March 2020
Accepted 1 April 2020

KEYWORDS
IL-17; PASI; ixekizumab; phase 3; psoriasis; UNCOVER

Introduction

Ixekizumab is a high-affinity monoclonal antibody that selectively targets interleukin-17A (IL-17A), a member of the proinflammatory IL-17 cytokine family critically involved in the pathogenesis of psoriasis and other immune-mediated diseases [1].

In clinical studies, ixekizumab has been shown to be effective in patients with moderate-to-severe chronic plaque psoriasis, demonstrating rapid clinical improvements and a favorable safety profile when compared with placebo [2–5], and in head-to-head studies versus etanercept [2], methotrexate, fumaric acid esters [6], the IL-12/23 inhibitor ustekinumab [7], or the IL-23 inhibitor guselkumab [8]. In phase 3 randomized studies, ixekizumab has been shown to be effective through 60 [9], 108 [10], 156 [11], and 204 [12] weeks of treatment.

Despite a growing understanding of the pathophysiology, impact, and nature of psoriasis, a comprehensive definition of disease severity for chronic plaque psoriasis is still missing. Even in the setting of clinical studies with stringent patient inclusion and exclusion criteria, study populations are heterogeneous, with skin disease severity scores ranging from moderate to severe using unified definitions of cutoff values [13]. On the other hand, disease severity is the basis for treatment decisions, and specific parameters have been established to determine the eligibility of patients for reimbursement of biologic treatments. In this context, disease severity is usually defined by specific Psoriasis Area and Severity Index (PASI) score cutoffs [14]. Evaluating the number of previous systemic therapies might be another parameter to assess disease severity in patients with chronic plaque psoriasis. Moreover, patients with severe psoriasis might not only differ in skin disease scores from those with moderate disease but also differ in other respects, including disease duration, onset, and response rates to therapies [15,16].

The objective of this subset analysis of data from two phase 3 clinical studies was to assess baseline parameters in patients with different degrees of psoriasis severity and to determine treatment responses to ixekizumab and safety outcomes in these subpopulations.

Materials and methods

Study design

The study design and patient demographics for UNCOVER-2 (NCT01597245) and -3 (NCT01646177) have been published

CONTACT PETER Foley, Associate Professor pfoley@skinhealthinstitute.org.au Skin Health Institute, 80 Drummond Street, Carlton, Victoria 3053, Australia
*Former employee, Eli Lilly Australia Pty Limited, West Ryde, Australia.

Supplemental data for this article can be accessed here.

previously [2,5]. Briefly, these studies included adult patients with a confirmed diagnosis of chronic plaque psoriasis at least 6 months before baseline (randomization), at least a moderate disease severity defined by a static Physician's Global Assessment (sPGA) score ≥3 (range 0 [clear] to 5 [very severe]), a body surface area (BSA) involvement of ≥10%, and a PASI score ≥12. During the 12-week placebo- and active comparator-controlled period in each of these phase 3 trials, patients were randomized to ixekizumab with a starting dose of 160 mg at week 0, followed by 80 mg every 2 weeks (Q2W) or every 4 weeks (Q4W), etanercept 50 mg twice weekly, or placebo.

In UNCOVER-3, all patients entered the long-term extension period at week 12, and received ixekizumab 80 mg Q4W from week 16 onwards. To assess long-term outcomes for this *post hoc* analysis, the intent-to-treat population receiving ixekizumab 80 mg Q2W until week 12 followed by ixekizumab 80 mg Q4W from weeks 16 to 60 was analyzed.

Patient and subgroup analysis

Patient subsets for this *post hoc* analysis were defined based on baseline PASI scores (PASI = 12–15 and PASI > 15), and baseline information about prior inadequate response, intolerance, or contraindication to ≥3 conventional systemic therapies for psoriasis (e.g. methotrexate, ciclosporin, retinoids) or psoralen and ultraviolet A and ultraviolet B phototherapy. Based on these parameters, three subgroups were defined: patients with a baseline PASI > 15 (group 1), patients with a baseline PASI > 15 and a history of ≥3 non-biologic systemic therapies (group 2), and patients with a baseline PASI = 12-15 (group 3).

Efficacy at week 12 and week 60 was evaluated by PASI response rates, defined as the proportion of patients achieving a 75%, 90%, or 100% improvement in PASI (PASI 75/90/100), and by evaluating the reduction in Dermatology Life Quality Index (DLQI) scores. Safety assessment included the number of patients who experienced treatment-emergent adverse events (TEAEs) or discontinued from the study because of a TEAE.

Statistical analysis

Detailed statistical methods have been published previously [2,5]. Baseline characteristics between the groups were compared using the Cochran–Mantel–Haenszel test stratified by study for categorical data and analysis of variance for continuous data with treatment and study as independent factors. Nonresponder imputation (NRI) was used for PASI, sPGA, and DLQI binary outcome measures. Cochran–Mantel–Haenszel test stratified by study was also used to compare the three groups for NRI response rates at weeks 12 and 60. Pairwise *p*-values are presented for within-group comparisons.

Cumulative benefit was determined by the total area under the curve (AUC) of the percentage of responders over 12 and 60 weeks for PASI 75, 90, and 100. The total AUC was calculated using the 'trapezoidal rule,' with time points in weeks as the *x*-axis and PASI response rates in percent as the y-axis, according to the methods presented by Armstrong et al. [17]. The percent cumulative benefit achieved for each therapy and dose was calculated as the total AUC/maximum AUC (1200 for 12 weeks and 6000 for 60 weeks) and then normalized to 0–100%.

Safety analyses were conducted on all patients who received at least one dose of the assigned study treatment during the study period. An adverse event (AE) was considered a TEAE if it first occurred or worsened after the start of treatment during a study period.

Results

Baseline patient characteristics

In total, 2709 patients were randomized in UNCOVER-2 and -3 to one of the following treatment arms: ixekizumab 80 mg Q2W ($n = 778$), ixekizumab 80 mg Q4W ($n = 771$), etanercept 50 mg weekly ($n = 789$), or placebo ($n = 371$) (Figure S1). Analysis of the baseline data according to disease severity revealed significant differences beyond PASI value cutoffs and prior treatment history. There were 1855 patients in group 1 (baseline PASI > 15), 139 patients in group 2 (baseline PASI > 15 and a history of ≥3 non-biologic systemic therapies), and 715 patients in group 3 (baseline PASI = 12–15). The proportion of male patients was significantly higher in groups 1 (70.0%; 1298/1855) and 2 (71.9%; 100/139) compared to patients in group 3 (61.7%; 441/715) ($p < 0.001$) (Table 1). The percentage of the patients who were overweight, obese, or extremely obese were similar across the groups. On an average, the age of onset was significantly different between the 3 groups ($p = 0.035$, overall). Patients in group 2 had longer mean disease duration ($p \leq 0.005$) compared to other groups.

In group 3, patients had significantly ($p < 0.001$) lower baseline sPGA score of 4 (severe) or 5 (very severe), and significantly lower ($p < 0.001$) mean BSA values compared to groups 1 and 2 (Table 1). In addition, compared to group 3, a significantly higher proportion of patients in group 2 suffered from psoriasis in difficult-to-treat areas, including the face (44.6% versus 36.7%; $p = 0.022$), palms and soles (37.4% versus 22.0%; $p < 0.001$), and nails (69.1% versus 56.6%; $p = 0.006$). Significantly more patients in group 2 had a diagnosis of psoriatic arthritis (31.7% versus 18.9%; $p < 0.001$) at baseline compared to group 3 (Table 1).

Patient-reported outcomes

In line with the higher clinical disease scores, mean [SD] DLQI scores were higher in group 2 (13.5 [7.2]) compared to groups 1 (12.7 [7.1]; $p = 0.181$) and 3 (10.8 [6.3]; $p < 0.001$). In groups 1 and 2, a significantly lower proportion of patients reported part-time employment compared to group 3 (group 1: 11.7%; group 2: 7.2%; group 3: 16.1%); however, fulltime employment was similar across the groups (approximately 60%). Overall, the Work Productivity and Activity Impairment (WPAI) score and subscores for work productivity loss, presenteeism, and activity impairment were higher in group 2 compared to the other groups (Table 1).

Previous therapies

Non-biologic systemic therapies were the most frequently reported previous treatments with significant differences between the three groups. Almost twice as many patients in group 2 and a higher proportion of patients in group 1 reported previous use of non-biologic therapies (group 2: 66.2%; group 1: 43.2%) or phototherapy (group 2: 79.1%; group 1: 43.8%) compared to group 3 (35.5% and 39.0%, respectively; $p < 0.001$). In group 2, only one patient had a history of exclusive use of biologics (0.7%; Table 2).

Table 1. Baseline characteristics (total intention-to-treat population) by Psoriasis Area and Severity Index (PASI) categories.

	Group 1 ($N = 1855$)	Group 2 ($N = 139$)	Group 3 ($N = 715$)	p value[a](overall)
Demographic characteristics				
Age (years)[b]	45.1 (13.0)	45.9 (12.5)	46.0 (13.2)	0.273
Gender (male)[c]	1298 (70.0)	100 (71.9)	441 (61.7)	<0.001
BMI (kg/m^2)[b]	30.8 (7.2)	29.7 (6.8)	30.1 (6.9)	0.040
Clinical characteristics				
Mean age at psoriasis onset (years)[b]	27.4 (14.1)	24.2 (12.6)	27.4 (14.9)	0.035
Age at psoriasis onset <40 (years)[c]	1465 (79.0)	121(87.1)	558 (78.4)	0.062
Duration of psoriasis (years)[b]	18.1 (12.0)	22.2 (11.2)	19.0 (13.1)	<0.001
Mean sPGA[b]	3.7 (0.6)	3.7 (0.6)	3.2 (0.4)	<0.001
Patients with sPGA = 3[c]	771 (41.6)	57 (41.0)	540 (75.8)	<0.001
Patients with sPGA = 4[c]	954 (51.4)	69 (49.6)	168 (23.6)	<0.001
Patients with sPGA = 5[c]	130 (7.0)	13 (9.4)	4 (0.6)	<0.001
Affected BSA[b]	31.4 (17.6)	33.1 (18.3)	16.1 (6.6)	<0.001
Nail psoriasis[c]	1174 (63.3)	96 (69.1)	405 (56.6)	0.001
Palmoplantar psoriasis[c]	531 (28.6)	52 (37.4)	157 (22.0)	<0.001
Facial psoriasis[c]	872 (47.1)	62 (44.6)	261 (36.7)	<0.001
Scalp psoriasis[c]	1698 (91.5)	124 (89.2)	629 (88.0)	0.020
Psoriatic arthritis[c]	427 (23.0)	44 (31.7)	135 (18.9)	0.002
PSSI score[b]	21.1 (14.8)	21.3 (15.0)	16.5 (12.8)	<0.001
Patient-reported outcomes				
DLQI[b]	12.7 (7.1)	13.5 (7.2)	10.8 (6.3)	<0.001
Part-time employment status[c]	214 (11.7)	10 (7.2)	113 (16.1)	0.011[d]
Full-time employment status[c]	1074 (58.9)	83 (60.1)	415 (58.9)	0.011[d]
WPAI-PSO				
WPAI-PSO presenteeism score[b]	24.3 (26.6)	28.6 (31.5)	19.3 (23.1)	<0.001
WPAI-PSO absenteeism score[b]	5.4 (17.8)	9.7 (21.7)	2.2 (10.7)	<0.001
WPAI-PSO work productivity loss score[b]	26.7 (28.7)	30.9 (32.9)	20.2 (23.9)	<0.001
WPAI-PSO activity impairment score[b]	33.1 (30.2)	36.0 (31.1)	24.8 (25.2)	<0.001

[a]p value is based on Cochran–Mantel–Haenszel test stratified by study for categorical data and analysis of variance for continuous data with treatment and study as independent factors.
[b]Data are mean (SD) based on the number of patients with non-missing values.
[c]Data are number of patients and percentages in the specified category. Calculations are based on the number of patients with non-missing values.
[d]p-value is reflected from employment status (full-time, part-time, unemployed due to study disease disability and other).
BMI: body mass index; BSA: body surface area; DLQI: Dermatology Life Quality Index; N: number of patients in the analysis population; PSSI: Psoriasis Scalp Severity Index; SD: standard deviation; sPGA: static Physician's Global Assessment; WPAI-PSO: Work Productivity and Activity Impairment-Psoriasis. Group 1: Baseline PASI > 15. Group 2: Baseline PASI > 15 and a history of ≥3 non-biologic systemic therapies. Group 3: Baseline PASI = 12–15.

Table 2. Previous systemic therapies (intent-to-treat population) by subgroup[a].

	Group 1 ($N = 1855$)	Group 2 ($N = 139$)	Group 3 ($N = 715$)	p-value (overall)[b]
Previous systemic therapy				<0.001
Currently not used/never used	696 (37.5)	6 (4.3)[c]	322 (45.0)	
Non-biologic only	801 (43.2)	92 (66.2)	254 (35.5)	
Biologic only	132 (7.1)	1 (0.7)	67 (9.4)	
Biologic and non-biologic	226 (12.2)	40 (28.8)	72 (10.1)	
Previous phototherapy (ever used)	813 (43.8)	110 (79.1)	279 (39.0)	<0.001

[a]Data are number of patients in the specified category (%).
[b]p-value is based on Cochran–Mantel–Haenszel test stratified by study.
[c]Patients were excluded from the study if they received non-biologic systemic therapy: inadequate response to, intolerance to, or contraindication to conventional therapy <3 therapies or ≥3 therapies within 4 weeks prior to baseline.
[d]p-value is reflected from previous phototherapy (never used and ever used).
N: number of patients in the analysis population; PASI: Psoriasis Area and Severity Index.
Group 1: Baseline PASI > 15. Group 2: Baseline PASI > 15 and a history of ≥3 non-biologic systemic therapies. Group 3: Baseline PASI = 12–15.

PASI responses

The integrated analysis of UNCOVER-2 and -3 studies demonstrated that patients treated with ixekizumab achieved high PASI 75, 90, and 100 response rates at week 12 (Table 3). The UNCOVER-3 analysis confirms that this effect was independent of the baseline disease severity and was evident as early as week 2, continuously increased up to week 12, and continued with high levels of clinical response rates up to week 60 in patients receiving ixekizumab 80 mg Q4W during the long-term extension period (Figure 1(a–c)).

The percentage cumulative benefit (AUC) of the PASI responder rate was similar in each of the "severity" groups for both weeks 12 and 60. AUC increased as PASI score decreased, and AUC was relatively higher at week 60 compared to week 12 results. However, there was a slightly higher AUC for group 2 compared to groups 1 and 3 at week 12 for PASI 90 and PASI 100, but this may not be clinically relevant (Figure 2).

Regardless of the disease severity as defined by baseline PASI levels and treatment history, psoriasis patients treated with ixekizumab achieved higher PASI response rates and a higher proportion of patients achieved higher DLQI (0,1) responses than in the placebo and etanercept arms at week 12 (Table 3). Patients treated with etanercept achieved higher PASI response rates at week 12 compared to placebo (Table 3).

Table 3. Psoriasis Area and Severity Index (PASI) responses and quality of life response rates at week 12 (intent-to-treat population) by PASI categories at baseline[a] (integrated analysis of UNCOVER-2 and -3 studies).

	Group 1[b]			Group 2[b]			Group 3[b]		
	PBO $N = 258$	ETN $N = 527$	IXEQ2W $N = 531$	PBO $N = 10$	ETN $N = 49$	IXEQ2W $N = 42$	PBO $N = 103$	ETN $N = 213$	IXEQ2W $N = 205$
PASI 75	5.0 (2.4, 7.7)	50.1 (45.8, 54.4)**	88.3 (85.6, 91.1)**§§	0 (0, 0)	51.0 (37.0, 65.0)**	78.6 (66.2, 91.0)**§	4.9 (0.7, 9.0)	41.8 (35.2, 48.4)**	88.8 (84.5, 93.1)**§§
PASI 90	2.3 (0.5, 4.2)	24.7 (21.0, 28.3)**	69.9 (66.0, 73.8)**§§	0 (0, 0)	30.6 (17.7, 43.5)*	71.4 (57.8, 85.1)**§§	1.0 (0, 2.9)	16.4 (11.5, 21.4)**	67.8 (61.4, 74.2)**§§
PASI 100	0.4 (0, 1.1)	6.5 (4.4, 8.5)**	37.9 (33.7, 42.0)**§§	0 (0, 0)	4.1 (0, 9.6)	40.5 (25.6, 55.3)*§§	0 (0, 0)	6.1 (2.9, 9.3)*	42.0 (35.2, 48.7)**§§
DLQI (0,1)	7.8 (4.5, 11.0)	39.1 (34.9, 43.3)**	63.3 (59.2, 67.4)**§§	0 (0, 0)	32.7 (19.5, 45.8)*	47.6 (32.5, 62.7)**	4.9 (0.7, 9.0)	38.5 (32.0, 45.0)**	67.3 (60.9, 73.7)**§§

[a]Data are % (95% CI);
[b]Off label dose (IXEQ4W) results are not included.
*$p < 0.05$ versus PBO; **$p < 0.01$ versus PBO; §$p < 0.05$ versus ETN; §§$p < 0.01$ versus ETN.
CI: confidence interval; DLQI: Dermatology Life Quality Index; ETN: etanercept 50 mg twice weekly; IXEQ2W: ixekizumab 80 mg every 2 weeks (loading dose 160 mg); IXEQ4W: ixekizumab 80 mg every 4 weeks; *N*: number of patients in the specified category; PBO: placebo.
Group 1: Baseline PASI > 15. Group 2: Baseline PASI > 15 and a history of ≥3 non-biologic systemic therapies. Group 3: Baseline PASI = 12–15.

Safety data

During the placebo-controlled period, TEAEs occurred more frequently in the etanercept and ixekizumab treatment arms compared to placebo. Nasopharyngitis was the most common TEAE across treatment arms and across disease severity groups. No significant difference across the three disease severity groups was observed. Across the treatment arms or across the different disease severity groups, no differences in the frequency of serious AEs and AEs leading to discontinuation were recorded (Table 4).

Discussion

This study analyzed data from two randomized, phase 3 clinical studies in subsets of patients defined by PASI cutoff levels. Evaluation of characteristics beyond PASI included demographic information and patient-reported outcome measures in patients with moderate-to-severe psoriasis and identified previous systemic therapies as one differentiator of disease severity in patients with severe psoriasis (defined by a baseline PASI > 15).

As for other chronic diseases, failure to respond to treatment can have a cumulative effect on patients with a negative impact on the overall quality of life [18]. In this analysis, the number of previous therapies was applied as one factor to determine disease severity in patients with PASI > 15. Patients with a baseline PASI > 15 and a history of ≥3 non-biologic systemic therapies (group 2) had the highest rate of prior non-biologic systemic therapies but were also found to have the lowest rate of previous use of biologics. Overall, patients in this group were younger at disease onset and had a significantly longer disease duration. In contrast, the patients with PASI = 12–15 at baseline (group 3) contained the highest proportion of non-biologic systemic therapy-naïve patients. This group also had the highest rate of previous use of biologics. For tumor necrosis factor (TNF)-blocking biologics, failure of the first-line biologics has been associated with a decreased response to the second- and third-line TNF-blocking biologics in psoriasis and psoriatic arthritis [19]. This effect has not been observed with ixekizumab, irrespective of whether patients had an inadequate response or were intolerant to TNF inhibitors [20,21]. In line with this, PASI 75, 90, and 100 responses did not significantly differ between the three disease severity groups, with a fast onset and comparable high efficacy outcomes for ixekizumab at week 12 and maintenance of response until week 60. Ixekizumab treatment resulted in both high PASI response rates and DLQI (0,1) responses for patients in all three disease severity subgroups.

Patients with PASI > 15 (groups 1 and 2) also had significantly higher rates of sPGA 4 and 5, higher involvement of BSA, and higher DLQI values at baseline. In addition, in groups 1 and 2, significantly higher proportions of patients had facial psoriasis, palmoplantar psoriasis, nail psoriasis, and were affected by psoriatic arthritis. These data highlight that severity is not only a function of PASI, but it also has a broader implication, such as the involvement of difficult-to-treat areas and the presence of comorbidities such as psoriatic arthritis, the latter potentially leading to irreversible structural damage if left untreated [22]. This *post hoc* analysis supports a comparable safety profile of ixekizumab in patients with severe disease compared to the overall population. This finding is relevant considering that these patients could potentially be at higher risk for comorbidities linked to earlier disease onset and potential organ toxicities of multiple previous systemic therapies [23,24].

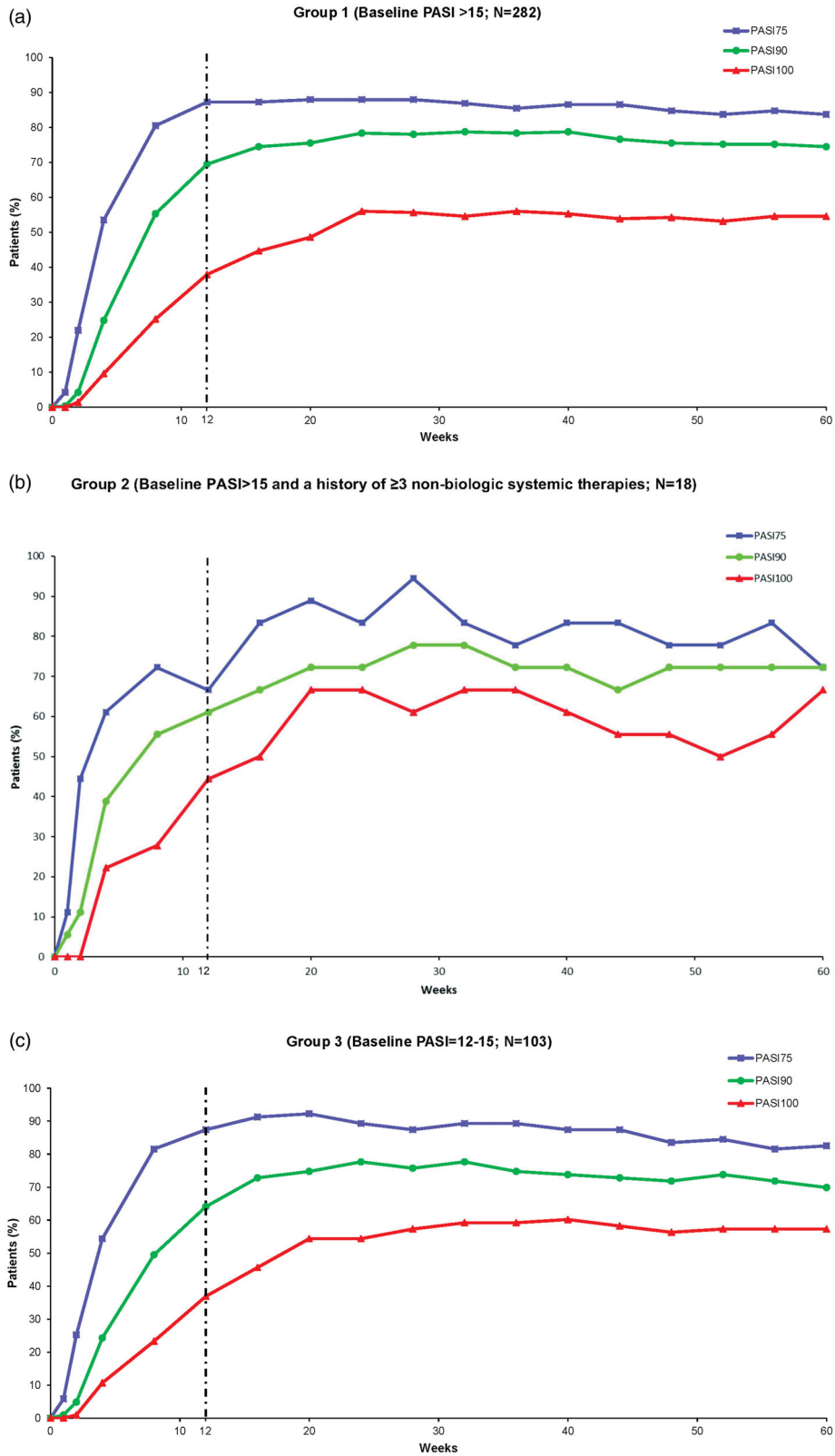

Figure 1. PASI 75, 90, and 100 response rates from week 0 (baseline) to week 60 (nonresponder imputation [NRI]; intent-to-treat population [ITT]; from UNCOVER-3 study). (a) Group 1: Baseline PASI $>$ 15 ($N = 282$). (b) Group 2: Baseline PASI $>$ 15 and a history of $\geq$3 non-biologic systemic therapies ($N = 18$). (c) Group 3: Baseline PASI $=$ 12–15 ($N = 103$).

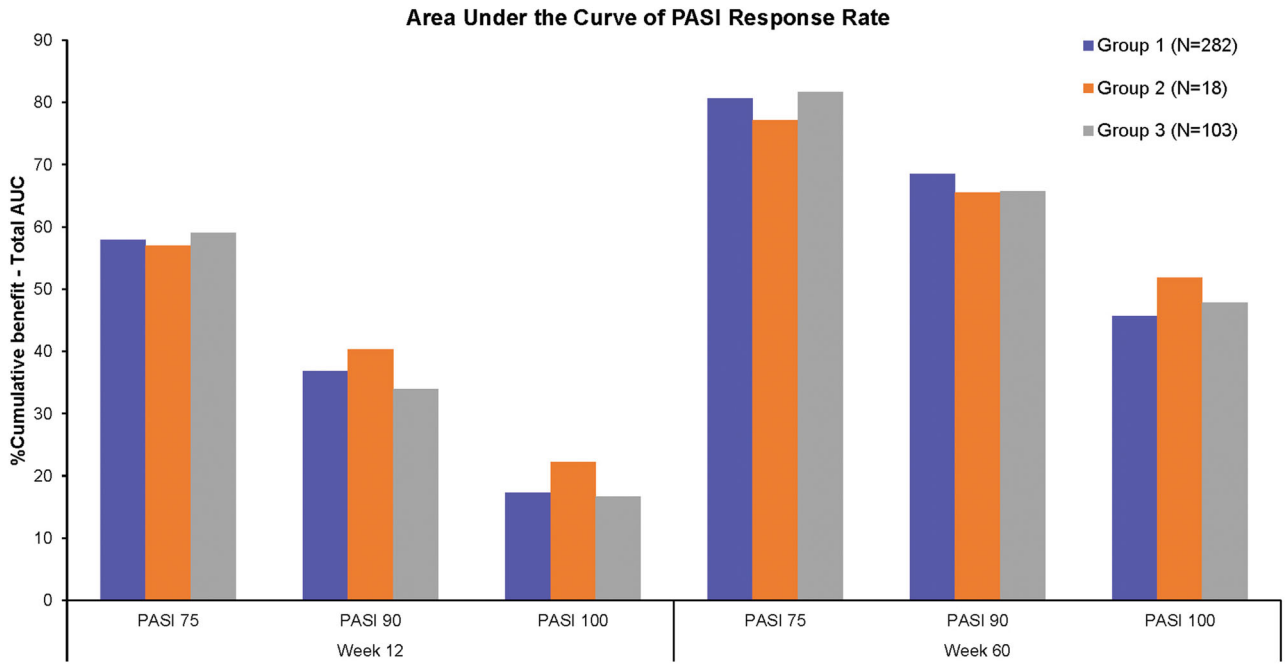

Figure 2. Percent cumulative benefit based on AUC of PASI 75, 90, and 100 response rates from week 0 (baseline) to weeks 12 and 60 (nonresponder imputation [NRI]; intent-to-treat population [ITT]; from UNCOVER-3 study). Group 1: Baseline PASI > 15 ($N = 282$). Group 2: Baseline PASI > 15 and a history of ≥3 non-biologic systemic therapies ($N = 18$). Group 3: Baseline PASI = 12–15 ($N = 103$).

Table 4. Safety anaylsis by baseline disease severity and treatment groups[a] (induction period, integrated analysis of UNCOVER-2 and -3 studies).

	Group 1[b]			Group 2[b]			Group 3[b]		
	PBO $N = 257$	ETN $N = 527$	IXEQ2W $N = 529$	PBO $N = 10$	ETN $N = 49$	IXEQ2W $N = 42$	PBO $N = 103$	ETN $N = 212$	IXEQ2W $N = 205$
Patients ≥1 TEAE	112 (43.6)	276 (52.4)	301 (56.9)	4 (40)	29 (59.2)	24 (57.1)	48 (46.6)	123 (58.0)	123 (60.0)
Patients ≥1 SAE	7 (2.7)	9 (1.7)	12 (2.3)	0 (0.0)	2 (4.1)	0 (0.0)	0 (0.0)	5 (2.4)	2 (1.0)
Patients discontinued due to AEs	2 (0.8)	5 (0.9)	9 (1.7)	0 (0.0)	0 (0.0)	2 (4.8)	1 (1.0)	4 (1.9)	3 (1.5)

[a]Data are number of patients in the specified category (%).
[b]Off label dose (IXEQ4W) results are not included.
AEs: adverse events; ETN: etanercept 50 mg twice weekly; IXEQ2W: ixekizumab 80 mg every 2 weeks (loading dose 160 mg); IXEQ4W: ixekizumab 80 mg every 4 weeks; *N*: number of patients in the analysis population; PBO: placebo; SAE: serious adverse event; TEAE: treatment emergent adverse event.
Group 1: Baseline PASI > 15. Group 2: Baseline PASI > 15 and a history of ≥3 non-biologic systemic therapies. Group 3: Baseline PASI = 12–15.

This *post hoc* analysis was not powered or prespecified and was conducted in a small patient population for the listed outcomes, posing a potential limitation. However, the alignment of these results with the primary outcomes of UNCOVER-2 and -3 [2] and other clinical trials of ixekizumab [4,5,7–10] demonstrates the validity of the results and supports the efficacy, early onset of action with a maintained response up to 60 weeks, and safety, of ixekizumab in line with previous trials.

Acknowledgments

The authors thank the patients, their families, the study sites, and the study personnel who participated in this clinical study. Andrea Rossi (former employee) and Geetha Rangegowda (full-time employee) are employees of Eli Lilly and Company, provided medical writing support.

Disclosure statement

Dr. Lynda Spelman has served on advisory Boards for AbbVie, Eli Lilly and Company, Galderma and Novartis, has undertaken sponsored clinical research for AbbVie, Amgen, Anacor, Ascend, Astellas, Australian Wool Innovation Limited, Biopharmaceuticals, Blaze Bioscience, Botanix, Celgene, Dermira, Eli Lilly and Company, Galderma, Genentech, GlaxoSmithKline, Janssen, Kythera, Leo Pharma, Merck, Novartis, Pfizer, Phosphagenics, Regeneron, Samumed, Sanofi, Sunpharma, and Trius, and has received sponsored travel from Abbott, Novartis, and Janssen-Cilag.

Dr. Diana Rubel has served as advisor, investigator and/or received travel honoraria from Abbvie, Amgen, Boehringer Ingelheim, Dermira, Eli Lilly and Company, Galderma, Leo, Janssen, Novartis, Regeneron, Sanofi, UCB.

Alan Brnabic and Elisabeth Riedl are full-time employees and stockholders of Eli Lilly and Company.

Nicole Burkhardt was full-time employee of Eli Lilly and Company (when the work was undertaken).

Dr. Peter Foley has served as an investigator, speaker, advisor, or received travel/grant/research support from 3M/iNova/Valeant, Abbott/AbbVie, Amgen, Ascent, Aspen, Australian Ultraviolet Services, Biogen Idec, Boehringer Ingelheim, Botanix, Bristol-Myers Squibb, Celgene, Celtaxsys, Clinuvel, Cutanea, Dermira, CSL, Eli Lilly and Company, Galderma, Genentech, GlaxoSmithKline/Stiefel, Janssen-Cilag,

Leo Pharma/Peplin, Merck Serono, Novartis, Regeneron, Roche, Sanofi, Schering-Plough/MSD, Sun Pharma, UCB Pharma, Valeant, and Wyeth/Pfizer.

Funding

Eli Lilly and Company sponsored this study.

References

1. Raychaudhuri SP. Role of IL-17 in psoriasis and psoriatic arthritis. Clin Rev Allerg Immunol. 2013;44(2):183–193.
2. Griffiths CE, Reich K, Lebwohl M, 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(9993):541–551.
3. Genovese MC, Van den Bosch F, Roberson SA, et al. LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a phase I randomized, double-blind, placebo-controlled, proof-of-concept study. Arthritis Rheum. 2010; 62(4):929–939.
4. Leonardi C, Matheson R, Zachariae C, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med. 2012;366(13):1190–1199.
5. Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med. 2016;375(4):345–356.
6. Reich K, Pinter A, Leutz A, et al. A 24-week, randomized, open-label comparison of ixekizumab versus fumaric acid esters and methotrexate in patients with moderate-to-severe plaque psoriasis naïve to systemic therapy. Abstract Presented at: 26th European Academy of Dermatology and Venereology Congress, September 13–17, 2017; Geneva, Switzerland.
7. Reich K, Pinter A, Lacour JP, on behalf of the IXORA-S Investigators, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. Br J Dermatol. 2017; 177(4):1014–1023.
8. Blauvelt A, Papp K, Gottlieb A, on behalf of the IXORA-R Investigators, et al. A head-to-head comparison of ixekizumab vs. guselkumab in patients with moderate-to-severe plaque psoriasis: 12-week efficacy, safety and speed of response from a randomized, double-blinded trial. Br J Dermatol. 2019. DOI:10.1111/bjd.18851
9. Reich K, Leonardi C, Lebwohl M, et al. Sustained response with ixekizumab treatment of moderate-to-severe psoriasis with scalp involvement: results from three phase 3 trials (UNCOVER-1, UNCOVER-2, UNCOVER-3). J Dermatolog Treat. 2017;28(4):282–287.
10. Blauvelt A, Gooderham M, Iversen L, et al. Efficacy and safety of ixekizumab for the treatment of moderate-to-severe plaque psoriasis: results through 108 weeks of a randomized, controlled phase 3 clinical trial (UNCOVER-3). J Am Acad Dermatol. 2017;77(5):855–862.
11. Leonardi C, Maari C, Philipp S, et al. Maintenance of skin clearance with ixekizumab treatment of psoriasis: three-year results from the UNCOVER-3 study. J Am Acad Dermatol. 2018;79(5):824–830.e2.
12. Lebwohl MG, Gordon KB, Gallo G, et al. Ixekizumab sustains high level of efficacy and favourable safety profile over 4 years in patients with moderate psoriasis: results from UNCOVER-3 study. J Eur Acad Dermatol Venereol. 2020;34(2):301–309.
13. Louden BA, Pearce DJ, Lang W, et al. A Simplified Psoriasis Area Severity Index (SPASI) for rating psoriasis severity in clinic patients. Dermatol Online J. 2004;10(2):7.
14. Australian Government Department of Human Services. Psoriasis – severe chronic plaque psoriasis – adult patients [Internet] [cited 2019 May 1]. Available from: https://www.humanservicesgov.au/organisations/health-professionals/enablers/severe-chronic-plaque-psoriasis.
15. Camisa C. Handbook of psoriasis. Malden (MA): Blackwell Publishing Ltd; 2004.
16. Di Lernia V, Ricci C, Lallas A, et al. Clinical predictors of non-response to any tumor necrosis factor (TNF) blockers: a retrospective study. J Dermatolog Treat. 2014;25(1): 73–74.
17. Armstrong AW, Feldman SR, Korman NJ, et al. Assessing the overall benefit of a medication: cumulative benefit of secukinumab over time in patients with moderate-to-severe plaque psoriasis. *J Dermatolog Treat. 2017;28(3): 200–205.
18. Costanzo A, Papoutsaki M, Mazzotta A, et al. Consecutive use of different biological therapies in the treatment of psoriasis. Br J Dermatol. 2007;157(2):394–394.
19. Costa L, Perricone C, Chimenti MS, et al. Switching between biological treatments in psoriatic arthritis: a review of the evidence. Drugs R D. 2017;17(4):509–522.
20. Blauvelt A, Papp KA, Griffiths CEM, et al. 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). Am J Clin Dermatol. 2017;18(2): 273–280.
21. Nash P, Kirkham B, Okada M, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet. 2017;389(10086):2317–2327.
22. McLaughlin M, Ostör A. Early treatment of psoriatic arthritis improves prognosis. Practitioner. 2014;258(1777): 21–24.
23. Kozub P, Simaljakova M. Systemic therapy of psoriasis: methotrexate. Bratisl Lek Listy. 2011;112(7):390–394.
24. Pearce DJ, Higgins KB, Stealey KH, et al. Adverse events from systemic therapies for psoriasis are common in clinical practice. J Dermatolog Treat. 2006;17(5):288–293.