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Efficacy of Tildrakizumab for Moderate-to-Severe Plaque Psoriasis:

Pooled Analysis of Three Randomised Controlled Trials at Weeks 12 and 28

Running Head: Pooled efficacy of tildrakizumab for psoriasis

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Abstract

Background: Efficacy of tildrakizumab for plaque psoriasis was demonstrated in randomised, placebo-controlled trials.

Objective: To consolidate tildrakizumab efficacy results by pooling data.

Methods: Data (N=2081) from tildrakizumab 100 mg, tildrakizumab 200 mg, and placebo groups in 3 trials were pooled.

Results: Proportions of Psoriasis Area and Severity Index (PASI) 75 responders at week 12 were better with tildrakizumab 100 mg (62.3%) and tildrakizumab 200 mg (64.8%) versus placebo (5.6%; $P<0.0001$) and for PASI 90, 100, and Physician's Global Assessment (PGA) 'clear' or 'minimal' versus placebo ($P<0.0001$). Responses increased from weeks 12 to 28. Week 12 PASI and PGA responses to tildrakizumab versus placebo were numerically greater in patients with lower versus higher body weight and were better with tildrakizumab 200 mg than tildrakizumab 100 mg for patients with higher body weight. Week 12 PASI 75 responses versus placebo with tildrakizumab 100 mg were similar between patients with (55.0%) or without (56.7%) prior biologics. PASI 90, 100, and PGA responses were generally higher in patients without prior biologics. Week 8 PASI 50 response predicted PASI 90 response.

Conclusion: Pooled data confirmed the efficacy of tildrakizumab for moderate-to-severe plaque psoriasis.

Introduction

Despite the improvement in outcomes for plaque psoriasis with biologic treatments, there remains a need for convenient, well-tolerated treatments with robust efficacy. Tildrakizumab is a high-affinity, humanised, IgG1 κ , anti-IL-23p19 monoclonal antibody under development for the treatment of moderate-to-severe plaque psoriasis. Tildrakizumab has a large available pooled data set, comprised of 2081 patients who were treated with tildrakizumab 100 or 200 mg, placebo, or etanercept (ETN; 1 trial only) in three Phase 2 and 3 randomised, placebo-controlled trials.^{1,2} Pooled data sets increase the number of patients available for analyses, allowing for subgroup and responder analyses that may not be sufficiently powerful in individual studies.

Relevant subgroups in the investigation of tildrakizumab efficacy include patients with higher body weight and patients with or without prior exposure to biologic agents for psoriasis. Overweight and obesity are common comorbidities in patients with plaque psoriasis.^{3,4} Furthermore, some biologics used to treat plaque psoriasis have been found to be less effective in heavier patients.⁵⁻⁷ Previous treatment with systemic or biologic treatment for psoriasis has also been found to be associated with reduced efficacy of some biologic agents.^{5,7} Therefore, it is important to determine the efficacy of

novel psoriasis treatments in the context of baseline body weight and previous biologic agent exposure.

The primary objective of this analysis was to consolidate the efficacy results for tildrakizumab by pooling data from three randomised, placebo-controlled trials of moderate-to-severe plaque psoriasis. Additional objectives were to use the pooled data to assess efficacy of tildrakizumab based on baseline body weight or prior exposure to biologic agents and to analyse predictors of response.

Methods

Trial designs

Three randomised, controlled, multicentre, international trials, P05495 (Phase 2; NCT01225731), reSURFACE 1 (Phase 3; NCT01722331), and reSURFACE 2 (Phase 3; NCT01729754) were included in the pooled analysis and have been previously described.^{1,2} Patients in the trials were adults with moderate-to-severe plaque psoriasis defined as $\geq 10\%$ body surface area, ≥ 3 Physician's Global Assessment (PGA), and Psoriasis Area and Severity Index (PASI) ≥ 12 .

Randomised patients in all 3 trials were stratified by body weight (≤ 90 kg, > 90 kg). In Part 1 (weeks 1–16) of trial P05495, patients were randomised to subcutaneous tildrakizumab 200 mg, 100 mg, 25 mg, 5 mg, or placebo and treatment was administered at weeks 0 and 4 (**Supplemental Figure**). In Part 2 (weeks 16–52), patients were re-randomised to tildrakizumab at week 16 based on PASI 75 responder status and received treatment every subsequent 12 weeks. In Part 1 (weeks 1–12) of reSURFACE 1 and 2, patients were randomised to subcutaneous tildrakizumab 100 mg, 200 mg, or placebo and treatment was administered at weeks 0 and 4 (**Supplemental Figure**). In Part 1 of reSURFACE 2, ETN 50 mg administered twice-weekly was an additional treatment arm. In Part 2 (weeks 12–28) of reSURFACE 1 and 2, all patients receiving placebo in Part 1 were re-randomised to tildrakizumab 100 mg or 200 mg and received tildrakizumab at weeks 12, 16, and 28. Patients in Part 1 who received tildrakizumab continued their originally randomised treatment and received a dose of study medication at week 16. Patients receiving ETN in Part 1 of reSURFACE 2

continued their ETN treatment once-weekly in Part 2. In Part 3 (weeks 28–64 for reSURFACE 1 and weeks 28–52 for reSURFACE 2), patients were re-randomised to tildrakizumab 100 mg or 200 mg (or placebo in reSURFACE 1) based on responder (PASI ≥ 75) and partial responder (PASI ≥ 50 and PASI < 75) status and received treatment every 12 weeks. Responders receiving ETN in reSURFACE 2 were discontinued in Part 3, and partial responders (PASI ≥ 50 and PASI < 75) and non-responders (PASI < 50) received tildrakizumab 200 mg. Results from Part 3 will be reported separately.

Endpoints

In P05495 the primary endpoint was the proportion of patients achieving PASI 75 at week 16. The proportions achieving PASI 75 at week 12 and a PGA score of 'clear' or 'minimal' at week 16 were key secondary endpoints; the proportions achieving a PGA score of 'clear' or 'minimal' at week 12, and PASI 90 and 100 at weeks 12 and 16 were additional secondary endpoints. In reSURFACE 1 and 2, the co-primary endpoints were the proportion of patients achieving at least PASI 75 and the proportion achieving a PGA score of 'clear' or 'minimal,' with at least a 2-grade reduction from baseline (PGA response) at week 12. The proportions achieving PASI 90 and 100 at week 12 were key secondary endpoints in reSURFACE 1 and 2. The proportions achieving PASI 75 and PGA score of 'clear' or 'minimal' with at least a 2-grade reduction from baseline (PGA response) at weeks 12 and 28 compared with ETN were key secondary endpoints in reSURFACE 2.

Statistical analysis

In this post-hoc analysis, PASI 75, 90, 100, and PGA response data from the tildrakizumab 100 mg and 200 mg treatment arms in the three trials were pooled and compared with the placebo pool using Part 1 data. Differences in response were analysed based on Miettinen and Nurminen method stratified by trial, body weight (≤ 90 kg, > 90 kg), and prior exposure to biologic agent therapy for psoriasis (yes/no). P values were not adjusted for multiplicity. The difference between tildrakizumab and ETN was not statistically tested in the pooled analysis. A similar method was used for the

subgroup analyses on body weight and on prior exposure to biologics for psoriasis. No p values were calculated for the subgroup analysis of outcomes by prior exposure to biologics for psoriasis.

All patients who received at least 1 dose of study medication were analysed in Part 1; all patients who completed Part 1 and received at least 1 dose of study medication in Part 2 were analysed for Part 2. Patients with missing data (through week 12) were treated as non-responders in Part 1; responses past Part 1 and over time were analysed as observed data only. Analyses of efficacy endpoints at week 28 presented here were for observed data only and included only subjects who were treated with tildrakizumab (or ETN in reSURFACE 2) from 0–28 weeks.

To assess predictors of response, continuous variables of mean baseline PASI, body mass index (BMI), PGA, and PASI component for head region, as well as dichotomous variables of baseline PASI $>$ or ≤ 20 and PASI 50 response or nonresponse at week 8, were evaluated. Response was defined in this analysis as PASI 50 or PASI 90 at weeks 12 and 28.

Results

Patients

In all, 2081 patients were treated with tildrakizumab 100 mg (n=705) or 200 mg (n=708), placebo (n=355), or ETN (n=313) and included in the pooled analysis. Nearly all (2000/2081; 96.1%) treated patients completed Part 1 and entered into Part 2 of the trials. Baseline demographics and disease characteristics of the randomised patients were similar among the treatment groups (**Table 1**).

<<Insert Table 1 here>>

Overall efficacy

Median PASI decreased with tildrakizumab treatment groups by week 12 (**Figure 1**). The proportions of PASI 75, 90, and 100 responders at week 12, as well as the proportion of PGA 'clear' or 'minimal' responders at week 12, were significantly better with both tildrakizumab doses compared with placebo ($P < 0.0001$ for all comparisons;

Table 2). Statistical analysis for tildrakizumab compared with ETN was prespecified in reSURFACE 2 and as previously reported, proportions of PASI 75, 90, and 100, and PGA responders were significantly higher with the tildrakizumab 200 mg dose at week 12 compared with ETN, as were the proportions of PASI 75, 90, and 100 with the tildrakizumab 100 mg dose.²

Responses with continuous tildrakizumab treatment with the same dose in reSURFACE 1 and 2 increased from week 12 to week 28 (observed data only; **Figure 2**). Responses reached 78% for PASI 75, 58% for PASI 90, 29% for PASI 100, and 70% for PGA ‘clear’ or ‘minimal’ by week 28 (**Table 2**).

<<Insert Table 2, Figure 1, and Figure 2 here>>

Efficacy in subgroups

Differences by baseline weight in PASI 75 and PGA responders with tildrakizumab versus placebo or ETN at week 12 are shown in **Table 3**. The difference in the proportion of patients achieving PASI 75 at week 12 with tildrakizumab 100 mg or 200 mg was significant compared with placebo across all weight subgroups (**Figure 3**). Similar response patterns were observed for PASI 90, PASI 100, and PGA response (**Figure 3**). PASI and PGA responses to tildrakizumab were numerically greater in patients with lower body weight compared with patients with higher body weight. Responses for patients with higher body weight were generally better with tildrakizumab 200 mg than with tildrakizumab 100 mg versus placebo or ETN.

Differences by history of prior exposure to biologic agents for psoriasis in PASI 75 and PGA responders with tildrakizumab versus placebo or ETN at week 12 are shown in **Table 4**. The difference in the proportion of patients achieving PASI 75 at week 12 with tildrakizumab 100 mg or 200 mg was higher compared with placebo in patients with and without prior exposure to biologic therapy for psoriasis and was comparable between the two groups (**Figure 4**). PASI 90 and PGA responses with tildrakizumab 100 mg and 200 mg versus placebo were greater in patients without prior exposure to biologics compared with patients with prior exposure (**Figure 4**). PASI 100 responses with the tildrakizumab 100 mg dose versus placebo were also greater in patients without

prior exposure to biologics compared with patients with prior exposure, whereas PASI 100 responses with the tildrakizumab 200 mg dose versus placebo were similar between the patients with and without prior biologic therapy (**Figure 4**).

<<Insert Table 3, Table 4, Figure 3, and Figure 4 here>>

The difference in the proportion of patients (95% CI) achieving PASI 75 at week 12 in the subgroup of white patients was 55.5% (50.2%, 60.4%) with tildrakizumab 100 mg and 60.2% (55.0%, 64.9%) with tildrakizumab 200 mg compared with placebo, and in the subgroup of Asian patients was 51.1% (37.8%, 62.2%) with tildrakizumab 100 mg and 53.2% (40.5%, 63.6%) with tildrakizumab 200 mg. A similar pattern of slightly higher proportions of patients in the white subgroup achieving response compared with patients in the Asian subgroup was also observed for PASI 90, PASI 100, and PGA responses. The number of patients in the black subgroup was too small to make definitive comparisons versus other racial subgroups.

Predictors of response

None of the continuous variables appeared to be consistently predictive of a PASI 90 response, nor were baseline PASI $>$ or ≤ 20 definitive predictors of a PASI 90 response (**Supplemental Table**). PASI response ≥ 50 versus PASI response < 50 at week 8 with tildrakizumab 100 mg appeared to be predictive of PASI 90 response at week 12 ($49.7\% \pm 2.4\%$ versus $3.3\% \pm 1.4\%$; **Table 5**) and week 28 ($64.4\% \pm 2.3\%$ versus $21.8\% \pm 3.4\%$; **Table 5**). Similar trends in predictive responses were observed with tildrakizumab 200 mg treatment (**Table 5**).

<<Insert Table 5 here>>

Discussion

Pooling data from multiple clinical trials allows for greater patient numbers to confirm results from individual trials. Pooling data also allows for more robust assessment of subgroups than is possible in individual trials. Efficacy of tildrakizumab 100 mg and tildrakizumab 200 mg doses was demonstrated by significantly higher PASI

and PGA responses compared with placebo in 3 individual phase 2 and phase 3 randomised controlled trials.^{1,8} The results from this pooled analysis of the 3 trials confirms the efficacy of tildrakizumab for moderate-to-severe chronic plaque psoriasis. Although no statistical analysis for pooled tildrakizumab compared with ETN was conducted in the current analysis, as previously reported in the individual phase 3 trial of tildrakizumab that used ETN as an active comparator, all but one of the PASI and PGA responses at week 12 (PGA with TIL 100 mg) were statistically significantly higher with tildrakizumab compared with ETN.⁸

Subgroup and responder analyses using the pooled data have provided novel insights into the efficacy of tildrakizumab. Subgroup analysis indicated that efficacy of tildrakizumab was greater in patients with lower body weight versus higher body weight. The efficacy of most biologics used to treat psoriasis is impacted by weight, particularly for fixed dose medications such as etanercept, adalimumab, and ustekinumab.^{6,9,10} The tildrakizumab results are also consistent with an analysis of pooled trials of tofacitinib for moderate-to-severe psoriasis, where PASI 75 responses were lower in patients with higher body weight versus lower body weight.⁵ Furthermore, responses were numerically higher with the tildrakizumab 200 mg dose compared with the tildrakizumab 100 mg dose in patients with higher body weight, suggesting higher doses of tildrakizumab may improve responses in heavier patients. Similar results were also demonstrated in the pooled trials of tofacitinib, in which PASI 75 responses with the 10 mg twice-daily dose were up to 19% higher than the 5 mg twice-daily dose among the subgroups of patients with weight ≥ 60 kg.⁵ The impact of weight on the efficacy of tildrakizumab may in part be due to pharmacokinetics. In pharmacokinetic analysis of ustekinumab for psoriasis, a decrease in serum ustekinumab was observed with increasing weight, which paralleled clinical response.¹¹ In patients receiving 45 mg doses of ustekinumab and weighing more than 100 kg, median trough serum ustekinumab concentrations were below the lower limit of detection.¹¹ Considering the high proportion of patients with psoriasis who have a body weight greater than 100 kg (approximately 25%-30% in clinical trials),¹⁰ further analysis of the impact of body weight on the efficacy of tildrakizumab is warranted.

In the current analysis, PASI 75 responses with both tildrakizumab doses versus placebo were similar between patients with and without prior exposure to biologic agents. However, responses for PASI 90, 100, and PGA were generally higher with both tildrakizumab doses in patients naive to biologics for psoriasis compared with patients with previous biologic exposure. The one exception was that PASI 100 responses with the tildrakizumab 200 mg dose were similar between patients with and without prior biologics exposure. Pooled analysis of tofacitinib trials and a retrospective analysis of ustekinumab also demonstrated higher PASI responses in patients without prior biologic exposure versus patients with prior exposure.^{5,7} No difference in PASI 75 responses between patients with and without prior biologic exposure were observed in a pooled analysis of 2 clinical trials of ixekizumab for moderate-to-severe psoriasis, although higher PASI 90 and 100 responses were observed in patients with prior biologic exposure compared with patients without previous exposure.¹²

In this pooled analysis, continuous variables of baseline PASI, PGA, and BMI were not predictive of PASI 90 response at weeks 12 or 28. Achievement of PASI ≥ 50 by week 8 was predictive of PASI ≥ 90 at weeks 12 and 28. Polymorphisms in genes related to immunologic response have been demonstrated to be predictors of response to biologics in patients with psoriasis,^{13,14} which may in part account for early response being indicative of overall response. Further research into genetic biomarkers may be more informative than continuous variables as predictors of tildrakizumab response.

A limitation of the current analysis is that per the trial protocols, placebo was only given for a short period (12 or 16 weeks). Thus, longer term analyses versus placebo were not possible.

In conclusion, pooled data from 3 randomised controlled trials confirmed the efficacy of tildrakizumab for moderate-to-severe chronic plaque psoriasis. Subgroup analysis indicated that higher doses of tildrakizumab may improve efficacy in heavier patients, and that patients naive to biologics for psoriasis may have greater responses to tildrakizumab than patients with previous biologic exposure. Of the continuous and categorical variables analysed, only PASI 50 responses at week 8 were predictive of PASI 90 responses at weeks 12 and 28.

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References

- 1 Papp K, Thaci D, Reich K et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomised placebo-controlled trial. *Br J Dermatol* 2015; **173**: 930-9.
- 2 Reich K, Papp KA, Blauvelt A et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet* 2017.
- 3 Fleischer AB, Jr. Characterization of obesity rates for dermatologic ambulatory office visits to United States physicians. *J Dermatolog Treat* 2017; **28**: 181-5.
- 4 Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. *Nutr Diabetes* 2012; **2**: e54.
- 5 Menter MA, Papp KA, Cather J et al. Efficacy of Tofacitinib for the Treatment of Moderate-to-Severe Chronic Plaque Psoriasis in Patient Subgroups from Two Randomised Phase 3 Trials. *J Drugs Dermatol* 2016; **15**: 568-80.
- 6 Papp KA, Langley RG, Lebwohl M et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; **371**: 1675-84.
- 7 Ruiz Salas V, Puig L, Alomar A. Ustekinumab in clinical practice: response depends on dose and previous treatment. *J Eur Acad Dermatol Venereol* 2012; **26**: 508-13.

- 8 Reich K, Papp KA, Blauvelt A et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet* 2017; **390**: 276-88.
- 9 Gordon K, Korman N, Frankel E et al. Efficacy of etanercept in an integrated multistudy database of patients with psoriasis. *J Am Acad Dermatol* 2006; **54**: S101-11.
- 10 Puig L. Obesity and psoriasis: body weight and body mass index influence the response to biological treatment. *J Eur Acad Dermatol Venereol* 2011; **25**: 1007-11.
- 11 Lebwohl M, Yeilding N, Szapary P et al. Impact of weight on the efficacy and safety of ustekinumab in patients with moderate to severe psoriasis: rationale for dosing recommendations. *J Am Acad Dermatol* 2010; **63**: 571-9.
- 12 Gottlieb AB, Lacour JP, Korman N et al. Treatment outcomes with ixekizumab in patients with moderate-to-severe psoriasis who have or have not received prior biological therapies: an integrated analysis of two Phase III randomised studies. *J Eur Acad Dermatol Venereol* 2017; **31**: 679-85.
- 13 van den Reek J, Coenen MJH, van de L'Isle Arias M et al. Polymorphisms in CD84, IL12B and TNFAIP3 are associated with response to biologics in patients with psoriasis. *Br J Dermatol* 2017; **176**: 1288-96.
- 14 Talamonti M, Galluzzo M, van den Reek JM et al. Role of the HLA-C*06 allele in clinical response to ustekinumab: evidence from real life in a large cohort of European patients. *Br J Dermatol* 2017; **177**: 489-96.

Table 1. Baseline demographics and disease characteristics for the randomised pooled trial population

	TIL 100 mg	TIL 200 mg	Placebo	ETN 50 mg
Characteristic	(n=705)	(n=708)	(n=357)	(n=313)
Men, %	71	73	70	71
Age, mean y (SD)	46 (13)	46 (13)	47 (13)	46 (14)

Race				
White, %	81	80	78	92
Asian, %	13	15	16	3
Weight, median, (interquartile range [Q3-Q1])	86.0 (26.2)	85.8 (26.8)	85.5 (27.9)	85.7 (28.3)
≤90 kg, n	416	415	211	180
>90 kg, n	289	293	144	133
≤100 kg, n	540	539	274	234
>100 kg, n	165	169	81	79
Baseline PASI, median, (interquartile range [Q3-Q1])	17.7 (8.4)	17.6 (9.0)	17.6 (7.4)	18.4 (9.3)
Baseline BSA %, median, (interquartile range [Q3-Q1])	26.0 (24.0)	26.0 (23.0)	26.0 (21.0)	28.0 (23.0)
History of psoriatic arthritis, yes, %	17	17	15	13
Prior exposure to biologics for psoriasis, yes, %	18	18	19	12
Prior phototherapy, yes, %	32	31	31	44

Prior conventional
systemic therapy*, 38 40 39 45
yes, %

BSA=body surface area; ETN=etanercept; PASI=Psoriasis Area and Severity Index;

TIL=tildrakizumab

*e.g., methotrexate, cyclosporine

Table 2. Percent of PASI 75, 90, 100 and PGA responders at weeks 12 and 28 in the pooled trial population (all patients as treated)

Treatment	PASI 75, %	PASI 90, %	PASI 100, %	PGA 'Clear' or 'Minimal', %
Week 12*				
TIL 100 mg (n=705)	62.3 [‡]	35.9 [‡]	13.2 [‡]	57.2 [‡]
TIL 200 mg (n=708)	64.8 [‡]	37.0 [‡]	12.9 [‡]	60.0 [‡]
Placebo (n=355)	5.6	2.0	0.6	5.6
ETN 50 mg (n=313)	48.2	21.4	4.8	47.6
Week 28[†]				
TIL 100 mg (n=575)	77.4	53.6	23.1	65.7
TIL 200 mg (n=581)	78.0	58.3	29.3	70.2
ETN 50 mg (n=277)	56.0	30.7	11.2	47.8

ETN=etanercept; PASI= Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; TIL=tildrakizumab.

*Non-responder imputation analysis.

†Observed data from phase 3 trials; subjects were treated with tildrakizumab or ETN from 0–28 weeks. ‡ $P < 0.0001$ vs. placebo. P values were not adjusted for multiplicity.

Table 3. Differences in PASI 75 and PGA responders by baseline weight with tildrakizumab versus placebo or ETN at week 12

Baseline Weight	Total N	PASI 75 Response, % (95% CI)		PGA 'Clear' or 'Minimal' Response, % (95% CI)	
		TIL 100 mg	TIL 200 mg	TIL 100 mg	TIL 200 mg
≤90 kg	1222				
vs. placebo		61.6 (55.6, 66.9)*	63.4 (57.4, 68.6)*	56.0 (49.8, 61.4)*	57.6 (51.5, 63.0)*
vs. ETN 50 mg biweekly		20.4 (10.3, 30.1)	21.1 (11.1, 30.8)	5.8 (−4.5, 15.9)	9.5 (−0.7, 19.4)
>90 kg	859				
vs. placebo		48.8 (41.8, 55.2)*	53.3 (46.3, 59.5)*	44.6 (37.5, 51.1)*	49.7 (42.7, 56.0)*

vs. ETN 50					
mg					
biweekly		3.1 (−8.9, 15.0)	12.3 (0.3, 24.0)	9.3 (−2.6, 20.9)	14.6 (2.7, 26.1)
≤100 kg	1587				
		58.4 (53.1,	61.5 (56.3,	52.9 (47.4,	55.2 (49.7,
vs. placebo		63.3)*	66.2)*	57.9)*	60.1)*
vs. ETN 50					
mg					
biweekly		14.1 (5.2, 22.8)	17.7 (8.9, 26.2)	5.7 (−3.3, 14.5)	9.4 (0.5, 18.1)
>100 kg	494				
		49.8 (40.3,	52.2 (42.6,	46.3 (36.8,	52.4 (43.3,
vs. placebo		58.3)*	60.4)*	54.7)*	60.5)*
vs. ETN 50					
mg			16.0 (−0.1,	11.6 (−4.2,	
biweekly		9.5 (−6.7, 25.2)	31.2)	26.9)	18.2 (2.3, 33.2)

ETN=etanercept; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; TIL=tildrakizumab

* $P < 0.0001$ vs. placebo. P values not adjusted for multiplicity.

Table 4. Differences in PASI 75 and PGA responders by prior exposure to biologic agents for psoriasis with tildrakizumab versus placebo or ETN at week 12

Prior Exposure	Total N	PASI 75 Response, % (95% CI)		PGA 'Clear' or 'Minimal' Response, % (95% CI)	
		TIL 100 mg	TIL 200 mg	TIL 100 mg	TIL 200 mg
With prior exposure to	357				

biologics				
for				
psoriasis				
	55.0 (45.1,	58.8 (49.5,	46.2 (35.4,	47.0 (36.7,
vs. placebo	64.0)	67.1)	55.9)	56.2)
vs. ETN 50				
mg	18.9 (-3.0,	11.8 (-10.8,	14.4 (-6.7,	9.2 (-12.8,
biweekly	39.0)	33.2)	34.4)	30.4)
Without				
prior				
exposure to				
biologics				
for				
psoriasis	1724			
	56.7 (51.5,	59.4 (54.2,	52.5 (47.3,	56.1 (51.0,
vs. placebo	61.4)	64.0)	57.2)	60.7)
vs. ETN 50				
mg		18.1 (10.0,		
biweekly	12.2 (3.9, 20.4)	26.1)	6.3 (-2.1, 14.5)	12.0 (3.8, 20.1)

ETN=etanercept; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; TIL=tildrakizumab

Table 5. Predictors of tildrakizumab PASI 90 response at weeks 12 and 28 by baseline PASI and PASI 50 response at week 8

Categorical Variable	PASI 90 Response at Week 12, %±SD		
	TIL 100 mg	TIL 200 mg	Placebo
Baseline PASI ≤20	39.8±2.5	36.2±2.5	2.1±1.0
Baseline PASI >20	34.5±3.2	38.9±3.2	2.1±1.5
PASI response ≥50 at week 8	49.7±2.4	48.1±2.3	13.0±5.0
PASI response <50 at week 8	3.3±1.4	2.8±1.4	0±0
PASI 90 Response at Week 28, %			
Baseline PASI ≤20	56.6±2.6	57.7±2.6	-
Baseline PASI >20	48.6±3.4	59.4±3.3	-
PASI response ≥50 at week 8	64.4±2.3	70.2±2.2	-
PASI response <50 at week 8	21.8±3.4	21.6±3.6	-

PASI=Psoriasis Area and Severity Index; TIL=tildrakizumab

Figure Legends

Figure 1. PASI from individuals in the pooled trial population. Figures indicate exclusive medians, quartiles, local maximum and minimum, and outliers (1.5 x interquartile range). Plots for tildrakizumab 100 mg, tildrakizumab 200 mg, and ETN indicate continuous treatment to the originally randomised treatment through Week 28. ETN=etanercept; PASI= Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; TIL=tildrakizumab.

Figure 2. Responses for PASI 75, PASI 90, PASI 100, and PGA 'clear' or 'minimal' over time in pooled phase 3 trials. Analysis is for observed data only. ETN=etanercept; PASI= Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; TIL=tildrakizumab.

Figure 3. Differences in PASI 75, 90, 100 and PGA responders by baseline weight with tildrakizumab versus placebo or ETN at week 12. ETN=etanercept; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; TIL=tildrakizumab.

Figure 4. Differences in PASI 75, 90, 100 and PGA responders by prior exposure to biologics for psoriasis with tildrakizumab versus placebo or ETN at week 12. ETN=etanercept; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; TIL=tildrakizumab.

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