Title

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ORIGINAL RESEARCH

Efficacy and Safety of Tildrakizumab for Treatment of Moderate-to-Severe Scalp Psoriasis in Patients with Obesity Over 52 Weeks

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ABSTRACT

Introduction: Obesity contributes to inflammation and may decrease psoriasis treatment efficacy. We investigated whether obesity affects the efficacy and safety of tildrakizumab, an anti-interleukin-23 p19 antibody approved for the treatment of adults with moderate-to-severe plaque psoriasis, for scalp psoriasis treatment.

Methods: This was a subgroup analysis of a randomized, double-blind, placebo-controlled, Phase 3b trial in patients with moderate-to-severe plaque psoriasis affecting the scalp. Patients receiving tildrakizumab 100 mg or placebo were analyzed by baseline obesity status (body mass index ≥ 30 versus < 30 kg/m^2). Efficacy outcomes included an Investigator Global Assessment (IGA) modified 2011 (scalp) (IGA mod 2011 [scalp]) score of "clear"/"almost clear" (0/1) with a ≥ 2-point reduction (IGA mod 2011 [scalp] response), ≥ 90% improvement in Psoriasis Scalp Severity Index (PSSI) score (PSSI 90 response), ≥ 4-point reduction in Scalp Itch-Numeric Rating Scale (Scalp Itch-NRS response; among patients scoring ≥ 4 at baseline), and percent change from baseline (%CFB) in affected scalp surface area (SSA). Safety was assessed from adverse events. The analysis was not prospectively powered to detect differences between subgroups.

Results: In the intention-to-treat population, 56/117 (47.9%) patients randomized to tildrakizumab and 57/114 (50.0%) to placebo had obesity (modified intention-to-treat population: tildrakizumab, 43/89 [48.3%]; placebo, 40/82 [48.8%]). At Week 16, significantly more patients treated with tildrakizumab versus those receiving placebo achieved IGA mod 2011 (scalp) (obesity, 21/43 [48.8%] versus 4/40 [10.0%], $p = 0.0002$; no obesity, 23/46 [50.0%] versus 2/42 [4.8%], $p < 0.0001$) and PSSI 90 responses

Prior presentation: Some of the data in this manuscript were previously presented as a poster (poster ID: 62633) at the American Academy of Dermatology Annual Meeting, 7–11 March 2025 in Orlando, FL.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-026-01774-2.

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(obesity, 27/43 [62.8%] versus 4/40 [10.0%], $p<0.0001$; no obesity, 27/46 [58.7%] versus 0/42 [0.0%], $p<0.0001$). Treatment effect was also maintained for Scalp Itch-NRS response ($p<0.0001$) and mean %CFB in affected SSA (no statistical testing), regardless of obesity status. Results in patients treated with tildrakizumab were similar through Week 52. No new safety signals were identified.

Conclusions: No statistically significant differences in efficacy or safety were observed between patients with and without obesity.

ClinicalTrials.gov Identifier: NCT03897088.

PLAIN LANGUAGE SUMMARY

Psoriasis is a skin and joint disease affecting about 60 million people worldwide. Obesity is more common in people with psoriasis than in those without psoriasis and may make psoriasis harder to treat. Tildrakizumab is one available injectable medication for treating moderate-to-severe plaque psoriasis in adults. This study used information from an already completed clinical trial carried out in the USA and Australia and finished in 2022. The purpose was to see whether obesity changes (1) how well tildrakizumab 100 mg works for the treatment of scalp psoriasis and (2) how safe tildrakizumab is for people with scalp psoriasis. Patients were grouped by body mass index (≥ 30 kg/m^2 considered obesity) and assessed for whether their psoriasis improved during treatment with either tildrakizumab or an injection with no treatment in it. The measures of improvement included how severely the skin on the scalp was affected, a scalp psoriasis score that combined how much scalp was affected and how severely the skin was affected, scalp itching, and how much scalp surface area was affected. Safety was measured on the basis of side effects during the treatment period. People with or without obesity who were treated with tildrakizumab had more improvement on all scalp psoriasis tests and were more likely to achieve target scores than those not receiving tildrakizumab. People with and without obesity who were treated with tildrakizumab had similar side effects. In conclusion, tildrakizumab seemed to work well and remain safe in people with scalp psoriasis and obesity.

Keywords: Plaque psoriasis; Obesity; Psoriasis Scalp Severity Index (PSSI); Investigator Global Assessment modified 2011 of the scalp (IGA mod 2011 [scalp]) score; Scalp psoriasis; Tildrakizumab

Key Summary Points
Why carry out this study?
Obesity is a common comorbidity of psoriasis and can decrease treatment efficacy.
This study examined whether obesity affected the efficacy or safety of the anti-interleukin-23 p19 monoclonal antibody tildrakizumab for the treatment of moderate-to-severe plaque psoriasis affecting the scalp.
What was learned from the study?
Irrespective of obesity status, people treated with tildrakizumab had more improvement in all measures of scalp psoriasis and were more likely to achieve prespecified outcomes than those receiving placebo.
The efficacy of tildrakizumab for the treatment of scalp psoriasis was consistent between patients with and without obesity, with no new safety signals.

INTRODUCTION

Psoriasis is an inflammatory autoimmune disease of the skin and joints that affects almost 8 million adults in the USA, or 3.0% of the population, and over 40 million people worldwide [1, 2]. The most common type of psoriasis is plaque psoriasis, which affects 80–90% of patients with psoriasis [3]. Due to its inflammatory nature, psoriasis is associated with several comorbidities [4, 5], including obesity [5], which is more common in patients with psoriasis than in individuals without psoriasis and has been

linked with more severe disease [6–11]. Obesity shares several inflammatory cytokine pathways with psoriasis [12, 13], suggesting a potential positive feedback loop that may make psoriasis more difficult to treat patients [6, 7, 12, 14, 15]. Some biologic treatments for psoriasis may be less effective in patients with versus without obesity [8].

Between 43% and 90% of patients with psoriasis have lesions on their scalp, which is considered a difficult-to-treat area [16–19]. Treatment guidelines consider the use of biologics and other systemic therapies reserved for moderate-to-severe plaque psoriasis to be appropriate for patients with involvement of special areas including the scalp, irrespective of the body surface area (BSA) affected [20, 21]. Tildrakizumab is an anti-interleukin-23 p19 monoclonal antibody approved for the treatment of adults with moderate-to-severe plaque psoriasis [22, 23]. In a Phase 3b trial (NCT03897088), tildrakizumab was significantly more effective than placebo for the treatment of moderate-to-severe plaque psoriasis affecting the scalp, with no new safety signals in this population [24]. The objective of this analysis was to investigate whether obesity affects the efficacy and safety of tildrakizumab treatment for patients with moderate-to-severe plaque psoriasis of the scalp using data from a post hoc analysis of the Phase 3b trial.

METHODS

Study Design

The clinical trial study design was described in detail previously [24]. Briefly, this was a 52-week, randomized, placebo-controlled, Phase 3b trial that evaluated the efficacy and safety of tildrakizumab 100 mg by subcutaneous injection for the treatment of moderate-to-severe plaque psoriasis affecting the scalp. For this subgroup analysis, patients receiving either tildrakizumab 100 mg or placebo were grouped by baseline obesity status (Supplementary Fig. 1). Patients with a body mass index (BMI) ≥ 30 kg/m^2 were considered to have obesity while patients with a BMI < 30 kg/m^2 were considered to not have obesity.

Ethics Statement

The study was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent prior to the start of the study. The study protocol was approved by the independent ethics committee or institutional review board for each study site, as follows: Advarra IRB, SSU00080233, SSU00080197, SSU00084622, SSU00086947, SSU00084651, SSU00089424, SSU00087208, SSU00089759, SSU00089600, SSU00089741, SSU00094701, SSU00091780, SSU00092189, SSU00097078, SSU00097587, SSU00108132, SSU00099234, SSU00105498, SSU00105150, SSU00101234, and SSU00103922; Belberry Human Research Ethics Committee, 2019-06-529-A-3, 2019-06-529-A-5, and 2019-06-529-A-8.

Patients

Detailed patient inclusion and exclusion criteria were previously reported [24]. Patients ≥ 18 years of age with moderate-to-severe plaque psoriasis of the scalp and whole body, at screening and baseline, were eligible. Moderate-to-severe plaque psoriasis of the scalp was defined as an Investigator Global Assessment modified 2011 of the scalp (IGA mod 2011 [scalp]) score ≥ 3, a Psoriasis Scalp Severity Index (PSSI) score of ≥ 12, and ≥ 30% of scalp surface area (SSA) affected. Moderate-to-severe plaque psoriasis was defined by an IGA mod 2011 (whole body) of at least moderate severity (score of ≥ 3 on a 5-point scale), a Psoriasis Area and Severity Index score of ≥ 12, and > 10% BSA involvement. Patients were required to have physical examination results within normal or clinically acceptable limits prior to Day 1, but there were no inclusion or exclusion criteria specific to body weight or obesity.

Treatments

The original clinical trial was divided into three parts. In Part 1 (Weeks 0–16), patients were randomized 1:1 to receive tildrakizumab

100 mg or placebo at Weeks 0 and 4. For Part 2 (Weeks 16–52), patients who were originally randomized to the placebo group were switched to tildrakizumab 100 mg at Weeks 16, 20, 32, and 44; patients who had been originally randomized to receive tildrakizumab 100 mg continued to receive the study drug every 12 weeks starting at Week 16. Finally, for Part 3 (Weeks 52–72), all patients entered a 20-week, treatment-free, observational safety follow-up period.

Assessments and Outcomes

Assessments included the IGA mod 2011 (scalp) score, PSSI score, patient-reported Scalp Itch-Numeric Rating Scale (NRS; where 0 denotes no itch and 10 denotes worst itch imaginable), and the percentage of SSA affected. All assessments were performed at screening, baseline, and Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, 40, 44, and 52.

Efficacy outcomes included an IGA mod 2011 (scalp) score of "clear (0)" or "almost clear (1)" with a ≥ 2-point reduction from baseline (IGA mod 2011 [scalp] response; measured at Week 16 as the primary endpoint in the main study), a ≥ 90% improvement from baseline in PSSI score (PSSI 90 response), a ≥ 4-point reduction from baseline in Scalp Itch-NRS among patients with a score of ≥ 4 at baseline, and the percent change from baseline in SSA affected.

Safety was assessed for the full study period from the frequency of adverse events (AEs), including treatment-emergent AEs (TEAEs) and severe AEs (SAEs).

Statistical Analysis

This post hoc subgroup analysis was not prospectively powered to detect differences between the subgroup with obesity and that without obesity and should be considered exploratory. All analyses were performed in subgroups of patients with obesity (BMI ≥ 30 kg/m^2) or those without obesity (BMI < 30 kg/m^2). Due to amendments to the parent trial protocol, two different populations were used for efficacy analyses. The modified intention-to-treat (mITT) population included all patients with a baseline IGA mod 2011 (scalp) assessment who were dispensed tildrakizumab and was used for the IGA mod 2011 (scalp) and PSSI 90 response analyses. The intention-to-treat (ITT) population included all randomized patients who were given tildrakizumab and was used for the Scalp Itch-NRS and SSA analyses. Safety was analyzed in all randomized patients who received ≥ 1 dose of tildrakizumab. A summary of the randomized, ITT, mITT, and safety analysis populations is provided in Supplementary Fig. 1.

For comparisons between tildrakizumab versus placebo within each subgroup as well as between patients with obesity versus those without obesity, the common risk differences and 95% confidence intervals (CIs) for IGA mod 2011 (scalp) response, PSSI 90 response, and a ≥ 4-point reduction from baseline in Scalp Itch-NRS were estimated by the Miettinen–Nurminen method stratified by body weight class (≤ 90 kg versus > 90 kg) and prior exposure to tumor necrosis factor-α inhibitors; *p*-values were obtained using a Cochran–Mantel–Haenszel test stratified by body weight (≤ 90 kg versus > 90 kg) and prior exposure to tumor necrosis factor-α inhibitors. SSA data were reported descriptively for each subgroup. For IGA mod 2011 (scalp) response, PSSI 90 response, and Scalp Itch-NRS analysis, missing data were imputed using non-responder imputation. For percent change from baseline in SSA affected, data were reported as observed.

RESULTS

Patient Demographics and Baseline Clinical Characteristics

Among the ITT population, 56/117 (47.9%) patients randomized to tildrakizumab 100 mg and 57/114 (50.0%) randomized to placebo had obesity; the proportion of patients with obesity was similar in the mITT population (43/89 [48.3%] patients randomized to tildrakizumab and 40/82 [48.8%] randomized to placebo; Supplementary Fig. 1). Obesity was generally associated with higher body weight; 77% of

patients with obesity weighed > 90 kg and 19% weighed ≥ 120 kg. Among patients without obesity, approximately 90% weighed ≤ 90 kg and none weighed ≥ 120 kg. Baseline patient characteristics, including measures of psoriasis severity, were similar between the subgroups with and without obesity (Table 1). A numerically higher proportion of patients with obesity had severe psoriasis overall (Physician Global Assessment for Skin score of 4; 21/113 [18.6%]) relative to patients without obesity (13/118 [11.0%]; Table 1).

Efficacy

At Week 16, significantly higher proportions of patients treated with tildrakizumab versus placebo achieved IGA mod 2011 (scalp) response among those with obesity (21/43 [48.8%] versus 4/40 [10.0%], response rate difference [95% CI]: 32.6% [15.1%, 50.1%], $p = 0.0002$) and without obesity (23/46 [50.0%] versus 2/42 [4.8%], response rate difference [95% CI]: 41.5% [25.4%, 57.6%], $p < 0.0001$; Fig. 1). The IGA mod 2011 (scalp) response rate improved from Week 16 to Week 52 in patients with obesity (26/43 [60.5%] at Week 52) and without obesity (30/46 [65.2%] at Week 52) who continuously received tildrakizumab. After patients originally randomized to placebo switched to tildrakizumab at Week 16, there was no significant difference in IGA mod 2011 (scalp) response at Week 52 between patients continuously treated with tildrakizumab versus those switched from placebo to tildrakizumab for those either with obesity (26/43 [60.5%] versus 20/40 [50.0%], $p = 0.2804$) or without obesity (30/46 [65.2%] versus 26/42 [61.9%], $p = 0.6393$) subgroup. There was no statistically significant effect of obesity on the response to tildrakizumab at Week 16 (0.2% response rate difference, $p = 0.9147$) or Week 52 (0.6% response rate difference, $p = 0.8875$).

Similarly, a significantly higher proportion of patients treated with tildrakizumab achieved PSSI 90 response at Week 16 compared with those treated with placebo, irrespective of obesity status (Fig. 2). For patients with obesity, 27/43 (62.8%) treated with tildrakizumab versus 4/40 (10.0%) treated with placebo achieved PSSI 90 response (response rate difference [95% CI]: 43.9% [27.0%, 60.8%], $p < 0.0001$), compared with 27/46 (58.7%) versus 0/42 (0.0%) patients without obesity (response rate difference [95% CI]: 53.9% [40.0%, 67.9%], $p < 0.0001$). The PSSI 90 response to tildrakizumab 100 mg was maintained through Week 52 (patients with obesity, 27/43 [62.8%]; patients without obesity, 31/46 [67.4%]). At Week 52, there was no significant difference between patients continuously treated with tildrakizumab versus those who switched from placebo to tildrakizumab among those either with obesity (27/43 [62.8%] versus 21/40 [52.5%], $p = 0.3060$) or without obesity (31/46 [67.4%] versus 26/42 [61.9%], $p = 0.4893$) subgroup. There was no significant difference between patients with versus without obesity who were treated with tildrakizumab at either Week 16 (–1.9% response rate difference, $p = 0.7851$) or Week 52 (–2.0% response rate difference, $p = 0.6058$).

Patients treated with tildrakizumab were significantly more likely to achieve a Scalp Itch-NRS ≥ 4-point reduction from baseline at Week 16 relative to patients receiving placebo irrespective of obesity status (Fig. 3). For the subgroup of patients with obesity, 27/48 (56.3%) patients treated with tildrakizumab versus 10/54 (18.5%) patients receiving placebo achieved a Scalp Itch-NRS ≥ 4-point reduction from baseline (response rate difference [95% CI]: 33.9% [17.2%, 50.6%], $p < 0.0001$). For the subgroup without obesity, this outcome was achieved by 28/53 (52.8%) patients treated with tildrakizumab versus 5/48 (10.4%) patients treated with placebo (response rate difference [95% CI]: 37.8% [22.1%, 53.6%], $p < 0.0001$). The Scalp Itch-NRS response rate improved from Week 16 to Week 52. The proportion of patients with obesity treated with tildrakizumab who achieved a Scalp Itch-NRS ≥ 4-point reduction from baseline increased from 27/48 (56.3%) at Week 16 to 31/40 (77.5%) at Week 52. Similarly, the proportion of patients without obesity who were treated with tildrakizumab and achieved a Scalp Itch-NRS ≥ 4-point reduction from baseline increased from 28/53 (52.8%) at Week 16 to 31/42 (73.8%) at Week 52. By Week 52, there was no significant difference between patients originally randomized to tildrakizumab versus those switched from placebo

Table 1 Demographics and baseline clinical characteristics by obesity status

Characteristic	No obesity (BMI < 30 kg/m^2)		Obesity (BMI ≥ 30 kg/m^2)	
	TIL 100 mg (*n* = 61)	Placebo (*n* = 57)	TIL 100 mg (*n* = 56)	Placebo (*n* = 57)
Sex				
Male	39 (63.9)	36 (63.2)	32 (57.1)	27 (47.4)
Female	22 (36.1)	21 (36.8)	24 (42.9)	30 (52.6)
Age, years, mean (SD)	44.0 (15.74)	44.6 (13.98)	47.4 (14.66)	45.1 (11.96)
Race				
White	48 (78.7)	45 (78.9)	44 (78.6)	45 (78.9)
Black or African American	3 (4.9)	4 (7.0)	7 (12.5)	5 (8.8)
Asian	7 (11.5)	5 (8.8)	1 (1.8)	4 (7.0)
American Indian or Alaska Native	1 (1.6)	1 (1.8)	3 (5.4)	0
Native Hawaiian or Other Pacific Islander	2 (3.3)	0	1 (1.8)	2 (3.5)
Other	0	2 (3.5)	0	1 (1.8)
Weight, kg, mean (SD)	73.42 (12.76)	75.48 (12.17)	104.61 (16.60)	103.78 (21.52)
> 90 kg, *n* (%)	7 (11.5)	5 (8.8)	42 (75.0)	45 (78.9)
≥ 120 kg, *n* (%)	0	0	12 (21.4)	10 (17.5)
BMI, kg/m^2, mean (SD)	25.69 (3.29)	25.96 (2.59)	36.39 (5.28)	36.73 (5.86)
Prior use of TNF-α inhibitors	8 (13.1)	6 (10.5)	7 (12.5)	9 (15.8)
IGA mod 2011 (scalp)[a], mean (SD)	3.1 (0.34)	3.2 (0.38)	3.2 (0.38)	3.2 (0.41)
PSSI score, mean (SD)	34.8 (15.66)	31.7 (14.52)	34.3 (14.90)	34.1 (16.39)
Scalp Itch-NRS score, mean (SD)	7.1 (2.40)	7.3 (2.22)	7.2 (2.24)	7.6 (2.35)
SSA involvement, %, mean (SD)	60.1 (24.28)	53.4 (20.58)	60.5 (25.76)	59.6 (24.40)
PASI score	18.97 (6.71)	18.68 (8.16)	18.91 (6.38)	18.32 (7.05)
PGA-S score				
3	54 (88.5)	51 (89.5)	44 (78.6)	47 (82.5)
4	7 (11.5)	6 (10.5)	12 (21.4)	9 (15.8)
Total BSA involvement, %, mean (SD)	22.84 (14.13)	22.86 (14.07)	23.69 (14.02)	22.20 (13.36)
Medical history[b]	13 (21.3)	15 (26.3)	33 (58.9)	18 (31.6)
Hypercholesterolemia	3 (4.9)	2 (3.5)	6 (10.7)	3 (5.3)

Table 1 continued

Characteristic	No obesity (BMI < 30 kg/m^2)		Obesity (BMI ≥ 30 kg/m^2)	
	TIL 100 mg (*n* = 61)	Placebo (*n* = 57)	TIL 100 mg (*n* = 56)	Placebo (*n* = 57)
Hyperglycemia	0	1 (1.8)	0	0
Hypertension	9 (14.8)	11 (19.3)	32 (57.1)	15 (26.3)
Hypertriglyceridemia	0	1 (1.8)	0	0
Type 2 diabetes mellitus	4 (6.6)	4 (7.0)	8 (14.3)	9 (15.8)

Data are shown as *n* (%) for the ITT analysis set, unless otherwise specified. *BMI* body mass index, *BSA* body surface area, *IGA mod 2011 (scalp)* Investigator Global Assessment modified 2011 of the scalp, *ITT* intention-to-treat, *mITT* modified intention-to-treat, *NRS* Numeric Rating Scale, *PASI* Psoriasis Area and Severity Index, *PGA-S* Physician Global Assessment for Skin, *PSSI* Psoriasis Scalp Severity Index, *SD* standard deviation, *SSA* scalp surface area, *TIL* tildrakizumab, *TNF* tumor necrosis factor

[a]IGA mod 2011 is reported for the mITT population

[b]Includes patients with ≥ 1 previous medical condition

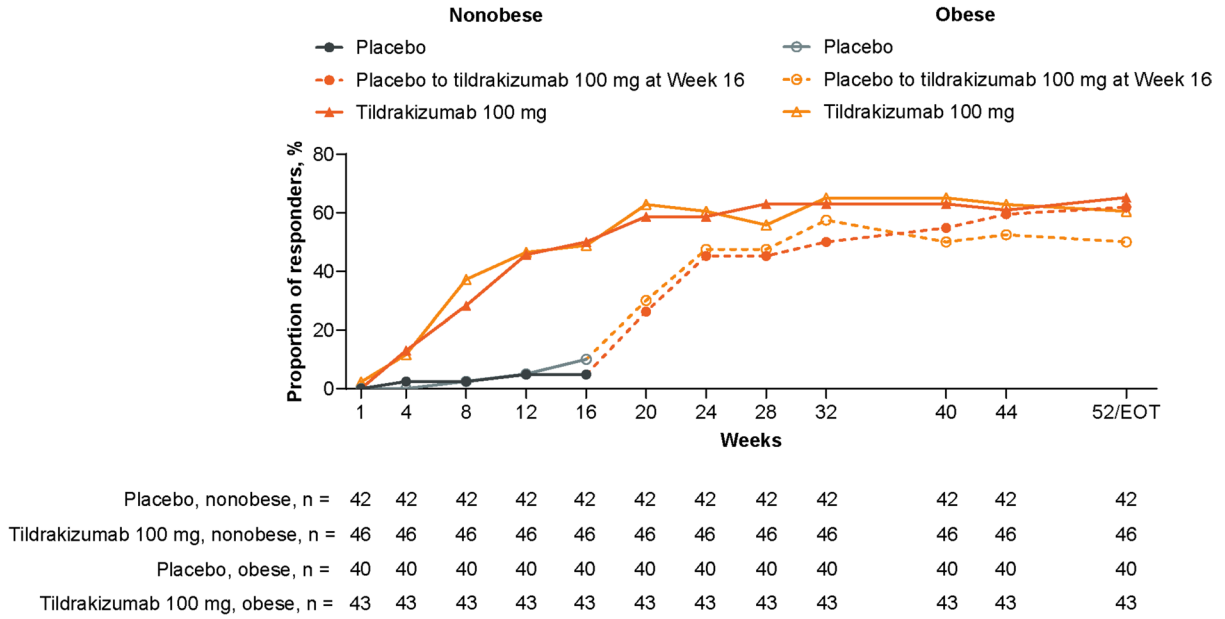
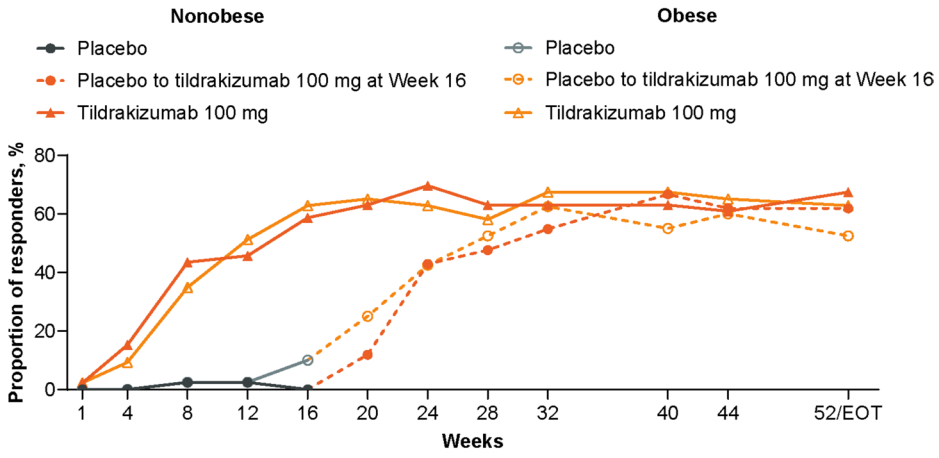


Fig. 1 IGA mod 2011 (scalp) response over 52 weeks by obesity status in the mITT set (NRI). Patients originally randomized to placebo were switched to tildrakizumab 100 mg after Week 16. *EOT* end of treatment, *IGA mod 2011 (scalp) response* Investigator Global Assessment modified 2011 of the scalp score of "clear"/"almost clear" (0/1) with a ≥ 2-point reduction from baseline, *mITT* modified intention-to-treat, *NRI* nonresponder imputation

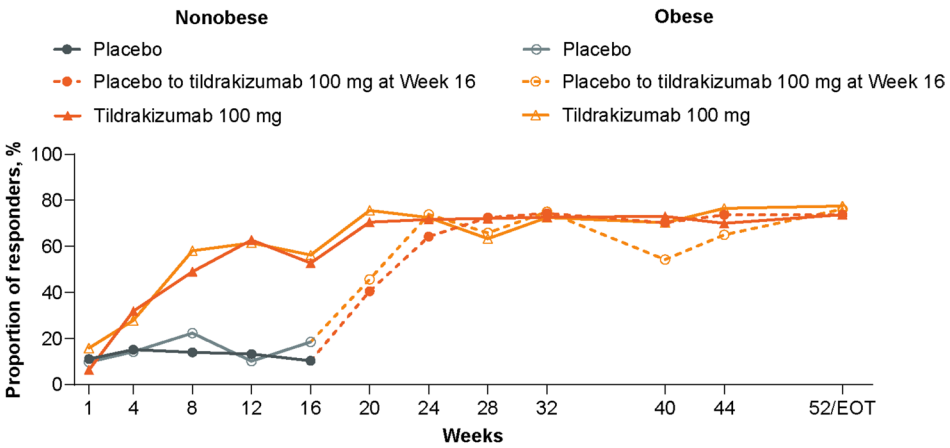
to tildrakizumab among those with obesity (31/40 [77.5%] versus 32/42 [76.2%], $p = 0.8394$) or without obesity (31/42 [73.8%] versus 28/38 [73.7%], $p = 0.8917$). Obesity had no significant effect on the response rate in patients treated with tildrakizumab at Week 16 (5.0% response rate difference, $p = 0.4685$) or Week 52 (2.8% response rate difference, $p = 0.5508$).

At Week 16, the mean (standard deviation [SD]) percent change from baseline in affected



Placebo, nonobese, n =	42	42	42	42	42	42	42	42	42	42	42	42
Tildrakizumab 100 mg, nonobese, n =	46	46	46	46	46	46	46	46	46	46	46	46
Placebo, obese, n =	40	40	40	40	40	40	40	40	40	40	40	40
Tildrakizumab 100 mg, obese, n =	43	43	43	43	43	43	43	43	43	43	43	43

Fig. 2 PSSI 90 response rates by obesity status over the 52-week study period in the mITT set (NRI). *EOT* end of treatment, *mITT* modified intention-to-treat, *NRI* nonresponder imputation, *PSSI 90 response* ≥ 90% improvement in Psoriasis Scalp Severity Index score



Placebo, nonobese, n =	45	46	43	45	48	42	42	40	39	37	38	38
Tildrakizumab 100 mg, nonobese, n =	47	47	51	43	53	44	46	43	44	37	40	42
Placebo, obese, n =	51	49	49	49	54	46	46	41	44	35	40	42
Tildrakizumab 100 mg, obese, n =	44	43	43	39	48	41	40	41	40	37	34	40

Fig. 3 Proportion of patients with a ≥ 4-point reduction in Scalp Itch-NRS from baseline by obesity status over the 52-week study period in the ITT set (NRI). *EOT* end of treatment, *ITT* intention-to-treat, *NRI* nonresponder imputation, *NRS* Numeric Rating Scale

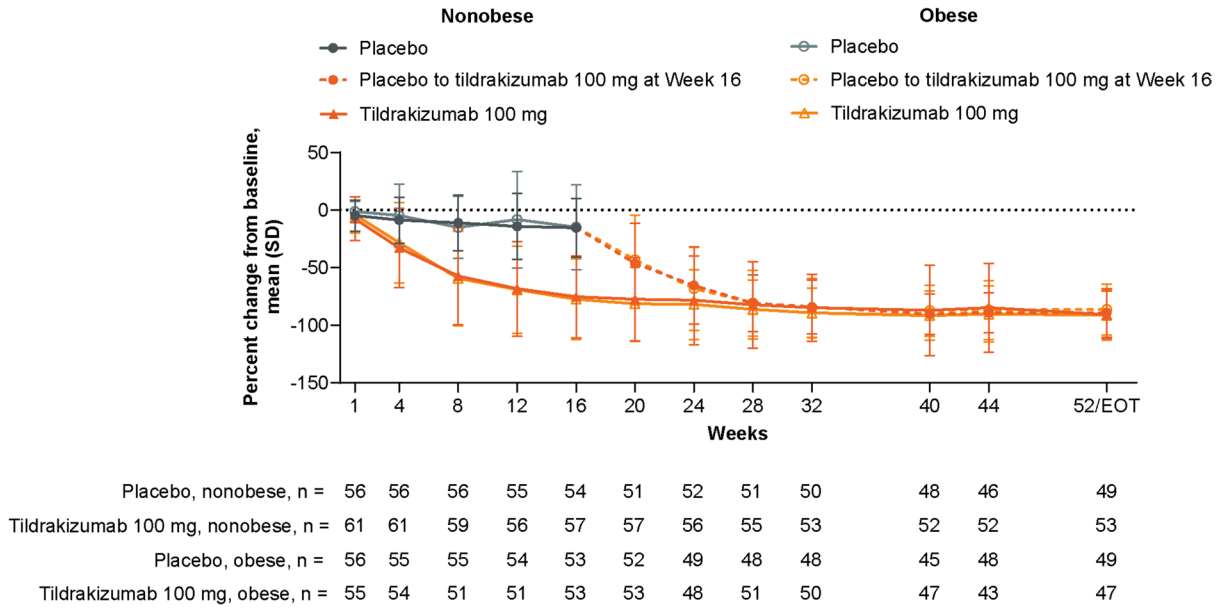


Fig. 4 Mean (SD) percent change from baseline in SSA by obesity status over the 52-week study period in the ITT set (as observed). *EOT* end of treatment, *ITT* intention-to-treat, *SD* standard deviation, *SSA* scalp surface area

SSA was larger in all patients treated with tildrakizumab versus placebo (–77.5% [34.97%] versus –14.9% [36.79%] for patients with obesity and –75.3% [35.65%] versus –15.5% [25.55%] for patients without obesity; Fig. 4). At Week 52, the mean (SD) percent change from baseline in affected SSA was similar in patients with and without obesity in the tildrakizumab versus placebo-to-tildrakizumab treatment arms (–91.2% [21.70%] versus –86.4% [22.19%] for patients with obesity and –91.0% [20.36%] versus –89.2% [20.95%] for patients without obesity; Fig. 4). Although no formal analysis was performed, the changes were numerically similar between patients with and without obesity who were treated with tildrakizumab.

Safety

Among the patients with obesity, 14/56 (25.0%) treated with tildrakizumab versus 11/57 (19.3%) treated with placebo experienced a TEAE from baseline to Week 16, compared with 25/61 (41.0%) versus 13/57 (22.8%) of patients without obesity; during the entire study period, 45/109 (41.3%) patients with obesity and 58/115 (50.4%) patients without obesity experienced a TEAE during treatment with tildrakizumab (Table 2). The most frequent TEAEs (those occurring in ≥ 3% of patients) were nasopharyngitis, headache, hypertension, and coronavirus disease 2019 infection. Only one patient with obesity treated with tildrakizumab discontinued treatment due to their TEAE (previously reported as a positive Cologuard test unrelated to treatment [25]). Investigators considered TEAEs to be related to treatment in 3.7–7.0% of patients across all four subgroups. For the full study period, the frequency of SAEs was also comparable between patients with or without obesity treated with tildrakizumab (3/109 [2.8%] or 4/115 [3.5%], respectively); none of the SAEs were considered related to treatment (Table 2). The observed SAEs included cardiac disorders in two patients with obesity and two patients without obesity, chronic obstructive pulmonary disease in one patient with obesity, exposure during pregnancy for one patient without obesity, and sciatica in one patient without obesity.

AEs of special interest were uncommon and similar between patients with and without obesity. A major adverse cardiovascular event

Table 2 Summary of AEs for the full study period

	No obesity (BMI < 30 kg/m^2)		Obesity (BMI ≥ 30 kg/m^2)	
	TIL 100 mg (*n* = 115)	**Placebo (*n* = 57)**	**TIL 100 mg (*n* = 109)**	**Placebo (*n* = 57)**
n (%)				
Any TEAE	58 (50.4)	13 (22.8)	45 (41.3)	11 (19.3)
Treatment-related TEAEs	6 (5.2)	4 (7.0)	4 (3.7)	3 (5.3)
SAEs	4 (3.5)	0	3 (2.8)	0
Treatment-related SAEs	0	0	0	0
TEAEs of clinical interest	0	0	0	0
TEAE leading to discontinuation	0	0	1 (0.9)	0
Deaths	0	0	0	0
AEs of special interest				
Injection-site reaction	0	1 (1.8)	0	0
MACE	2 (1.7)	0	2 (1.8)	0
NMSC	1 (0.9)	0	1 (0.9)	0
Treatment-related hypersensitivity	1 (0.9)	1 (1.8)	1 (0.9)	0
Total follow-up, PYs	113.3	17.4	106.7	16.8
EAIR[a]				
Injection-site reaction	0	1 (5.8)	0	0
MACE	2 (1.8)	0	2 (1.9)	0
NMSC	1 (0.9)	0	1 (0.9)	0
Treatment-related hypersensitivity	1 (0.9)	1 (5.7)	1 (0.9)	0

All TEAEs were summarized under the treatment group to which each AE was attributed. All AEs that occurred after Week 16 were counted in the tildrakizumab 100 mg group. *AE* adverse event, *BMI* body mass index, *MACE* major adverse cardiovascular event, *EAIR* exposure-adjusted incidence rate, *NMSC* nonmelanoma skin cancer, *PY* patient-year, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event, *TIL* tildrakizumab

[a]Data shown as *n* (number of events per 100 PYs of exposure). EAIR = number of patients with the event/total exposure time (PYs) × 100

(MACE) was recorded for two (1.8%) patients with obesity and two (1.7%) patients without obesity, all during tildrakizumab treatment; all four of these patients had relevant medical history as previously described [25]. There were no deaths during the study (Table 2).

DISCUSSION

In this post hoc subgroup analysis, obesity did not appear to affect the efficacy or safety of tildrakizumab treatment for patients with moderate-to-severe plaque psoriasis affecting the scalp.

Significantly larger proportions of patients with or without obesity who were treated with tildrakizumab 100 mg versus placebo achieved IGA mod 2011 (scalp) response, PSSI 90 response, and a ≥ 4-point reduction from baseline in Scalp Itch-NRS at Week 16, with no statistically significant effect of obesity; descriptive results for the percent change from baseline in affected SSA were similar. The frequencies of TEAEs and SAEs, including MACEs, were similar between patients with and without obesity who were treated with tildrakizumab, with no new safety signals identified in either subgroup. Because the analysis was not prospectively powered to detect differences between BMI subgroups, the absence of a statistically significant between-subgroup effect should not be interpreted as evidence of equivalence.

To our knowledge, this post hoc analysis is the first to directly investigate the effect of obesity on the efficacy of a biologic treatment for scalp psoriasis specifically. Psoriasis and obesity are believed to be interconnected, with a complex pathophysiology involving shared inflammatory pathways [12]. Obesity is characterized by chronic low-grade inflammation [12] and is therefore suggested to drive inflammation in patients with psoriasis, as adipose tissue inflammation can exacerbate psoriasis-related immune dysregulation [12, 13]. In a longitudinal systematic review and meta-analysis including 201,831 patients with psoriasis, those with moderate-to-severe psoriasis had greater odds of having obesity than those with mild psoriasis, implying a connection between obesity and psoriasis severity [7]. This relationship can affect response to treatment, with lower efficacy of some biologics in patients with psoriasis with obesity or high BMI. This effect was known for etanercept and adalimumab as early as 2011 [26]. In a real-world study of patients with psoriasis published in 2021, those with a BMI ≥ 30 kg/m^2 had poorer clinical response to biological drugs, especially ixekizumab, secukinumab, and ustekinumab [8].

The BMI is an anthropometric measure that does not directly capture adipose tissue distribution, visceral adiposity, insulin resistance, or metabolic risk factors [27–31]. Therefore, BMI-defined obesity may not distinguish patients with metabolically healthy obesity from those with metabolically unhealthy obesity, the latter of whom may have greater systemic inflammatory burden and cardiometabolic risk [32]. This distinction may be particularly relevant in psoriasis, where metabolic syndrome and obesity-related inflammation may contribute to disease severity and potentially influence treatment response [26]. Body weight in patients with obesity may also influence pharmacokinetics and therefore the response to treatment. Population pharmacokinetic analyses and subgroup analyses of the clinical trials of tildrakizumab suggest that higher body weight may modestly reduce exposure and early response, while overall efficacy remains clinically meaningful and the incremental benefit of dose escalation appears limited [33–35]. In a post hoc study of the pivotal Phase 3 reSURFACE clinical trials assessing the effect of different body weight thresholds, rather than BMI, on the efficacy and safety of tildrakizumab treatment (100 mg or 200 mg) for patients with moderate-to-severe psoriasis [36], the proportion of patients receiving treatment who achieved efficacy outcomes was comparable between those with a body weight < 90 kg or ≥ 90 kg [36]; however, patients with a higher body weight (≥ 120 kg) appeared to benefit from a higher tildrakizumab dose (200 mg) [36]. Safety outcomes were also similar irrespective of treatment dose and/or weight. Although obesity decreased some measures of tildrakizumab efficacy in a recent analysis of reSURFACE 1 and reSURFACE 2, the effect was not consistently significant across measures and time points [37]. These results, although not conclusive, suggested that obesity may not decrease the efficacy of tildrakizumab to the same extent as observed with some other biologics.

Limitations

This analysis was limited by its post hoc nature, as it was not prospectively powered to detect differences between subgroups with or without obesity and should thus be considered exploratory. Subgroup sizes, particularly in the mITT population, were relatively small, limiting the ability to draw definitive conclusions regarding between-subgroup differences. Therefore, the absence of statistically significant differences between BMI

subgroups should not be interpreted as establishing equivalence, but rather as indicating that no between-subgroup difference was detected within the available sample size. In addition, the patient subgroups with and without obesity were established using BMI, which does not capture central adiposity, metabolic syndrome status, or inflammatory burden and may not adequately distinguish BMI-defined obesity from metabolically unhealthy obesity [12, 27–32]. Waist circumference was not collected in the parent trial; consequently, this analysis could not address whether central adiposity or metabolic dysfunction modified tildrakizumab response beyond BMI classification alone. Further examination by obesity subcategory (eg, obesity Class I and Class III) or alternative indicators specific to chronic inflammation and metabolic dysfunction could reveal subtle impacts on the efficacy or safety of treatment for plaque psoriasis of the scalp; analyses by body weight could also clarify the effects of pharmacokinetic differences in larger patients versus those of obesity-related inflammatory burden.

CONCLUSIONS

This post hoc subgroup analysis demonstrated consistent efficacy of tildrakizumab with no new safety signals identified in patients both with and without obesity concomitant with moderate-to-severe plaque psoriasis affecting the scalp. These findings should be interpreted with caution given the small sample subgroup sizes. Tildrakizumab treatment improved efficacy outcomes compared with placebo in patients both with and without obesity, and there was no statistically significant effect of obesity. Further research in larger populations using more specific indicators of chronic inflammation is needed to confirm whether obesity-driven inflammation may have subtler effects on the efficacy of tildrakizumab for the treatment of psoriasis.

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Declarations

Conflict of Interest. Howard L. Sofen has served as a clinical investigator for AbbVie, Alumis, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant Sciences, Eli Lilly, Janssen, LEO Pharma, Novartis, Oruka Therapeutics, Sun Pharma, UCB, and Vyne Therapeutics. Ranga Gogineni is an employee of Sun Pharmaceutical Industries, Inc. Tushar Nishandar is an employee of Sun Pharmaceutical Industries Limited. Jerry Bagel has received research funds for the Psoriasis Treatment Center from AbbVie, Amgen, Arcutis Biotherapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Celgene Corporation, Corrona, Dermavant Sciences, Dermira, Glenmark Pharmaceuticals, Janssen, Kadmon Corporation, LEO Pharma, Lilly, Lycera, Menlo

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