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ORIGINAL ARTICLE

Tildrakizumab efficacy and safety in patients with psoriasis and concomitant metabolic syndrome: *post hoc* analysis of 5-year data from reSURFACE 1 and reSURFACE 2

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Abstract

Background Limited data are available on long-term efficacy and safety of biologics in patients with psoriasis and metabolic syndrome (MetS), a common comorbidity.

Objectives This analysis updates tildrakizumab efficacy and safety for up to 5 years in patients with and without MetS.

Methods This was a *post hoc* analysis of the double-blind, randomized, placebo-controlled, phase 3 reSURFACE 1 (NCT01722331) and reSURFACE 2 (NCT01729754) trials in adult patients with moderate to severe chronic plaque psoriasis. Analyses included data through Week 244 from patients who continuously received tildrakizumab 100 (TIL100) or 200 mg (TIL200) and entered the extension studies, stratified by baseline MetS status. Efficacy was assessed *via* Psoriasis Area and Severity Index (PASI) scores. Safety was evaluated from exposure-adjusted incidence rates (EAIRs) of treatment-emergent adverse events (TEAEs).

Results reSURFACE 1 and reSURFACE 2 analyses included 26 and 44 TIL100-treated patients with MetS, 98 and 167 TIL100-treated patients without MetS, 34 and 30 TIL200-treated patients with MetS, and 111 and 130 TIL200-treated patients without MetS, respectively. There were no clinically relevant differences in PASI 75/90/100 response rates at Week 244 between patients with *vs* without MetS. The proportion of patients with *vs* without MetS achieving absolute PASI score <3 at Week 244 was 53.8% *vs* 69.4% and 77.3% *vs* 80.8% in reSURFACE 1 and 2, respectively, for TIL100-treated patients and 58.8% *vs* 72.1% and 63.3% *vs* 72.3%, respectively, for TIL200-treated patients. In both studies, median reduction from baseline PASI score at all time points in patients with *vs* without MetS was >83% *vs* >89% for TIL100 and >85% *vs* >90% for TIL200. Pooled EAIRs of TEAEs, serious TEAEs, and TEAEs of special interest were similar in patients with and without MetS.

Conclusions Tildrakizumab maintains efficacy and a favorable safety profile over 5 years in patients with psoriasis regardless of MetS status.

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Conflicts of interest

APF has received grants and/or honoraria as a consultant, investigator, and/or speaker for AbbVie, Alexion, Corbus, Mallinckrodt, Novartis, UCB, Pfizer, and Kyowa Kirin. ED has been an advisory board member and consultant, has received grants and research support, has participated in clinical trials, and has received honorarium for speaking with or from the following pharmaceutical companies: AbbVie/Abbott, Almirall, Amgen, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, MSD-Schering-Plough, Novartis, Pfizer, and UCB. 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KG has received grants and/or honoraria as a consultant, investigator, and/or speaker for AbbVie, Abbott Labs, Amgen, Anacor, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Merck, Novartis, Regeneron, Sandoz Biopharmaceuticals, Sanofi-Aventis, Schering-Plough, Sun Pharmaceutical Industries, Inc., UCB, and Wyeth Pharma; and has been on an advisory board for AbbVie, Amgen, Boehringer Ingelheim, Eli Lilly, Janssen, and LEO Pharma. YT has received honoraria for research from AbbVie, Celgene, Eisai, Eli Lilly, Kyowa Hakko Kirin, LEO Pharma, Maruho, Meiji Seika Pharma, Taiho, and Torii, and for lecturing from Maruho, AbbVie, Celgene, Eli Lilly, Janssen, Kyowa Hakko Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe Pharma Co., Novartis Pharma K.K., Taiho, and UCB. JPL has been a consultant for, has received grants from, and/or has served as a speaker for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis, and Pfizer. 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NNM is a full-time employee of the US government, has received fees for research consulting from LEO Pharma, Amgen, AstraZeneca, MedImmune, and has received support in the form of grants to the National Institutes of Health from AbbVie, Celgene, Janssen, and Novartis.

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Introduction

Metabolic syndrome (MetS) is characterized by metabolic risk factors—such as obesity, dyslipidemia, hypertension, and increased fasting blood glucose—that increase the risk of cardiovascular (CV) disease (CVD) and diabetes.[1,2] Individuals with MetS have an increased risk of CV and diabetic events, CVD-related mortality, and overall mortality compared to those without MetS.[1,3] Patients with psoriasis have an estimated >2-fold increased risk of MetS compared with the general population,[4–7] and the risk of MetS is positively correlated with psoriasis severity.[6–10] Some therapeutic agents for psoriasis treatment, such as tumour necrosis factor (TNF) inhibitors and anti-interleukin (IL)-17A agents, may be less effective in patients with MetS,[11,12] although no data are available on the long-term efficacy and safety of biologics in patients with psoriasis and concomitant MetS.

Tildrakizumab is a humanized, immunoglobulin G1κ, monoclonal antibody specifically targeting anti–IL-23p19[13] approved for the treatment of plaque psoriasis in patients who are candidates for systemic therapy.[13] The usual recommended dose is tildrakizumab 100 mg at weeks 0 and 4 and every 12 weeks thereafter; in the EU, tildrakizumab 200 mg may be considered in patients with high disease burden.[13–16] The efficacy and safety of tildrakizumab were established in two phase 3 randomized controlled trials (reSURFACE 1 [NCT01722331] and reSURFACE 2 [NCT01729754])[13] with results through 5 years of follow-up.[17] In *post hoc* evaluations of tildrakizumab safety and efficacy in patients from reSURFACE 1 and reSURFACE 2 with or without MetS based on initial data (52 weeks of follow-up)[18] and a longer-term assessment (3 years for efficacy, 5 years for safety),[19] tildrakizumab efficacy and safety were not meaningfully altered by MetS status in patients with psoriasis. This analysis updates the efficacy and safety of tildrakizumab through up to 5 years of follow-up in reSURFACE 1 and reSURFACE 2 patients with psoriasis with and without concomitant MetS.

Materials and methods

Study design

This was a *post hoc* analysis of the previously published 3-part, multinational, double-blind, randomized, placebo-controlled, phase 3 reSURFACE 1 and reSURFACE 2 clinical trials.[13] Patients achieving ≥50% improvement from baseline Psoriasis Area and Severity Index (PASI) score at the end of the reSURFACE 1 and reSURFACE 2 base studies (Week 64 and Week 52, respectively) were eligible to enter the optional long-term extension periods. The study protocols were reviewed and approved by local institutional review boards or ethics panels, and all patients provided informed written consent.

Patients and treatments

The inclusion/exclusion criteria and treatment protocols for reSURFACE 1 and 2 were previously described.[13] Briefly, patients ≥18 years of age with moderate to severe chronic plaque psoriasis at baseline (defined as a body surface area involvement ≥10%), Physician's Global Assessment (PGA) ≥3, and PASI score ≥ 12 were eligible. Tildrakizumab 100 or 200 mg was administered *via* subcutaneous injection at Weeks 0 and 4 and every 12 weeks thereafter. Additional patients in reSURFACE 2 received etanercept twice weekly to Week 12 and once weekly to Week 28. These analyses include only patients who received tildrakizumab 100 or 200 mg[13] continuously throughout the base studies and entered the long-term extensions.

Baseline MetS status was defined using National Cholesterol Education Program criteria[2] with the exception that body mass index (BMI) was used as a surrogate for waist circumference, because waist circumference was not measured in reSURFACE 1 and reSURFACE 2; BMI correlates well with waist circumference and MetS status.[20,21] Patients were classified as having MetS if they had ≥3 of the following: BMI >30 kg/m^2, triglycerides ≥150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL in men or <50 mg/dL in women, systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, and fasting glucose ≥110 mg/dL.[2]

Assessments and outcomes

Efficacy was assessed by evaluating changes from baseline PASI score. In part 3 and the extension periods, PASI was evaluated at weeks 28, 32, 36, 40, 52, 60, and 64; every 12 weeks to Week 148; and every 24 weeks thereafter. Outcomes included the proportions of patients achieving ≥75%, ≥90%, and ≥100% improvement from baseline PASI score (ie, PASI 75, 90, and 100 response rates); percentage median improvement from baseline PASI score; and the proportion of patients achieving absolute PASI score <3. Safety was assessed at all study visits and evaluated from exposure-adjusted incidence rates (EAIRs) of treatment-emergent adverse events (TEAEs), Tier 1 TEAEs, and serious AEs (SAEs) using the Medical Dictionary for Regulatory Activities System Organ Class codes. Tier 1 TEAEs included serious infections (reported as SAEs or requiring intravenous

Table 1 Patient demographics and disease characteristics by trial, treatment group, and metabolic syndrome status

	reSURFACE 1				reSURFACE 2			
	TIL 100 mg		TIL 200 mg		TIL 100 mg		TIL 200 mg	
	Without MetS (*n* = 98)	With MetS (*n* = 26)	Without MetS (*n* = 111)	With MetS (*n* = 34)	Without MetS (*n* = 167)	With MetS (*n* = 44)	Without MetS (*n* = 130)	With MetS (*n* = 30)
Age, years	46.1 ± 14.0	49.1 ± 12.7	46.1 ± 13.6	50.7 ± 11.0	43.1 ± 13.3	45.9 ± 12.7	44.5 ± 13.2	48.7 ± 12.4
Sex, male, *n* (%)	65 (66.3)	18 (69.2)	79 (71.2)	19 (55.9)	119 (71.3)	34 (77.3)	82 (63.1)	23 (76.7)
Race, White, *n* (%)	64 (65.3)	21 (80.8)	67 (60.4)	27 (79.4)	153 (91.6)	41 (93.2)	118 (90.8)	29 (96.7)
Weight, kg	80.8 ± 18.1	106.4 ± 29.6	82.1 ± 17.4	111.8 ± 32.2	82.5 ± 17.1	106.9 ± 21.7	82.0 ± 17.8	108.2 ± 17.6
BMI, kg/m^2	27.9 ± 6.0	35.6 ± 8.5	28.4 ± 5.8	38.5 ± 8.3	27.4 ± 5.3*	35.6 ± 6.1	27.3 ± 5.3	37.6 ± 9.8
BSA, %	29.4 ± 16.7	32.2 ± 16.6	32.1 ± 19.0	30.1 ± 19.4	33.7 ± 18.1	30.3 ± 18.9	31.3 ± 17.2†	27.6 ± 12.9
Disease duration, years	17.2 ± 12.6	16.2 ± 12.3	16.7 ± 11.6	16.7 ± 12.9	15.9 ± 10.6	15.2 ± 11.2	18.0 ± 13.5	20.1 ± 14.8
Baseline PASI score	19.9 ± 7.1	20.5 ± 7.1	21.3 ± 9.3	20.6 ± 9.7	19.5 ± 6.9	20.8 ± 8.8	19.5 ± 7.2	19.2 ± 6.3
Baseline PGA score	3.3 ± 0.6	3.3 ± 0.6	3.4 ± 0.5	3.5 ± 0.6	3.3 ± 0.5	3.4 ± 0.6	3.3 ± 0.6†	3.4 ± 0.6
CV disorders, *n* (%)	14 (14.3)	17 (65.4)	30 (27.0)	16 (47.1)	29 (17.4)	17 (38.6)	27 (20.8)	17 (56.7)
Diabetes, *n* (%)	8 (8.2)	8 (30.8)	11 (9.9)	8 (23.5)	5 (3.0)	7 (15.9)	11 (8.5)	7 (23.3)
PsA, *n* (%)	16 (16.3)	5 (19.2)	18 (16.2)	9 (26.5)	24 (14.4)	11 (25.0)	17 (13.1)	4 (13.3)
Response to ≥1 systemic therapy‡, *n* (%)	22 (44.9)	5 (71.4)	39 (66.1)	8 (57.1)	108 (64.7)	24 (54.5)	80 (61.5)	17 (56.7)
Prior biologic exposure, *n* (%)	16 (16.3)	8 (30.8)	20 (18.0)	7 (20.6)	22 (13.2)	5 (11.4)	17 (13.1)	7 (23.3)

Data provided as mean ± standard deviation unless otherwise indicated.
*n = 166.
†n = 129.
‡For reSURFACE1, percentages are based on the subset of patients who received methotrexate, cyclosporine, or phototherapy.
BMI, body mass index; BSA, body surface area; CV, cardiovascular; MetS, metabolic syndrome; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; PsA, psoriatic arthritis; TIL, tildrakizumab.

antibiotics), malignancies, nonmelanoma skin cancer, melanoma, confirmed extended major adverse cardiovascular events (MACE; ie, nonfatal myocardial infarction, nonfatal stroke, and CV deaths confirmed as CV or sudden), and drug-related hypersensitivity reactions.

Statistical analysis

The efficacy and safety populations included all patients in the *post hoc* analysis; data through treatment Week 244 for efficacy and 256 weeks for safety were analysed. Baseline characteristics were summarized descriptively for patients with and without MetS. Efficacy outcomes (ie, PASI 75/90/100 responses, change from baseline PASI score, PASI <3) were compared between patients with and without MetS. The primary analysis used a multiple imputation (MI) model to account for missing data using demographic variables and baseline disease characteristics such as age, sex, BMI, presence of psoriatic arthritis, prior exposure to biologics, baseline PASI, baseline PGA, or baseline body surface area as covariates. Following imputation, dichotomized responses (ie, PASI 75, 90, or 100; PASI <3) were computed for each dataset and then reported as the average from 10 imputed datasets. Sensitivity analyses were performed using nonresponse imputation (NRI; ie, patients with missing data were treated as nonresponders) and last observation carried forward (LOCF) analyses. Safety data for patients with and without MetS are presented as pooled EAIRs. There were no power calculations, and no formal hypothesis testing was performed.

Results

Patients

Of the 124 patients in reSURFACE 1 who received tildrakizumab 100 mg continuously and entered the extension study, there were 26 patients with MetS and 98 patients without MetS (Fig. S1a). Of these, 20 patients with MetS and 72 without MetS completed treatment through Week 256. In reSURFACE 2, there were 44 patients with MetS and 167 patients without MetS who received tildrakizumab 100 mg continuously and entered the extension study (Fig. S1b), including 36 with MetS and 130 without MetS who completed treatment through Week 244.

In reSURFACE 1, the 145 patients who received tildrakizumab 200 mg continuously and entered the extension study included 34 patients with MetS and 111 patients without MetS. Among patients with and without MetS, 31 and 83 completed treatment through Week 256, respectively. Of the 160 patients in reSURFACE 2 who received tildrakizumab 200 mg continuously and entered the extension study, there were 30 patients with MetS and 130 patients without MetS; 22 patients with MetS and 130 patients without MetS completed treatment through Week 244.

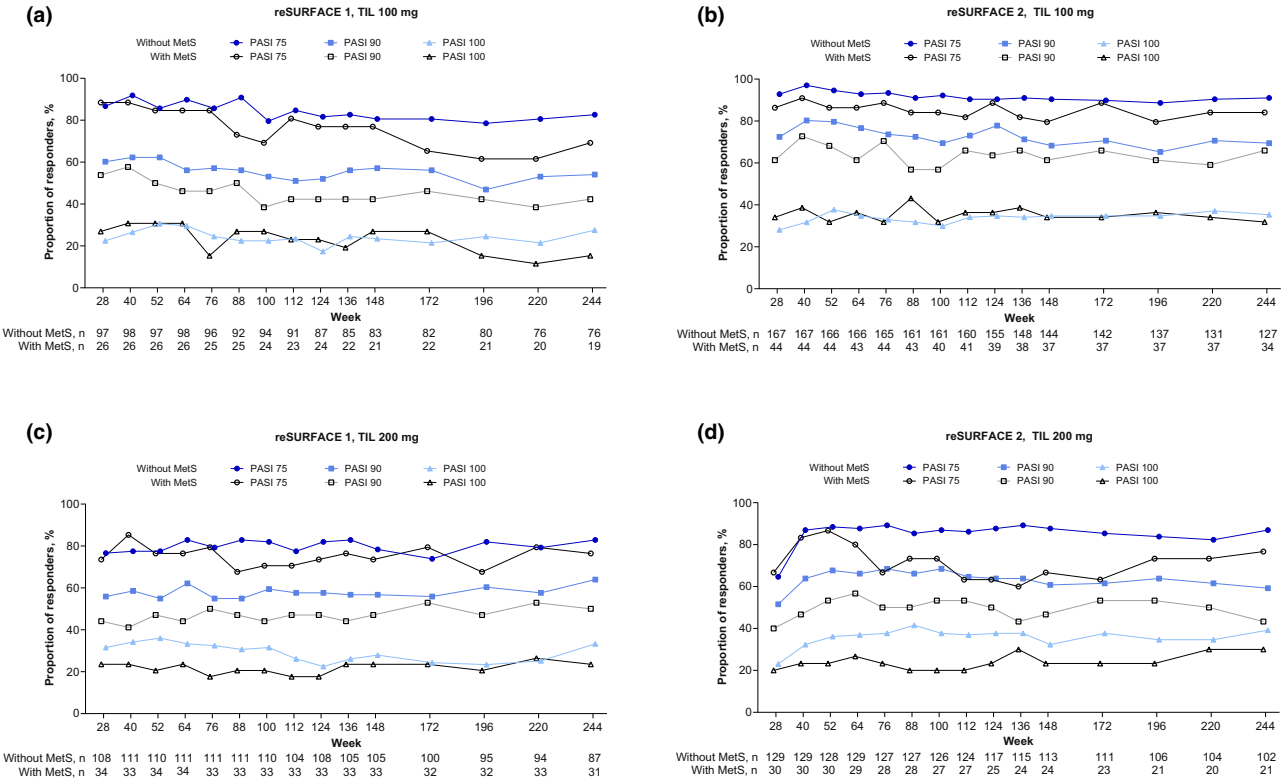

Figure 1 Percentage of PASI 75, 90, and 100 responders receiving continuous tildrakizumab over time by baseline metabolic syndrome status in (a) reSURFACE 1 patients receiving 100 mg of tildrakizumab, (b) reSURFACE 2 patients receiving 100 mg of tildrakizumab, (c) reSURFACE 1 patients receiving 200 mg of tildrakizumab, and (d) reSURFACE 2 patients receiving 200 mg of tildrakizumab. Numbers below graph represent number of patients with available data at each time point. Missing data were handled using MI. MetS, metabolic syndrome; MI, multiple imputation; PASI 75/90/100, 75%/90%/100% improvement from baseline Psoriasis Area and Severity Index score; TIL 100, tildrakizumab 100 mg; TIL 200, tildrakizumab 200 mg.

Patient demographics and disease characteristics by trial and MetS status are summarized in Table 1. The study population for this analysis was generally similar to that of the original study population.[13] Baseline disease severity and duration were similar in patients with and without MetS, but patients with MetS in both reSURFACE 1 and 2 had a numerically higher prevalence of pre-existing CVD, diabetes, and psoriatic arthritis, and greater weight and BMI, compared with those without MetS (Table 1).

Efficacy

In both reSURFACE 1 and 2, proportions of tildrakizumab-treated patients achieving PASI 75/90/100 responses from Weeks 28 to 244 remained numerically similar between those with and without MetS (Fig. 1). The proportions (95% confidence interval [CI]) of reSURFACE 1 patients with *vs* without MetS who received tildrakizumab 100 mg and achieved PASI 75/90/100 responses were 88.5% (69.9%–97.6%)/53.9% (33.4%–73.4%)/26.9% (11.6%–47.8%) *vs* 86.7% (78.4%–92.7%)/60.2% (49.8%–70.0%)/22.5% (14.6%–32.0%) at Week 28 and 69.2% (48.2%–85.7%)/42.3% (23.4%–63.1%)/15.4% (4.4%–34.9%) *vs* 82.7% (73.7%–89.6%)/54.1% (43.7%–64.2%)/27.6% (19.0%–37.5%) at Week 244 (Fig. 1a). In reSURFACE 2 (Fig. 1b), PASI 75/90/100 response rates (95% CI) in tildrakizumab 100 mg-treated patients with *vs* without MetS were 86.4% (72.7%–94.8%)/61.4% (45.5%–75.6%)/34.1% (20.5%–49.9%) *vs* 92.8% (87.8%–96.2%)/72.5% (65.0%–79.1%)/28.1% (21.5%–35.6%) at Week 28 and 84.1% (69.9%–93.4%)/65.9% (50.1%–79.5%)/31.8% (18.6%–47.6%) *vs* 91.0% (85.6%–94.9%)/69.5% (61.9%–76.3%)/35.3% (28.1%–43.1%) at Week 244.

Among patients receiving tildrakizumab 200 mg in reSURFACE 1, PASI 75/90/100 response rates were 73.5% (55.6%–87.1%)/44.1% (27.2%–62.1%)/23.5% (10.8%–41.2%) in patients with MetS *vs* 76.6% (67.6%–84.1%)/55.9% (46.1%–65.3%)/31.5% (23.0%–41.0%) in patients without MetS at Week 28 and 76.5% (58.8%–89.3%)/50.0% (32.4%–67.6%)/23.5% (10.8%–41.2%) in patients with MetS *vs* 82.9% (74.6%–89.4%)/64.0% (54.3%–72.9%)/33.3% (24.7%–42.9%) in patients without MetS at Week 244 (Fig. 1c). In reSURFACE 2, 66.7%

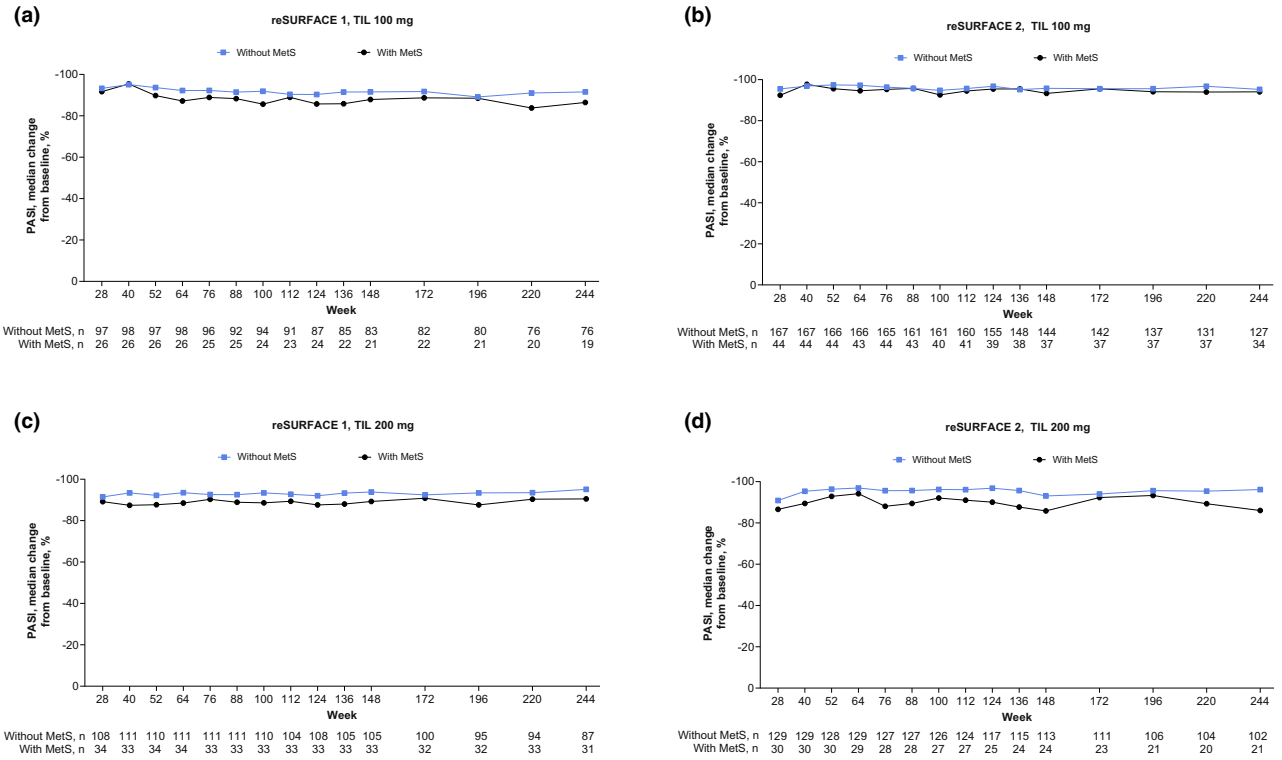

Figure 2 Median change from baseline PASI score over time in patients receiving continuous tildrakizumab stratified by metabolic syndrome status in (a) reSURFACE 1 patients receiving 100 mg of tildrakizumab, (b) reSURFACE 2 patients receiving 100 mg of tildrakizumab, (c) reSURFACE 1 patients receiving 200 mg of tildrakizumab, and (d) reSURFACE 2 patients receiving 200 mg of tildrakizumab (MI analysis). Numbers below graph represent number of patients with available data at each time point. Missing data were handled using MI. MetS, metabolic syndrome; MI, multiple imputation; PASI, Psoriasis Area and Severity Index score; TIL 100, tildrakizumab 100 mg; TIL 200, tildrakizumab 200 mg.

(47.2%–82.7%)/40.0% (22.7%–59.4%)/20.0% (7.7%–38.6%) of patients with MetS *vs* 64.6% (55.8%–72.8%)/51.5% (42.6%–60.4%)/23.1% (16.1%–31.3%) without MetS who received tildrakizumab 200 mg achieved PASI 75/90/100 response at Week 28, and 76.7% (57.7%–90.1%)/43.3% (25.5%–62.6%)/30.0% (14.7%–49.4%) of tildrakizumab 200 mg-treated patients with MetS *vs* 86.9% (79.9%–92.2%)/59.2% (50.3%–67.8%)/39.2% (30.8%–48.2%) without MetS achieved PASI 75/90/100 response at Week 244 (Fig. 1d). Sensitivity analyses using NRI and LOCF imputation are shown in Figs S2 and S3.

The median percent change from baseline PASI score over time in patients with and without MetS receiving continuous tildrakizumab 100 or 200 mg in reSURFACE 1 and 2 is illustrated in Fig. 2. Among patients with MetS receiving tildrakizumab 100 mg, median reductions from baseline in PASI score between Weeks 28 and 244 were >83% at all time points in reSURFACE 1 and >92% at all time points in reSURFACE 2. In patients without MetS, median decline in PASI score was >89% at all time points in reSURFACE 1 and reSURFACE 2. Among patients receiving tildrakizumab 200 mg, median reduction from baseline PASI score in patients with MetS was >85% at all time points between Weeks 28 and 244 in both reSURFACE 1 and reSURFACE 2; in patients without MetS, median reduction from baseline PASI score was >90% in reSURFACE 1 and reSURFACE 2 at all time points between Weeks 28 and 244. The NRI and LOCF sensitivity analyses are shown in Figs S4 and S5. Median absolute reduction in PASI score is shown in Fig. S6.

The substantial reductions in PASI scores resulted in high proportions of patients achieving an absolute PASI score <3 (Fig. 3). At Week 244, the proportion (95% CI) of patients receiving tildrakizumab 100 mg who achieved an absolute PASI score <3 was 53.8% (33.4%–73.4%) and 77.3% (62.2%–88.5%) of patients with MetS and 69.4% (59.3%–78.3%) and 80.8% (74.0%–86.5%) of those without MetS in reSURFACE 1 and reSURFACE 2, respectively. For patients receiving tildrakizumab 200 mg, the proportion (95% CI) in reSURFACE 1 and reSURFACE 2 who achieved an absolute PASI score <3 was 58.8% (40.7%–75.4%) and 63.3% (43.9%–80.1%) of patients with

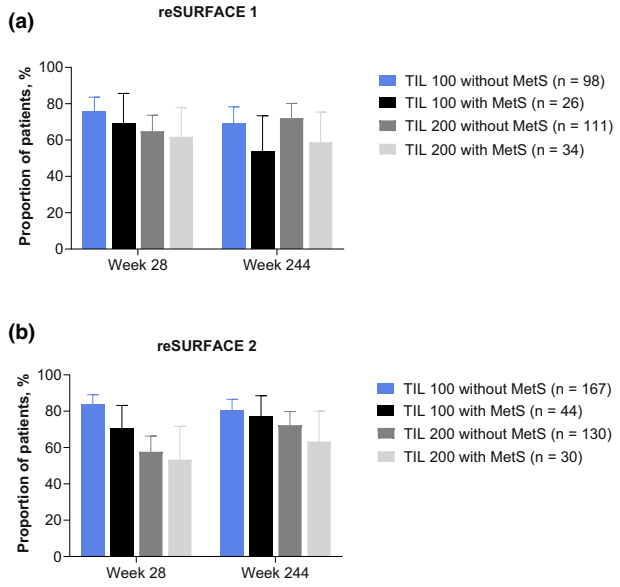

Figure 3 Percentage of patients receiving continuous tildrakizumab 100 or 200 mg who achieved a PASI score <3 over time by baseline metabolic syndrome status in (a) reSURFACE 1 and (b) reSURFACE 2. Missing data were handled using MI. MetS, metabolic syndrome; MI, multiple imputation; PASI, Psoriasis Area and Severity Index; TIL 100, tildrakizumab 100 mg; TIL 200, tildrakizumab 200 mg.

MetS and 72.1% (62.8%–80.2%) and 72.3% (63.8%–79.8%) of patients without MetS, respectively. Sensitivity analyses using NRI and LOCF are shown in Fig. S7.

Safety

Pooled safety data from reSURFACE 1 and reSURFACE 2 collected over 5 years in patients with and without MetS treated with tildrakizumab 100 or 200 mg were generally consistent with the known safety profile of tildrakizumab. The overall EAIRs of Tier 1 TEAEs in patients with or without MetS were similar between those with *vs* without MetS receiving tildrakizumab 100 (1.97 *vs* 2.09 per 100 patient-years) or 200 mg (5.22 *vs* 2.55 per 100 patient-years) (Table 2). The most common Tier 1 TEAEs in patients receiving tildrakizumab 100 or 200 mg were serious infections/infestations and malignancies excluding melanoma and nonmelanoma skin cancer. In patients with *vs* without MetS, the EAIRs of infections/infestations were 0.66 *vs* 0.87 per 100 patient-years for those receiving tildrakizumab 100 mg and 2.09 *vs* 1.23 per 100 patient-years for those receiving tildrakizumab 200 mg. The EAIRs of malignancies excluding melanoma and nonmelanoma skin cancer were 0.33 *vs* 0.44 per 100 patient-years in patients with *vs* without MetS receiving tildrakizumab 100 mg and 1.04 *vs* 0.38 per 100 patient-years in those receiving tildrakizumab 200 mg.

Through the base and extension studies, of patients receiving tildrakizumab 100 mg, 22/70 (31.4%) with MetS and 53/265 (20.0%) without MetS experienced at least 1 SAE, with exposure-adjusted SAE rates of 7.23 *vs* 4.61 per 100 patient-years for patients with *vs* without MetS. Of patients receiving tildrakizumab 200 mg, 24/64 (37.5%) with MetS and 52/241 (21.6%) without MetS experienced at least 1 SAE with exposure-adjusted SAE rates of 8.35 *vs* 4.92 per 100 patient-years for patients with *vs* without MetS. For patients receiving tildrakizumab 100 or 200 mg, the most common SAEs by system organ class for patients with and without MetS were gastrointestinal disorders, neoplasms, infections and infestations, and cardiac disorders (Table 2).

In reSURFACE 1 (Fig. S1a), 7 patients treated with tildrakizumab 100 mg, all without MetS, discontinued therapy due to an AE (neoplasms, 5; asthma, 1; and arthritis, 1); in reSURFACE 2 (Fig. S1b), 1 patient with MetS and 4 patients without MetS discontinued therapy due to AEs (psoriatic arthropathy, 2; psoriasis, 1; ovarian cancer, 1; diverticulitis, 1). Three patients receiving tildrakizumab 200 mg in reSURFACE 1, all without MetS, discontinued due to an AE (psoriatic arthropathy, hepatitis E, and papillary thyroid cancer, 1 each). In reSURFACE 2, discontinuation due to AEs occurred in 4 tildrakizumab 200 mg-treated patients with MetS (bronchitis, chronic obstructive pulmonary disease, psoriasis, and rectal adenocarcinoma, 1 each) and 3 tildrakizumab 200 mg-treated patients without MetS (arthritis, colon cancer, and prostate cancer, 1 each).

Discussion

The mechanisms linking MetS and psoriasis are incompletely understood but may include shared inflammation-related signalling, dysregulation of adipocytokine secretion, and insulin resistance.[22,23] With these shared pathways, it is important to establish whether antipsoriasis biologic therapies are effective and safe during long-term therapy in patients with MetS. There are limited data evaluating biologics in this subgroup of patients, but lower drug survival of biologics in patients with psoriasis with *vs* without MetS suggests the former experience reduced treatment efficacy over time.[24] In a real-life study evaluating patients with psoriasis who switched from other biologics to adalimumab, the presence of MetS was associated with significantly lower PASI response at 3, 6, and 12 months compared with patients without MetS.[12] In another analysis of pooled data from phase 2 trials in patients with moderate to severe psoriasis, significantly fewer patients with *vs* without MetS achieved response to therapy with secukinumab and ustekinumab.[11]

Our findings extend previously reported findings[18,19] demonstrating numerically similar efficacy of tildrakizumab in patients with psoriasis with or without MetS based on PASI responses and median PASI score improvement through up to 5 years, the longest duration of follow-up to our knowledge in this subgroup of patients. Further, the findings were robust to sensitivity

Table 2 AEs of special interest and SAEs through Week 256/244 of reSURFACE 1/2

	reSURFACE 1 and reSURFACE 2			
	TIL 100 mg		TIL 200 mg	
	Without MetS (*n* = 265) (1149.1 PY)	With MetS (*n* = 70) (304.1 PY)	Without MetS (*n* = 241) (1057.1 PY)	With MetS (*n* = 64) (287.6 PY)
Tier 1 TEAEs	24 (2.09)	6 (1.97)	27 (2.55)	15 (5.22)
Drug hypersensitivity	2 (0.17)	1 (0.33)	1 (0.09)	2 (0.70)
Serious infections and infestations	10 (0.87)	2 (0.66)	13 (1.23)	6 (2.09)
Malignancies (excluding melanoma and NMSC)	5 (0.44)	1 (0.33)	4 (0.38)	3 (1.04)
Melanoma skin cancer	2 (0.17)	0	0	0
NMSC	3 (0.26)	1 (0.33)	6 (0.57)	1 (0.35)
Confirmed extended MACE	3 (0.26)	1 (0.33)	3 (0.28)	3 (1.04)
Injection site reactions*	1 (0.09)	0	0	0
SAEs, MedDRA SOC	53 (4.61)	22 (7.23)	52 (4.92)	24 (8.35)
Blood and lymphatic system disorders	0	0	3 (0.28)	0
Cardiac disorders	4 (0.35)	3 (0.99)	3 (0.28)	3 (1.04)
Ear and labyrinth disorders	1 (0.09)	0	0	0
Endocrine disorders	0	1 (0.33)	1 (0.09)	0
Eye disorders	0	0	0	1 (0.35)
Gastrointestinal disorders	8 (0.70)	5 (1.64)	7 (0.66)	1 (0.35)
General disorders and administrative site conditions	0	2 (0.66)	3 (0.28)	0
Hepatobiliary disorders	3 (0.26)	1 (0.33)	2 (0.19)	1 (0.35)
Infections and infestations	10 (0.87)	2 (0.66)	11 (1.04)	6 (2.09)
Injury, poisoning, and procedural complications	8 (0.70)	1 (0.33)	5 (0.47)	2 (0.70)
Investigations	0	0	1 (0.09)	0
Metabolism and nutrition disorders	1 (0.09)	0	0	1 (0.35)
Musculoskeletal and connective tissue disorders	3 (0.26)	3 (0.99)	7 (0.66)	2 (0.70)
Neoplasms benign, malignant, and unspecified†	12 (1.04)	3 (0.99)	10 (0.95)	5 (1.74)
Nervous system disorders	6 (0.52)	1 (0.33)	6 (0.57)	4 (1.39)
Pregnancy, puerperium, and perinatal conditions	1 (0.09)	0	1 (0.09)	0
Product issues	0	0	1 (0.09)	0
Psychiatric disorders	2 (0.17)	1 (0.33)	2 (0.19)	0
Renal and urinary disorders	1 (0.09)	0	4 (0.38)	1 (0.35)
Reproductive system and breast disorders	1 (0.09)	0	1 (0.09)	1 (0.35)
Respiratory, thoracic, and mediastinal disorders	1 (0.09)	1 (0.33)	3 (0.28)	2 (0.70)
Skin and subcutaneous tissue disorders	2 (0.17)	0	0	0
Vascular disorders	4 (0.35)	2 (0.66)	4 (0.38)	2 (0.70)

Data presented as *n* (exposure-adjusted rate as number of patients with the event per 100 PY of exposure).
*Injection site reaction was categorized as Tier 1 AE per the criteria in the Integrated Summary of Safety in base study, but not collected in the extension study.
†Includes cysts and polyps.
AE, adverse event; MACE, major adverse cardiovascular event; MedDRA SOC, Medical Dictionary for Regulatory Activities System Organ Class; MetS, metabolic syndrome; NMSC, nonmelanoma skin cancer; PY, patient-years; SAE, serious AE; TEAE, treatment-emergent AE; TIL, tildrakizumab.

analyses using alternative statistical methodology (ie, NRI and LOCF analyses).

Biologics targeting IL-17 and IL-23 are generally well tolerated in patients with psoriasis.[25] Our results suggest that the safety profile of tildrakizumab is similar in patients with and without MetS through up to 5 years. Consistent with earlier reports, the overall EAIRs of Tier 1 TEAEs were similar in patients with and without MetS.[18,19] The absence of tildrakizumab dose effect on incidence of confirmed extended MACE in this analysis is consistent with data suggesting that biologics are not associated with an increased risk of CV events in patients with psoriasis[26] and is reassuring, given the increased CVD risk for patients with MetS.

There is also concern about the risk of cancer and serious infections with the use of biologic agents, although evidence to date suggests no increased risk.[27–29] The incidence of serious infections and malignancy were low and comparable between patients with and without MetS in this study.

This analysis was limited by the fact that there was no analysis based on the individual components that are used to determine MetS status. Additionally, BMI was used as a surrogate for the waist circumference component. In patients with psoriasis, elevated body weight and BMI are associated with decreased efficacy for many biologic therapies, including TNF inhibitors, ustekinumab, and secukinumab.[11,30–32] It was previously reported that the efficacy of tildrakizumab trended lower in heavier *vs* lighter patients with psoriasis after 12 weeks of treatment.[33] In a separate analysis based on body weight deciles, tildrakizumab efficacy was also modestly reduced in heavier patients after 12 weeks of treatment, but the effect of weight diminished over time, with tildrakizumab efficacy being similar between heavier and lighter patients after 28 weeks of treatment; tildrakizumab efficacy was maintained through Week 52 in all weight deciles.[34] In the current analyses of data from the extension studies for reSURFACE 1/2, the first assessed efficacy timepoint occurs at Week 28; while baseline body weight and BMI were numerically higher in patients with MetS, there did not appear to be a notable difference in tildrakizumab efficacy at any time point.

Other limitations of this analysis include its *post hoc* design and the relatively small number of patients with MetS. Given these limitations as well as the challenges associated with long-term follow-up, data was primarily assessed using an MI model; NRI and LOCF analyses were used as sensitivity analyses. The current analysis also assumed that the 5 individual components used to assess MetS status carried the same impact on results and did not differentiate between patients with controlled *vs* uncontrolled MetS.

Conclusion

The results of these analyses showed both doses of tildrakizumab maintained efficacy and had a favorable safety profile in patients with psoriasis, regardless of MetS status.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Patient flow diagram for (a) reSURFACE 1 patients and (b) reSURFACE 2 patients.
Figure S2 Percentage of PASI 75, 90, and 100 responders receiving continuous tildrakizumab over time by baseline metabolic syndrome status in (a) reSURFACE 1 patients receiving 100 mg of tildrakizumab, (b) reSURFACE 2 patients receiving 100 mg of tildrakizumab, (c) reSURFACE 1 patients receiving 200 mg of tildrakizumab, and (d) reSURFACE 2 patients receiving 200 mg of tildrakizumab (NRI analysis).
Figure S3 Percentage of PASI 75, 90, and 100 responders receiving continuous tildrakizumab over time by baseline metabolic syndrome status in (a) reSURFACE 1 patients receiving 100 mg of tildrakizumab, (b) reSURFACE 2 patients receiving 100 mg of tildrakizumab, (c) reSURFACE 1 patients receiving 200 mg of tildrakizumab, and (d) reSURFACE 2 patients receiving 200 mg of tildrakizumab (LOCF analysis).
Figure S4 Median percent change from baseline PASI score over time in patients receiving continuous tildrakizumab stratified by metabolic syndrome status in (a) reSURFACE 1 patients receiving 100 mg of tildrakizumab, (b) reSURFACE 2 patients receiving 100 mg of tildrakizumab, (c) reSURFACE 1 patients receiving 200 mg of tildrakizumab, and (d) reSURFACE 2 patients receiving 200 mg of tildrakizumab (NRI analysis).
Figure S5 Median percent change from baseline PASI score over time in patients receiving continuous tildrakizumab stratified by metabolic syndrome status in (a) reSURFACE 1 patients receiving 100 mg of tildrakizumab, (b) reSURFACE 2 patients receiving 100 mg of tildrakizumab, (c) reSURFACE 1 patients receiving 200 mg of tildrakizumab, and (d) reSURFACE 2 patients receiving 200 mg of tildrakizumab (LOCF analysis).
Figure S6 Median absolute change from baseline PASI score over time in patients receiving continuous tildrakizumab stratified by metabolic syndrome status in (a) reSURFACE 1 patients receiving 100 mg of tildrakizumab, (b) reSURFACE 2 patients receiving 100 mg of tildrakizumab, (c) reSURFACE 1 patients receiving 200 mg of tildrakizumab, and (d) reSURFACE 2 patients receiving 200 mg of tildrakizumab.
Figure S7 Percentage of patients receiving continuous tildrakizumab 100 mg who achieved a PASI score <3 over time by baseline metabolic syndrome status using MI, NRI, and LOCF in (a) reSURFACE 1 patients receiving 100 mg of tildrakizumab, (b) reSURFACE 2 patients receiving 100 mg of tildrakizumab, (c) reSURFACE 1 patients receiving 200 mg of tildrakizumab, and (d) reSURFACE 2 patients receiving 200 mg of tildrakizumab.