Tildrakizumab efficacy, drug survival, and safety are comparable in patients with psoriasis with and without metabolic syndrome: Long-term results from 2 phase 3 randomized controlled studies (reSURFACE 1 and reSURFACE 2)

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Background: Data for the effect of metabolic syndrome (MetS) on the efficacy and safety of biologic agents for psoriasis treatment are limited.

Objective: To evaluate long-term tildrakizumab efficacy, drug survival, and safety in patients with psoriasis by baseline MetS status.

Methods: Post hoc analyses of up to 3 years of efficacy data and 5 years of safety data from the phase 3, double-blind, randomized controlled reSURFACE 1 and 2 trial (NCT01722331 and NCT01729754) base and extension studies were conducted for patients receiving continuous tildrakizumab 100 or 200 mg.

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Results: Of 338 (n = 124/214 in reSURFACE 1/2) and 307 (n = 147/160 in reSURFACE 1/2) patients continuously receiving tildrakizumab 100 and 200 mg, respectively, throughout the studies, 26/44 (21%/21%) and 34/30 (23%/19%) met MetS criteria. Proportions of patients who achieved a 75% improvement in the Psoriasis Area and Severity Index (PASI) in reSURFACE 1/2 were generally comparable among those with versus without MetS at week 52 (tildrakizumab 100 mg, 85%/86% vs 86%/94%; tildrakizumab 200 mg, 76%/87% vs 76%/87%) and through week 148. Results were similar for responders with 90% and 100% improvement in the PASI. Tildrakizumab's safety profile did not vary by MetS status.

Limitations: Small sample size and post hoc analysis limit interpretation.

Conclusion: Long-term tildrakizumab efficacy and safety were comparable between patients with and without MetS. (J Am Acad Dermatol 2021;84:398-407.)

Key words: clinical research; dermatology; efficacy; interleukin 23; metabolic syndrome; psoriasis; safety; tildrakizumab.

CAPSULE SUMMARY

- Limited data are available on the efficacy and safety of biologics in patients with psoriasis who have metabolic syndrome.
- Tildrakizumab efficacy was comparable and durable in patients with psoriasis with versus without metabolic syndrome for up to 3 years; safety was consistent with the known profile of tildrakizumab.

Psoriasis is a systemic inflammatory disease associated with comorbidities such as psoriatic arthritis; depression; obesity; cardiovascular (CV) disease (CVD); and metabolic syndrome (MetS),[1-5] a combination of risk factors including hypertension, dyslipidemia, increased fasting glucose, and central obesity.[6] Patients with psoriasis have increased prevalence of MetS (14%-40%) and its components compared with the general population,[7-10] and MetS frequency increases—with risk rates up to 98%—with increasing severity of psoriasis.[11-13] Presence of MetS increases the risk of CV and diabetic events and CV and all-cause mortality compared with individuals without MetS.[6,14] In patients with psoriasis, MetS is linked with reduced Psoriasis Area and Severity Index (PASI) response after treatment with most biologic or conventional systemic therapies, such as fixed-dose anti−tumor necrosis factor and anti−interleukin (IL) 17 agents.[15,16] Consequently, many features of MetS should be considered when selecting psoriasis therapy.[17,18]

Tildrakizumab is a high-affinity, humanized, immunoglobulin G1κ, IL-23p19 monoclonal antibody.[19] Tildrakizumab 100 mg is approved in the United States, the European Union, Australia, and Japan for the treatment of moderate to severe plaque psoriasis.[20-22] In tildrakizumab psoriasis clinical trials, patients treated with tildrakizumab versus placebo had significantly greater improvement from baseline PASI and Physician's Global Assessment scores at week 12.[19,23] Tildrakizumab was well tolerated, with low frequencies of serious adverse events (SAEs) and discontinuations due to adverse events (AEs).[19,24] We previously reported tildrakizumab efficacy, drug survival, and safety in patients meeting National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III criteria for MetS compared with patients without MetS during the base studies of 2 phase 3 clinical trials (reSURFACE 1/2 [NCT01722331/NCT01729754]).[25] These findings are now substantiated up to 4 years for efficacy and 5 years for safety. Here, we present complete tildrakizumab efficacy data through up to 3 years and all reported safety data through up to 5 years of tildrakizumab exposure, stratified by MetS status, from the reSURFACE 1/2 base and extension studies.

MATERIALS AND METHODS

Study design

This was a post hoc analysis of 2 phase 3, 64-/52-week, double-blind, randomized, placebo-controlled studies (reSURFACE 1/2)[19] with optional long-term extension periods. Some patients who met prespecified efficacy criteria received more than 1 treatment during the base studies (Supplemental Fig 1; available via Mendeley at http://doi.org/10.17632/j5gd4ndd2g.1). Patients completing the base studies with 50% or greater improvement from baseline PASI score could enter the long-term extensions receiving the same tildrakizumab dose. This analysis included only patients who received the same dose of tildrakizumab

Abbreviations used:

AE:	adverse event
BMI:	body mass index
CV:	cardiovascular
CVD:	cardiovascular disease
IL:	interleukin
MACE:	major adverse cardiovascular event
MedDRA SOC:	Medical Dictionary for Regulatory Activities System Organ Class
MetS:	metabolic syndrome
NCEP ATP III:	National Cholesterol Education Programme Adult Treatment Panel III
PASI:	Psoriasis Area and Severity Index
PY:	patient-years
SAE:	serious adverse event
TEAE:	treatment-emergent adverse event

continuously throughout the base studies and into the long-term extensions.

Local institutional review boards or ethics panels reviewed and approved the protocols. The study was conducted according to the principles of the Declaration of Helsinki.[26] All patients provided informed consent.

Patients

The reSURFACE 1/2 inclusion and exclusion criteria have been previously described.[19] Briefly, adults with moderate to severe chronic plaque psoriasis (body surface area involvement ≥10%, Physician Global Assessment score ≥3, and PASI score ≥12) were eligible.

Treatments and assessments

The reSURFACE 1/2 base study procedures have been previously described.[19] Tildrakizumab 100 or 200 mg was administered by subcutaneous injection at week 0, at week 4, and every 12 weeks thereafter. The PASI score was evaluated as scheduled during the base studies and every 12 weeks through week 148. Patients were monitored for AEs throughout treatment and for 20 weeks after the last dose of tildrakizumab.

Retrospective clinical evaluation of baseline MetS status was based on NCEP ATP III criteria.[27] Waist circumference was not measured in reSURFACE 1/2, so body mass index (BMI)—which correlates well with waist circumference and MetS status[28-33]—was used as a surrogate for the abdominal obesity component of MetS. Patients meeting 3 or more of the following 5 criteria were classified as having MetS: BMI of greater than 30 kg/m^2, triglyceride levels of 150 mg/dl or greater, high-density lipoprotein cholesterol of less than 40 mg/dl for men or less than 50 mg/dl for women, blood pressure of 130 mm Hg or greater (systolic) and/or 85 mm Hg or greater (diastolic), and fasting glucose of 110 mg/dl or greater.

Tildrakizumab efficacy was assessed from the proportions of patients achieving 75%, 90%, and 100% improvement from baseline PASI score (PASI 75, 90, and 100 response rates) and the percentage median PASI change from baseline at weeks 52, 100, and 148. Safety was evaluated from exposure-adjusted rates (patients with events per 100 patient-years [PY] of exposure) of treatment-emergent AEs (TEAEs), tier 1 TEAEs, and SAEs by Medical Dictionary for Regulatory Activities System Organ Class (MedDRA SOC), stratified by tildrakizumab dose and baseline MetS status. Tier 1 TEAEs included infections reported as SAEs or requiring intravenous antibiotics, malignancies, nonmelanoma skin cancer, melanoma, confirmed major adverse CV events (MACE) (comprising nonfatal myocardial infarction, nonfatal stroke, and CV deaths confirmed as *CV* or *sudden*), and drug-related hypersensitivity reactions.

Statistical analysis

Efficacy and safety analysis sets included all patients in the post hoc analysis. Efficacy data through treatment week 148 and all available safety data through July 24/June 22, 2018, for reSURFACE 1/2 were analyzed. Baseline characteristics were summarized for patients with and without MetS by treatment arm using descriptive statistics. Proportions of PASI responders and absolute and percent change from baseline in median PASI score were compared between patients with and without MetS by treatment arm. Missing data at a given visit were imputed as nonresponse for PASI response rates and using last observation carried forward methodology for PASI scores. No formal hypothesis testing was performed.

RESULTS

Patient population

Of 1862 patients entering reSURFACE 1 (n = 772) and 2 (n = 1090), 338 (n = 124/214 in reSURFACE 1/2, respectively) and 307 (n = 147/160 in reSURFACE 1/2, respectively) continuously received tildrakizumab 100 and 200 mg, respectively, throughout the base studies and into the long-term extensions. Of these, 26/44 (21%/21%) patients receiving tildrakizumab 100 mg and 34/30 (23%/19%) receiving tildrakizumab 200 mg in reSURFACE 1/2, respectively, met criteria for MetS (Supplemental Figs 2 and 3; available via Mendeley at http://doi.org/10.17632/j5gd4ndd2g.1).

Patient demographics were similar to the base study analysis.[25] The majority of patients were white and male (Table I). Patients with versus without MetS had greater prevalence of pre-existing CVD and diabetes and higher median baseline weight and BMI (Table I).[25] Proportions of patients who discontinued study treatment before week 148 were comparable for those with versus without MetS in reSURFACE 1 (7.7% vs 11.2% and 0% vs 5.4% for tildrakizumab 100 and 200 mg, respectively) and reSURFACE 2 (15.9% vs 12.6% and 16.6% vs 12.4% for tildrakizumab 100 and 200 mg, respectively). The most frequent reason for discontinuation in both studies was withdrawal by patient; 2 patients with MetS receiving tildrakizumab 200 mg in reSURFACE 2 withdrew due to an AE (Supplemental Figures 2 and 3); confirmed AEs leading to study discontinuation after database lock and cleaning are listed in Supplemental Table 1 (available via Mendeley at http://doi.org/10.17632/j5gd4ndd2g.1).

Efficacy outcomes

In reSURFACE 1/2, PASI 75/90/100 response rates in patients receiving tildrakizumab 100 and 200 mg were generally comparable between those with and without MetS at weeks 52, 100, and 148 (Fig 1 and Supplemental Figs 4 and 5; available via Mendeley at http://doi.org/10.17632/j5gd4ndd2g.1). The PASI 75 response rates at weeks 100 and 148 and the PASI 90 and 100 response rates at weeks 52, 100, and 148 were numerically lower among patients with versus without MetS receiving tildrakizumab 200 mg in reSURFACE 2 (Fig 1, *B*).

In both reSURFACE 1 and reSURFACE 2, median PASI scores decreased from baseline through week 28 (end of base study part 2) and remained low through week 148 in patients with or without MetS (Supplemental Figs 6 and 7; available via Mendeley at http://doi.org/10.17632/j5gd4ndd2g.1). The percent decrease in median PASI score from baseline to weeks 52, 100, and 148 was 83% or greater for patients receiving tildrakizumab 100 or 200 mg with or without MetS in both studies and was generally comparable between patients with versus without MetS (Fig 2).

Safety

Across reSURFACE 1/2, exposure-adjusted rates of TEAEs were 20.9 or less per 100 PY in patients with or without MetS at baseline receiving tildrakizumab 100 or 200 mg. By MedDRA SOC, there were 15.4 or fewer patients with infections and infestations, 6.7 or fewer with metabolism and nutritional disorders, 5.0 or fewer with vascular disorders, 1.8 or fewer with cardiac disorders, and 0.7 or fewer with endocrine disorders per 100 PY among those with or without MetS receiving either dose of tildrakizumab; metabolic, vascular, and cardiac disorders were more frequent in patients with versus without MetS. Exposure-adjusted rates of tier 1 TEAEs were 2.1 or less per 100 PY in patients with or without MetS receiving tildrakizumab 100 or 200 mg and were generally comparable between patients with and without MetS (Table II). After adjustment for exposure, the most frequent tier 1 TEAEs by MedDRA SOC were serious infections and infestations in patients without MetS receiving tildrakizumab 100 mg (n = 11; 1.0/100 PY) and in patients with (n = 6; 2.1/100 PY) and without MetS (n = 11; 1.1/100 PY) receiving tildrakizumab 200 mg; the most common tier 1 TEAEs in patients with MetS receiving tildrakizumab 100 mg were malignancies (excluding nonmelanoma skin cancer and melanoma) and confirmed extended MACE (both n = 3; 1.0/100 PY) (Table II).

Through the base and extension studies, 25/70 (35.7%) versus 66/265 (24.9%) patients with versus without MetS receiving tildrakizumab 100 mg reported at least 1 SAE (exposure-adjusted rate, 8.5 vs 5.9 per 100 PY) (Table II). In patients receiving tildrakizumab 200 mg, 29/64 (45.3%) versus 70/241 (29.0%) patients with versus without MetS reported at least 1 SAE (10.3 vs 6.8 per 100 PY) (Table II). The most commonly reported class of SAEs in patients with versus without MetS receiving tildrakizumab 100 mg was gastrointestinal disorders (n = 5; 1.7/100 PY vs n = 8; 0.7/100 PY). In patients receiving tildrakizumab 200 mg, the most commonly reported class of SAEs in patients with versus without MetS was infections and infestations (n = 6; 2.1/100 PY vs n = 11; 1.1/100 PY) (Table II).

Diabetes mellitus was reported in 1 and 6 patients with MetS receiving tildrakizumab 100 and 200 mg, compared with 4 and 5 patients without MetS receiving tildrakizumab 100 and 200 mg, respectively. Myocardial infarction occurred in 1 patient with MetS receiving tildrakizumab 100 mg, and acute myocardial infarction occurred in 1 patient with MetS and 2 patients without MetS receiving tildrakizumab 200 mg (Table II).

There were 3 deaths in patients receiving tildrakizumab 100 mg: 1 (1.4%; 0.3 per 100 PY) patient with MetS (unknown cause) and 2 (0.8%; 0.2 per 100 PY) patients without MetS (cardiac failure chronic and completed suicide). Two deaths occurred in patients receiving tildrakizumab 200 mg, both in patients without MetS (0.8%; 0.2 per 100 PY) (acute myocardial infarction and completed suicide).

Table I. 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	
Patient Characteristics	Without MetS (n = 98)	With MetS (n = 26)	Without MetS (n = 113)	With MetS (n = 34)	Without MetS (n = 170)	With MetS (n = 44)	Without MetS (n = 130)	With MetS (n = 30)
Age, y, mean ± SD	46.1 ± 14.0	49.1 ± 12.7	46.2 ± 13.5	50.7 ± 11.0	43.2 ± 13.2	45.9 ± 12.7	44.5 ± 13.2	48.7 ± 12.4
Sex, male, n (%)	65 (66.3)	18 (69.2)	80 (70.8)	19 (55.9)	120 (70.6)	34 (77.3)	82 (63.1)	23 (76.7)
Race, white, n (%)	64 (65.3)	21 (80.8)	67 (59.3)	27 (79.4)	156 (91.8)	41 (93.2)	118 (90.8)	29 (96.7)
Weight at baseline, kg, mean ± SD	80.8 ± 18.1	106.4 ± 29.6	81.7 ± 17.5	111.8 ± 32.2	82.6 ± 17.0	106.9 ± 21.7	82.0 ± 17.8	108.2 ± 17.6
BMI, kg/m^2, mean ± SD	27.9 ± 6.0	35.6 ± 8.5	28.3 ± 5.8	38.5 ± 8.3	27.5 ± 5.3*	35.6 ± 6.1	27.3 ± 5.3	37.6 ± 9.8
Body surface area, %, mean ± SD	29.4 ± 16.7	32.2 ± 16.6	32.6 ± 19.5	30.1 ± 19.4	34.1 ± 18.4	30.3 ± 18.9	31.3 ± 17.2	27.6 ± 12.9
Disease duration, y, mean ± SD	17.2 ± 12.6	16.2 ± 12.3	16.6 ± 11.5	16.7 ± 12.9	16.1 ± 10.6	15.2 ± 11.2	18.0 ± 13.5	20.1 ± 14.8
Baseline PASI score, mean ± SD	19.9 ± 7.1	20.5 ± 7.1	21.5 ± 9.3	20.6 ± 9.7	19.6 ± 6.9	20.8 ± 8.8	19.5 ± 7.2	19.2 ± 6.3
Baseline PGA score, mean ± SD	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)	31 (27.4)	16 (47.1)	29 (17.1)	17 (38.6)	27 (20.8)	16 (53.3)
Diabetes, n (%)	8 (8.2)	8 (30.8)	11 (9.7)	8 (23.5)	5 (2.9)	7 (15.9)	11 (8.5)	7 (23.3)
Psoriatic arthritis, n (%)	16 (16.3)	5 (19.2)	19 (16.8)	9 (26.5)	24 (14.1)	11 (25.0)	17 (13.1)	4 (13.3)
Response to ≥1 traditional systemic medicine, n (%)‡	22 (44.9)	5 (71.4)	40 (65.6)	8 (57.1)	111 (65.3)	24 (54.6)	80 (61.5)	17 (56.7)
Prior exposure to biologic therapy for psoriasis, n (%)	16 (16.3)	8 (30.8)	20 (17.7)	7 (20.6)	23 (13.5)	5 (11.4)	17 (13.1)	7 (23.3)

BMI, Body mass index; *CV,* cardiovascular; *MetS,* metabolic syndrome; *PASI,* Psoriasis Area and Severity Index; *PGA,* Physician's Global Assessment; *SD,* standard deviation; *TIL,* tildrakizumab.

*n = 169.

†n = 129.

‡For reSURFACE1, percentages are based on the subset of patients who received methotrexate, cyclosporine, or phototherapy.

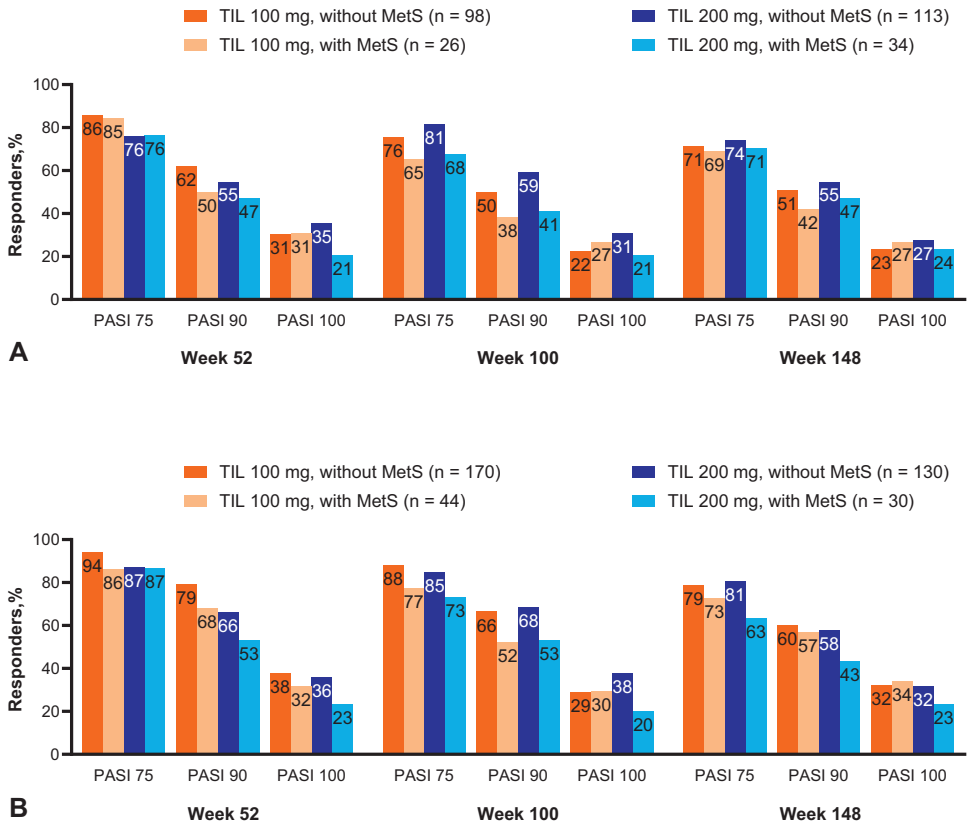

Fig 1. Proportions of patients with and without MetS who achieved PASI 75, 90, and 100 through week 148 in (**A**) reSURFACE 1 and (**B**) reSURFACE 2. All patients who continuously received the same dose of tildrakizumab and entered the extension studies, nonresponder imputation. *MetS,* Metabolic syndrome; *PASI 75/90/100,* 75%/90%/100% improvement from baseline in Psoriasis Area and Severity Index score; *TIL,* tildrakizumab.

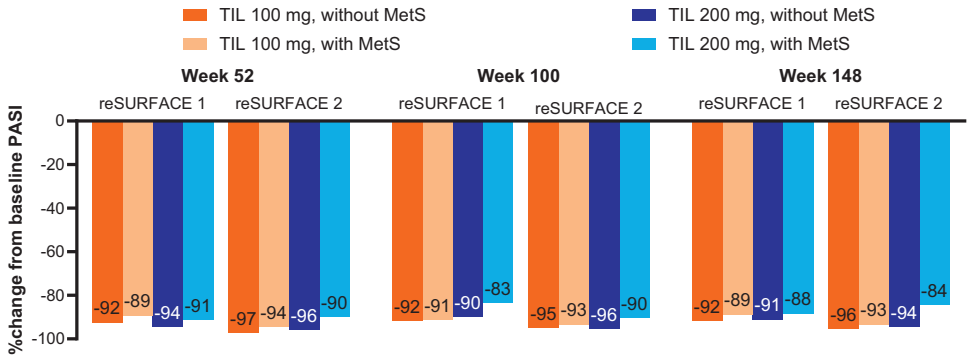

Fig 2. Percent change in PASI score from baseline to weeks 52, 100, and 148 in patients with and without MetS in reSURFACE 1 and reSURFACE 2. All patients who continuously received the same dose of tildrakizumab and entered the extension studies, last observation carried forward. *MetS,* Metabolic syndrome; *PASI,* Psoriasis Area and Severity Index; *TIL,* tildrakizumab.

DISCUSSION

In this post hoc analysis of long-term extension data from reSURFACE 1/2, MetS status did not affect tildrakizumab efficacy or safety in patients with moderate to severe chronic plaque psoriasis. The efficacies of tildrakizumab 100 and 200 mg were comparable, without evidence of reduced drug survival, and were maintained over 148 weeks in patients with versus without MetS. Despite the higher prevalence of psoriatic arthritis, pre-existing CVD,

Table II. Exposure-adjusted rates of tier 1 TEAEs and SAEs by MetS status through up to 5 years of exposure

TEAEs and SAEs	TIL 100 mg		TIL 200 mg	
	Without MetS (n = 265; 1112.0 PY)	With MetS (n = 70; 295.4 PY)	Without MetS (n = 241; 1025.0 PY)	With MetS (n = 64; 281.5 PY)
Tier 1 TEAEs, n (exposure-adjusted rate)*				
Drug hypersensitivity	0	0	0	0
Serious infections and infestations	11 (1.0)	2 (0.7)	11 (1.1)	6 (2.1)
Malignancies (excluding NMSC and melanoma)†	7 (0.6)	3 (1.0)	6 (0.6)	4 (1.4)
Melanoma‡	2 (0.2)	0	0	0
NMSC§	2 (0.2)	1 (0.3)	5 (0.5)	1 (0.4)
Confirmed extended MACE	4 (0.4)	3 (1.0)	3 (0.3)	4 (1.4)
SAEs, MedDRA SOC, n (exposure-adjusted rate)*				
All SAEs	66 (5.9)	25 (8.5)	70 (6.8)	29 (10.3)
Blood and lymphatic system disorders	0	0	2 (0.2)	0
Cardiac disorders	4 (0.4)	3 (1.0)	3 (0.3)	4 (1.4)
Ear and labyrinth disorders	1 (0.1)	0	0	0
Endocrine disorders	0	1 (0.3)	1 (0.1)	0
Eye disorders	0	0	0	1 (0.4)
Gastrointestinal disorders	8 (0.7)	5 (1.7)	6 (0.6)	1 (0.4)
General disorders and administration site conditions	0	2 (0.7)	3 (0.3)	0
Hepatobiliary disorders	3 (0.3)	1 (0.3)	2 (0.2)	1 (0.4)
Infections and infestations	11 (1.0)	2 (0.7)	11 (1.1)	6 (2.1)
Injury, poisoning, and procedural complications	8 (0.7)	1 (0.3)	7 (0.7)	2 (0.7)
Investigations	0	0	1 (0.1)	0
Metabolism and nutritional disorders	2 (0.2)	0	0	1 (0.4)
Musculoskeletal and connective tissue disorders	3 (0.3)	3 (1.0)	8 (0.8)	2 (0.7)
Neoplasms: benign, malignant, and unspecified	13 (1.2)	3 (1.0)	11 (1.1)	5 (1.8)
Pregnancy, puerperium, and perinatal conditions	1 (0.1)	0	1 (0.1)	0
Product issues	0	0	1 (0.1)	0
Psychiatric disorders	3 (0.3)	1 (0.3)	2 (0.2)	0
Renal and urinary disorders	1 (0.1)	0	3 (0.3)	1 (0.4)
Reproductive system and breast disorders	1 (0.1)	0	1 (0.1)	1 (0.4)
Respiratory, thoracic, and mediastinal disorders	1 (0.1)	1 (0.3)	3 (0.3)	2 (0.7)
Skin and subcutaneous tissue disorders	2 (0.2)	0	0	0
Vascular disorders	4 (0.4)	2 (0.7)	4 (0.4)	2 (0.7)

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 adverse event; *TEAE,* treatment-emergent adverse event; *TIL,* tildrakizumab.

*Numbers in parentheses represent the number of patients with the event per 100 PY of exposure.

†Including preferred terms bladder cancer, breast cancer, clear cell renal cell carcinoma, colon cancer, endometrial cancer, lobular breast carcinoma in situ, ovarian cancer, papillary thyroid cancer, prostate cancer, rectal adenocarcinoma, and thyroid cancer after database lock and cleaning.

‡Including preferred terms malignant melanoma and malignant melanoma in situ after database lock and cleaning.

§Including preferred terms basal cell carcinoma and Bowen's disease after database lock and cleaning.

and diabetes in patients with versus without baseline MetS, rates of prespecified AEs of interest and SAEs were similar regardless of MetS status. To our knowledge, this is the longest study to date of both the efficacy and safety of biologic treatment of psoriasis in patients with concomitant MetS.

The pathogenetic mechanisms underlying the relationship between obesity and psoriasis are not fully defined. Proposed mechanisms include shared underlying inflammatory pathways,[34] including T helper 1 and 17 cells[35,36]; dysregulation of adipocytokine secretion[35-38]; and insulin resistance.[8,35,38,39]

Adipocytokines may link psoriasis and comorbidities,[40] possibly by mediating cutaneous inflammation[40-42]; anti–IL-17 therapies show limited positive effects on adipocytokine levels.[43]

In patients with psoriasis treated with adalimumab, MetS is associated with statistically significant reduction in PASI response rates relative to patients without MetS.[16] Baseline MetS and obesity were more frequent among nonresponders (PASI <50) to secukinumab relative to responders (PASI >50).[15] Patients with psoriasis with versus without MetS also have lower drug survival after long-term treatment with most biologics studied.[44] Greater body weight and high BMI are associated with lower efficacy of many biologics.[45,46] We previously reported a modest association between body weight and tildrakizumab efficacy, with a trend toward lower efficacy after 12 weeks among heavier versus lighter patients; these differences dissipated at weeks 28 and 52.[47] However, the current analysis detected no decrease in tildrakizumab efficacy or drug survival despite greater baseline mean body weight and BMI in patients with versus without MetS.

The incidence of MACE is closely monitored in studies of biologic therapies; to date, most are not associated with increased MACE risk.[48-51] Despite evidence that anti-inflammatory therapies can reduce incidence of CV events and associated complications,[52,53] adalimumab treatment for psoriasis did not influence vascular inflammation compared with phototherapy and placebo,[54] and ustekinumab treatment for 12 weeks only transiently improved endothelial function.[55] The IL-12/23 inhibitor briakinumab was withdrawn from development because of MACE-related concerns; however, other IL-12/23 inhibitors were used safely in psoriasis.[56] In this study, 39% to 65% of patients with MetS had pre-existing CVD, and no increased incidence of MACE was observed in patients with versus without MetS over up to 5 years of treatment.

Despite controversy over ILs as biochemical markers of diabetes pathogenesis,[57,58] the rarity of new-onset diabetes through up to 5 years of follow-up in this analysis is consistent with observations of positive correlation between IL-23 and fasting glucose in patients with psoriasis and MetS.[59] More prospective studies are needed to elucidate the association between IL-23 inhibition and fasting glucose levels.

Short-term (ie, 12-16 weeks) treatment with tumor necrosis factor antagonists and IL-17 and IL-12/23 inhibitors is generally well tolerated in patients with moderate to severe psoriasis.[48,49,60,61] However, risk for serious infections (eg, lower respiratory tract infections and skin/soft tissue infections) after psoriasis treatment is well documented for some biologic therapies.[62-64] In this study, the incidence of serious infections was low and comparable among patients regardless of MetS status. Malignancy rates were comparable to previous reports in patients with psoriasis and numerically higher in patients with vs without MetS, consistent with increased risk for many cancers associated with MetS.[65,66] Understanding the long-term safety profile of biologic therapies, particularly with regard to CVD, serious infections, and malignancies in patients predisposed to these conditions, will be important to decision making in psoriasis treatment.

These post hoc analyses were not powered to assess statistical differences between MetS-based subgroups, and populations were not matched for smoking history and other potential cofactors. Relatively few patients had MetS, and very few met 3 or more risk factors for MetS when BMI was excluded; therefore, further stratification (eg, by weight) or evaluation of the effect of weight only on differences in treatment efficacy and safety between patients with and without MetS was not feasible. By study design, patients who underwent dose escalation or de-escalation were not included in this analysis. Further analyses of these populations could strengthen the reported findings. These study limitations may temper our observations and suggest that further prospective studies are needed to support these findings.

CONCLUSIONS

The efficacy of tildrakizumab 100 and 200 mg was comparable and maintained without evidence of reduced durability of response through 148 weeks of treatment—despite higher weight—in patients with versus without MetS. Safety outcomes over a 5-year period were comparable regardless of MetS status and consistent with the known safety profile of tildrakizumab; no difference in the incidence of CV events or worsening diabetes was observed—despite higher risk for CV events, diabetes, and obesity-related events—between patients with and without MetS across tildrakizumab doses.

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