Rates of individual and composite cardiovascular events through 5 years of tildrakizumab exposure in 2 phase 3 clinical trials

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INTRODUCTION

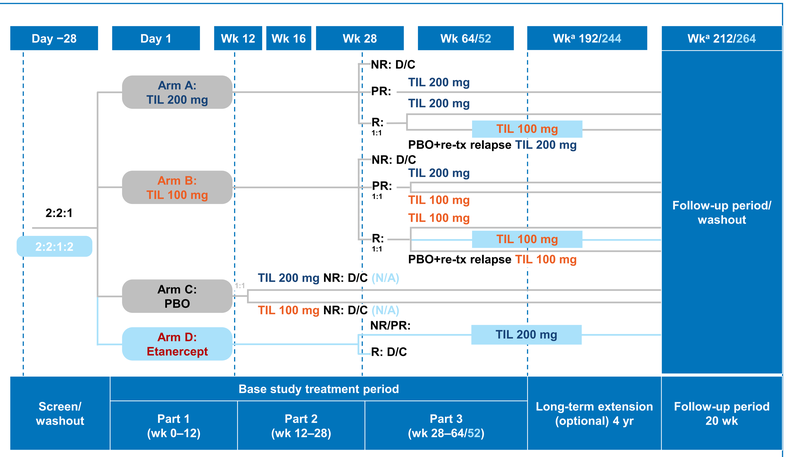
- Tildrakizumab is a high-affinity, humanized, anti–interleukin-23p19 monoclonal antibody approved for the treatment of moderate to severe plaque psoriasis in the US, EU, Australia, and Japan[1–3]
- Tildrakizumab was evaluated in patients with moderate to severe plaque psoriasis in 2 large phase 3, randomized, controlled trials, reSURFACE 1 (NCT01722331) and reSURFACE 2 (NCT01729754)[1,2]
  - In both studies, confirmed cardiovascular events were uncommon over 3 years of exposure to tildrakizumab[1–3]
- This post hoc analysis evaluates the rates of positively adjudicated cardiovascular events over 5 years in reSURFACE 1 and 2

METHODS

Study Design

- This analysis includes data from all patients exposed to tildrakizumab 100 or 200 mg in the 3-part, double-blind, randomized, placebo-controlled, phase 3 reSURFACE 1 (64 weeks) and reSURFACE 2 (52 weeks) trials who received at least one dose of tildrakizumab during the optional long-term extension periods[1]
- Adult patients with moderate to severe chronic plaque psoriasis were eligible for the base studies[1]
- Patients received tildrakizumab 100 or 200 mg monotherapy at weeks 0 and 4 and every 12 weeks thereafter, or placebo; reSURFACE 2 included an etanercept treatment arm up to week 28.[1] Eligible patients who enrolled in the extension studies received the same dose of tildrakizumab as at base study completion[1,2]
- Patients could be rerandomized or reassigned to a different treatment based on prespecified efficacy criteria. The integrated study design is shown in **Figure 1**[1,2]

Figure 1. Design of the reSURFACE 1 and reSURFACE 2 trials with base and extension periods



Light blue color indicates differences between reSURFACE 1 and reSURFACE 2.
[a]Weeks 192 and 212 start from extension week 0 of reSURFACE 1.
D/C, discontinued; N/A, not applicable; NR, nonresponder (<50% improvement from baseline Psoriasis Area and Severity Index score [PASI <50 response]); PBO, placebo; PR, partial responder (PASI 50–<75 response); R, responder (PASI 75 response); re-tx, retreatment. Screen, screening; TIL, tildrakizumab; wk, week; yr, year.

Safety Outcomes

- Safety was assessed from exposure-adjusted incidence rates (EAIRs) of positively adjudicated major adverse cardiovascular events (MACE)
  - All MACE and extended MACE were adjudicated by an external clinical adjudication committee
  - MACE included nonfatal myocardial infarction, nonfatal stroke, and cardiovascular (CV) deaths confirmed as "cardiovascular" or "sudden"
  - Extended MACE included nonfatal myocardial infarction, nonfatal stroke, unstable angina, coronary revascularization, resuscitated cardiac arrest, and CV deaths confirmed as "cardiovascular" or "sudden"
- The safety analysis group was the all patients as-treated population, including all patients who entered the extension study and received ≥1 dose of the same treatment as in the base study
  - Analyses for tildrakizumab 100 mg included all patients who received tildrakizumab 100 mg during any part of the study
  - Analyses for tildrakizumab 200 mg included all patients who received tildrakizumab 200 mg during any part of the study
- EAIRs were calculated as cumulative incidence per 100 patient-years (PY) of exposure in all patients as-treated

RESULTS

Patients

- Base study patient characteristics were previously published.[1] There were 506 patients who entered the reSURFACE 1 extension and 730 patients who entered the reSURFACE 2 extension (**Table 1**)

Table 1. Baseline demographics for patients in the extension phase

	reSURFACE 1		reSURFACE 2	
	TIL 100 mg (n = 239)	TIL 200 mg (n = 267)	TIL 100 mg (n = 381)	TIL 200 mg (n = 349)
Sex, male, n (%)	159 (66.5)	183 (68.5)	291 (76.4)	242 (69.3)
Age, years, mean ± SD	46.9 ± 13.0	47.1 ± 13.0	44.2 ± 13.3	45.6 ± 12.8
Race, n (%)				
White	163 (68.2)	173 (64.8)	351 (92.1)	329 (94.3)
Asian	60 (25.1)	80 (30.0)	7 (1.8)	8 (2.3)
Weight, kg, mean ± SD	87.1 ± 24.4	87.8 ± 24.2	88.4 ± 21.4	89.0 ± 21.5
Baseline PASI score, mean ± SD	20.0 ± 7.6	21.3 ± 9.6	19.8 ± 7.7	19.3 ± 6.9
Body surface area, %, mean ± SD	30.2 ± 17.5	31.7 ± 19.6	32.6 ± 18.0	30.1 ± 15.8
Duration of treatment,[a] weeks, mean	237.4	265.0	227.7	226.1

Data shown as mean ± SD unless otherwise noted.
[a]Duration of treatment during base and extension phases.
PASI, Psoriasis Area and Severity Index; SD, standard deviation; TIL, tildrakizumab.

- In reSURFACE 1, there were 1165 PY of exposure to tildrakizumab 100 mg and 1366 PY of exposure to tildrakizumab 200 mg in the base and extension studies
- In reSURFACE 2, there were 1671 PY of exposure to tildrakizumab 100 mg and 1568 PY of exposure to tildrakizumab 200 mg in the base and extension studies

Cardiovascular Events

- EAIRs for all confirmed CV events were <1.0 event per 100 PY in patients receiving either tildrakizumab 100 or 200 mg in both studies (**Table 2**)

Table 2. Summary of exposure-related cardiovascular events over 5 years

	reSURFACE 1		reSURFACE 2	
Adverse event, n[a] (EAIR)[b]	TIL 100 mg (n = 256) (1164.8 PY)	TIL 200 mg (n = 267) (1365.8 PY)	TIL 100 mg (n = 398) (1671.3 PY)	TIL 200 mg (n = 454) (1567.5 PY)
≥1 confirmed composite adjudicated CV events[c]	7 (0.6)	12 (0.9)	7 (0.4)	10 (0.6)
Confirmed CV events				
MACE[d]	6 (0.5)	6 (0.4)	5 (0.3)	9 (0.6)
Extended MACE[e]	6 (0.5)	9 (0.7)	5 (0.3)	9 (0.6)
Fatal/nonfatal thrombotic/embolic/ischemic CV events[f]	5 (0.4)	11 (0.8)	6 (0.4)	10 (0.6)
Individual cardiovascular events				
Cardiac events	2 (0.2)	4 (0.3)	4 (0.2)	9 (0.6)
Acute myocardial infarction	0	1 (0.1)	3 (0.2)	7 (0.4)
Coronary revascularization	1 (0.1)	4 (0.3)	1 (0.1)	6 (0.4)
Resuscitated cardiac arrest	0	1 (0.1)	0	0
Cardiac arrhythmias, no evidence of ischemia	0	0	2 (0.1)	2 (0.1)
Severe/accelerated hypertension	1 (0.1)	0	0	0
Cerebrovascular events	6 (0.5)	6 (0.4)	1 (0.1)	2 (0.1)
Hemorrhagic stroke or hemorrhagic change	3 (0.3)	1 (0.1)	0	0
Ischemic stroke	4 (0.3)	4 (0.3)	1 (0.1)	2 (0.1)
Other brain imaging finding	0	1 (0.1)	0	0
Cerebrovascular revascularization	1 (0.1)	0	0	0
Peripheral vascular events	1 (0.1)	3 (0.2)	1 (0.1)	2 (0.1)
Peripheral venous thrombosis	1 (0.1)	2 (0.1)	1 (0.1)	0
Pulmonary embolism	1 (0.1)	3 (0.2)	0	0
Peripheral arterial thrombosis/thromboembolism	0	0	1 (0.1)	1 (0.1)
Cardiovascular death	0	0	1 (0.1)	1 (0.1)

[a]Includes patients who received TIL 100 or 200 mg at any time during the study. [b]Numbers in parentheses represent the number of patients with the event per 100 PY of exposure. [c]Includes confirmed MACE, extended MACE, and fatal or nonfatal thrombotic/embolic/ischemic CV events. [d]Includes nonfatal myocardial infarction, nonfatal stroke, and CV deaths confirmed as "cardiovascular" or "sudden." [e]Includes nonfatal myocardial infarction, nonfatal stroke, unstable angina, coronary revascularization, resuscitated cardiac arrest, and CV deaths confirmed as "cardiovascular" or "sudden." [f]Includes fatal and nonfatal events—acute myocardial infarction, ischemic stroke, unstable angina, coronary revascularization, transient ischemic attack, pulmonary embolism, peripheral arterial thrombosis/thromboembolism, venous thrombosis, resuscitated cardiac arrest, and CV deaths confirmed as "cardiovascular" or "sudden."
CV, cardiovascular; EAIR, exposure-adjusted incidence rate; MACE, major adverse cardiovascular event; PY, patient-years; TIL, tildrakizumab.

CONCLUSIONS

- Through 5 years of treatment, EAIRs of individual and composite cardiovascular events were low and similar between tildrakizumab doses for up to 5 years
- No new safety signals were observed

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ACKNOWLEDGMENTS

We thank the patients for their participation. The studies were funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; analyses were funded by Sun Pharmaceutical Industries, Inc., Princeton, NJ, USA. Medical writing and editorial support was provided by Hilary Durbano, PhD, of AlphaBioCom, LLC, and funded by Sun Pharmaceutical Industries, Inc.

DISCLOSURES

CT has served on speaker's bureaus for Abbvie; Amgen; Eli Lilly; Janssen; LEO Pharma; Novartis; Pfizer; Ortho-Dermatologics; Sanofi-Genzyme; and Sun Pharmaceutical Industries, Inc. **RG** has served on advisory boards and/or received lecture honoraria from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, LEO Pharma, Mallinckrodt, Merck, and Novartis. **DTW** has served as a consultant for Dermtech, Galderma, and Pfizer, and as an advisory board member for DEF conference. **AMM** is a former employee of Sun Pharmaceutical Industries, Inc., and has individual shares in Johnson and Johnson, and as part of retirement account/mutual funds. **SJR** is an employee of Sun Pharmaceutical Industries, Inc. **SD** is an investigator for AbbVie, Dermira, Eli Lilly, Foamix, Galderma, Incyte, Moberg, Novartis, Solgel, and Valeant; and a speaker for Pfizer and Dermira.

Presented at American Academy of Dermatology 2021 Virtual Meeting Experience, April 23–25, 2021