Efficacy and safety of tildrakizumab 100 mg for plaque psoriasis in patients randomized to treatment continuation vs treatment withdrawal with retreatment upon relapse in reSURFACE 1

Wendy Cantrell,[1] Patricia Lee,[2] Alan M Mendelsohn,[3] Jeff Parno,[3] Stephen J Rozzo,[3] Wilson Liao[4]

[1]Village Dermatology, Birmingham, AL, USA; [2]Center for Clinical Studies, Webster, TX, USA; [3]Sun Pharmaceutical Industries, Inc., Princeton, NJ, USA; [4]Department of Dermatology, University of California San Francisco, San Francisco, CA, USA

INTRODUCTION

- Tildrakizumab is a high-affinity, humanized, immunoglobulin G1κ, anti–interleukin-23p19 monoclonal antibody approved in the US, Europe, and Australia for the treatment of moderate to severe plaque psoriasis
- Two large, phase 3, randomized, controlled trials (reSURFACE 1, NCT01722331; and reSURFACE 2, NCT01729754) of tildrakizumab were conducted in patients with moderate to severe chronic plaque psoriasis[1]
  - Tildrakizumab significantly improved psoriasis response rates vs placebo measured with the Psoriasis Area and Severity Index (PASI) responses (PASI 75, PASI 90, and PASI 100) and Physician's Global Assessment (PGA), by week 12 (primary endpoint) and week 28 (secondary endpoint)
  - Tildrakizumab was well tolerated with low frequencies of serious adverse events (AEs) and discontinuations due to AEs[2]
- Treatment efficacy in patients who discontinue medication, relapse, and are retreated is important for clinical practice

OBJECTIVE

- To assess residual disease in plaque psoriasis in patients successfully treated with tildrakizumab 100 mg who interrupted treatment, relapsed, and were retreated vs continuously treated patients in a post hoc analysis of the phase 3 reSURFACE 1 trial

METHODS

Study design

- reSURFACE 1 was a 3-part, double-blind, randomized, controlled, 64-week phase 3 study in adult patients with moderate to severe plaque psoriasis[1]
- Participants ≥18 years with moderate to severe chronic plaque psoriasis (body surface area ≥10%, PGA ≥3, PASI ≥12) were eligible
- The base study consisted of 3 parts:
  - In Part 1 (weeks 0–12), patients were randomly assigned (1:2:2) to blinded administration of subcutaneous placebo or tildrakizumab 100 or 200 mg at weeks 0 and 4
  - In Part 2 (weeks 12–28), patients previously receiving placebo were rerandomized to tildrakizumab 100 or 200 mg, administered at weeks 12 and 16 and then every 12 weeks. Patients receiving tildrakizumab received a placebo injection at week 12 to maintain the blinded treatment, then received the same dose of tildrakizumab at week 16 and then every 12 weeks
    - At week 28, tildrakizumab nonresponders (those who did not achieve PASI ≥50) discontinued treatment
    - Tildrakizumab responders (PASI ≥75) and partial responders (PASI ≥50 and <75) continued the study
  - In Part 3 (weeks 28–64), patients who had received tildrakizumab from the start of the study were rerandomized to placebo, tildrakizumab 100 mg, or tildrakizumab 200 mg based on their level of response to treatment; patients received tildrakizumab every 12 weeks or placebo every 4 weeks
  - After rerandomization to placebo, treatment was reinitiated if patients experienced a relapse (a reduction in maximum PASI response by ≥50%) or a rebound (>125% worsening of PASI scores from baseline values)
    - This analysis focuses on the tildrakizumab 100 mg responders (patients who achieved ≥75% relative improvement in PASI score from baseline) who were rerandomized at week 28 to receive either placebo or continue tildrakizumab 100 mg
    - Responders who were rerandomized to placebo were retreated with tildrakizumab 100 mg at relapse, 4 weeks later, and then every 12 weeks

Populations analyzed

- This analysis was performed on tildrakizumab 100 mg patients with a PASI 75 response at week 28 who either continued tildrakizumab 100 mg treatment or received placebo in Part 3
- Patients who received >1 dose of treatment after week 28 and those retreated for ≥12 weeks were included in efficacy analyses

Efficacy

- Residual disease was assessed as median (first quartile [Q1], third quartile [Q3]) PASI scores, scale 0–72, every 4 weeks through week 64
- Relative clinical improvement was evaluated as proportion of patients who achieved 75%, 90%, or 100% PASI improvement from baseline or a PGA of 0 or 1 (with >2-point decrease from study baseline)
- Time to loss and to regain efficacy were calculated as median (Q1, Q3) number of days
- Missing data were imputed using last observation carried forward method
  - No relapse designations were attributed to missed visits

Safety

- For analysis of tildrakizumab safety only, both PASI 75 responders and partial responders at week 28 were included
- AEs were evaluated every 4 weeks through week 64; all analyses were performed as observed

RESULTS

- At study initiation, 309 patients were randomized to tildrakizumab 100 mg
- At week 28, a total of 229 patients receiving tildrakizumab 100 mg who achieved PASI ≥75 were rerandomized to receive placebo (n = 113) or continue tildrakizumab 100 mg (n = 116)
- Baseline demographics and disease characteristics were similar between patients rerandomized at week 28 (Part 3) compared with patients who were randomized to tildrakizumab 100 mg at study initiation (week 0, Part 1) (**Table 1**)

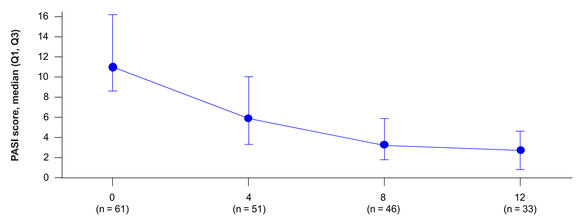
Table 1. reSURFACE 1 baseline demographics and disease characteristics

	TIL 100 mg arm, baseline (n = 309)	TIL 100 mg arm, Week 28 PASI 75 responders rerandomized in Part 3 (n = 229)
Sex, male, n (%)	207 (67.0)	148 (64.7)
Age, years	46.4 ± 13.1	46.4 ± 13.4
Race, White, n (%)	217 (70.2)	172 (75.1)
Weight, kg	88.5 ± 23.9	88.8 ± 23.3
BSA, %	29.7 ± 17.4	28.7 ± 17.1
PASI score	20.0 ± 7.9	19.6 ± 7.6
PGA ≥3	308 (99.7)	228 (99.6)

Data are mean ± standard deviation unless otherwise indicated.
BSA, body surface area; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; TIL, tildrakizumab.

- Of the 113 patients rerandomized to placebo, 54.0% (n = 61) relapsed and were retreated by week 64; 5 patients missed a single visit
- Median (Q1, Q3) time to relapse was 238 (167, 294) days; no patient experienced rebound
- Of the patients who were retreated, 59 completed Part 3 out to week 64; 2 discontinued prior to week 64
  - Duration of retreatment was measured from the start of retreatment to either week 64 or discontinuation date for patients who completed Part 3 or discontinued during Part 3, respectively
- The mean (standard deviation) and median (Q1, Q3) duration of retreatment was 92.7 (58.6) days and 85.0 (56, 141) days, respectively
- Among 51 patients with ≥12 weeks of retreatment data, median (Q1, Q3) time to regain response was 28 (28, 48) days
  - Of these patients, 49 (96.1%) regained response in <12 weeks; 2 (3.9%) patients regained response after >12 weeks of retreatment
- After 4 (n = 51), 8 (n = 46), and 12 weeks (n = 33) of retreatment, median (Q1, Q3) PASI scores were 5.9 (3.3, 10.0), 3.2 (1.8, 5.9), and 2.7 (0.8, 4.6), respectively (**Figure 1**)

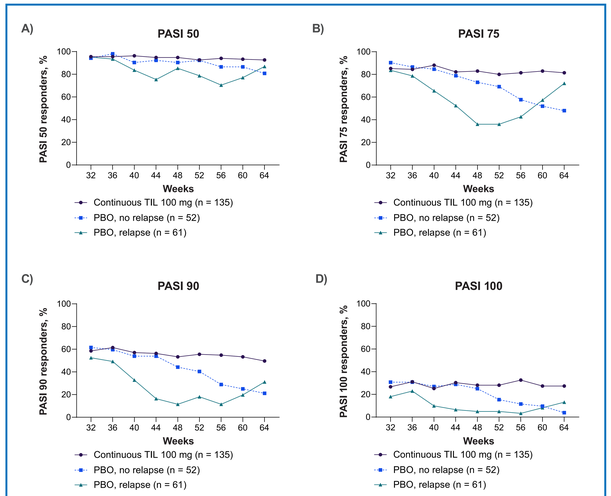
Figure 1. Median absolute PASI scores after relapse and retreatment with tildrakizumab 100 mg



Values on X-axis represent number of weeks after retreatment in patients who relapsed upon rerandomization to placebo. Error bars represent first and third quartiles.
PASI, Psoriasis Area and Severity Index; Q1, first quartile; Q3, third quartile.

- At week 64, 72.1% (n = 44), 31.1% (n = 19), and 13.1% (n = 8) of the patients who were retreated after relapse achieved PASI 75, PASI 90, and PASI 100 responses, respectively (**Figure 2**)

Figure 2. Rate of **A)** PASI 50, **B)** PASI 75, **C)** PASI 90, and **D)** PASI 100 responders over time by treatment condition in Part 3 of reSURFACE 1



Plot shows data from weeks 32–64 of Part 3, reSURFACE 1.
PASI, Psoriasis Area and Severity Index; PBO, placebo; TIL, tildrakizumab.

- **Table 2** compares median (Q1, Q3) PASI scores for patients who did not relapse upon rerandomization to placebo, relapsed upon rerandomization to placebo and were retreated, or received continuous tildrakizumab 100 mg

Table 2. Median absolute PASI scores of patients by treatment condition and time point during Part 3 of reSURFACE 1

	Week 28	Week 52	Week 64
PBO, no relapse (n = 52)	0.8 (0.0, 3.2)	2.6 (0.8, 5.2)	4.0 (2.0, 7.4)
Continuous TIL 100 mg, no relapse (n = 108)	1.0 (0.0, 2.2)	1.0 (0.0, 2.4)	1.2 (0.0, 3.0)
	Baseline	**Week 28**	**Time of relapse**
PBO, relapse (n = 61)	20.3 (14.3, 22.9)	0.8 (0.0, 2.2)	11.0 (8.6, 16.2)

Numbers are median (Q1, Q3).
PASI, Psoriasis Area and Severity Index; PBO, placebo; Q1, first quartile; Q3, third quartile; TIL, tildrakizumab.

- Of 116 patients who were continuously treated with tildrakizumab 100 mg in Part 3, 6.9% (n = 8) relapsed after week 28
  - Seven patients relapsed on a single visit; 10 patients missed a single visit
  - The remaining 108 patients completed the study with a median (Q1, Q3) PASI score of 1.2 (0.0, 3.0) (**Table 2**)

Safety

- Of the 135 patients (PASI 75 responders and partial responders) who continued to receive tildrakizumab 100 mg, 128 (94.8%) patients completed 64 weeks of the study; 7 (5.2%) patients discontinued
  - Reasons for discontinuation were withdrawal by subject (1.5%), AE (0.7%), lost to follow-up (0.7%), noncompliance with study drug (0.7%), physician decision (0.7%), and protocol violation (0.7%)
- Of the 113 patients randomized to placebo at week 28, 103 (91.2%) completed the study, and 10 (8.8%) discontinued
  - Reasons for discontinuation were withdrawal by subject (4.4%), lost to follow-up (2.6%), AE (0.9%), and other protocol-specified criteria (0.9%)
- Incidence of Tier 1 AEs (defined as severe infections [any infection that was a serious AE or required intravenous antibiotics], malignancies [excluding carcinoma in situ of the cervix], nonmelanoma skin cancer, melanoma skin cancer, confirmed extended major adverse cardiovascular events, and drug-related hypersensitivity reactions) in patients rerandomized to placebo or tildrakizumab is shown in **Table 3**

Table 3. Tier 1 adverse events by preferred term at week 28

	Rerandomized to TIL 100 mg (n = 135[a])	Rerandomized to PBO (n = 113)
At least one Tier 1 AE	3 (2.2%)	2 (1.8%)
Basal cell carcinoma	1 (0.7%)	1 (0.9%)
Bowen's disease	1 (0.7%)	0
Carcinoma in situ of skin	1 (0.7%)	0
Sinusitis	1 (0.7%)	0
Cerebellar infarction	0	1 (0.9%)

[a]Includes subjects who were partial responders at week 28.
AE, adverse event; PBO, placebo; TIL, tildrakizumab.

- Two Tier 1 AEs occurred in 1.8% (n = 2) of the 113 responders rerandomized to placebo after week 28 who did not relapse (cerebellar infarction and basal cell carcinoma)
- Of the 135 patients rerandomized to tildrakizumab 100 mg after week 28 (including partial responders), 2.2% (n = 3) reported 4 Tier 1 AEs (basal cell carcinoma, Bowen's disease, carcinoma in situ of the skin, and sinusitis)
- No Tier 1 AEs were reported in patients who were rerandomized to placebo at week 28 and relapsed either on placebo or tildrakizumab 100 mg

CONCLUSIONS

- In Part 3 of the reSURFACE 1 trial (weeks 28–64), tildrakizumab 100 mg had a durable response profile
  - A large proportion (46%) of tildrakizumab 100 mg responders did not relapse after rerandomization to placebo for 48 weeks after receiving their last dose of drug
- In patients who relapsed upon tildrakizumab withdrawal and were retreated, residual disease resolved in the majority of cases within a median of 28 days after receiving tildrakizumab 100 mg, and the rate of AEs was low
- Continuation of tildrakizumab 100 mg was associated with low residual disease and a low rate of AEs

REFERENCES

1. Reich K, et al. *Lancet.* 2017;390:276–88.
2. Blauvelt A, et al. *Br J Dermatol.* 2018;179:615–22.

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DISCLOSURES

WC has no disclosures on file. **PL** has served as an investigator for Merck. **AMM** is an employee of Sun Pharmaceutical Industries, Inc.; and has individual shares in Johnson and Johnson, and as part of retirement account/mutual funds. **JP** is an employee of Sun Pharmaceutical Industries, Inc.; and has served as statistical consultant for Sun Pharmaceutical Industries, Inc.; and Kyowa Kirin Pharmaceutical Development, Inc. **SJR** is an employee of Sun Pharmaceutical Industries, Inc. **WL** has conducted research funded by AbbVie, Amgen, Janssen, Novartis, Pfizer, and Regeneron/Sanofi.

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