Efficacy and safety of long-term tildrakizumab for plaque psoriasis: 4-year results from reSURFACE 1 and reSURFACE 2

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INTRODUCTION

- Tildrakizumab is a high-affinity, humanized, immunoglobin G1κ, anti–interleukin-23p19 monoclonal antibody approved 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 75, PASI 90, and PASI 100) and Physician's Global Assessment (PGA) score, by week 12 (primary endpoint)
  - Tildrakizumab was well tolerated with low frequencies of serious adverse events (AEs) and discontinuations due to AEs[2]

OBJECTIVES

- To evaluate the 4-year efficacy data for tildrakizumab in the ongoing long-term extension period of the phase 3 reSURFACE 1 and reSURFACE 2 studies
- To evaluate the 4-year safety data for the base and extension periods of reSURFACE 1 and reSURFACE 2

METHODS

Base study

- Participants ≥18 years of age with moderate to severe chronic plaque psoriasis (body surface area involvement ≥10%, PGA score ≥3, and PASI score ≥12) were eligible
- **Part 1 (weeks 1–12).** Patients were randomized (1:2:2) to blinded subcutaneous placebo or tildrakizumab 100 or 200 mg at weeks 0 and 4. reSURFACE 2 also contained an etanercept arm (50 mg twice a week)
- **Part 2 (weeks 12–28).** Patients previously receiving placebo were rerandomized to tildrakizumab 100 or 200 mg at weeks 12 and 16 and every 12 weeks (Q12W) thereafter. Patients continuing tildrakizumab from Part 1 received a placebo injection at week 12 to maintain the blind and a dose of tildrakizumab at weeks 16 and 28. Patients previously receiving etanercept 50 mg twice a week in reSURFACE 2 continued etanercept once a week. At week 28, tildrakizumab nonresponders (PASI <50) and etanercept responders discontinued
- **Part 3 (weeks 28–64/52).** Tildrakizumab responders (PASI ≥75) were rerandomized to receive placebo every 2 weeks (reSURFACE 1) or tildrakizumab 100 or 200 mg Q12W (reSURFACE 1 and 2). Responders who were rerandomized to placebo were retreated with the same tildrakizumab dose upon relapse (defined as reduction in maximum PASI response by 50%). In reSURFACE 2, etanercept partial responders (PASI ≥50 and PASI <75) or nonresponders transitioned to tildrakizumab 200 mg
- reSURFACE 1 base study was 64 weeks; reSURFACE 2 base study was 52 weeks

Extension study

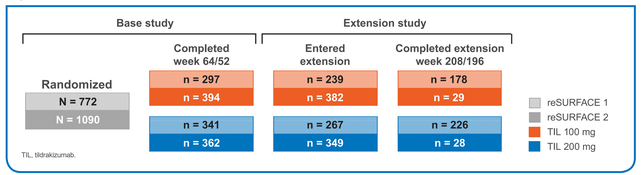
- Patients who completed the base study with PASI ≥50 and received tildrakizumab within 12 weeks of base study end could enter a long-term, open-label extension study (up to 192 weeks)
- In the extension study (reSURFACE 1: weeks 64–256; reSURFACE 2: weeks 52–240), patients received the same dose of tildrakizumab as at completion of base study

Efficacy and safety

- Efficacy was evaluated using PASI and PGA response for all patients who received ≥1 dose during the extension study (Full Analysis Set [FAS] population) with no imputation of missing data (up to 4 years)
- Safety: AEs were evaluated for all patients who received ≥1 dose during the base or extension study (up to 5 years)
  - Cumulative and yearly AE incidence rates calculated using base and extension study data
  - Discontinuation rates analyzed for FAS population

RESULTS

Figure 1. Patient flow



TIL, tildrakizumab.

- The patient flow from randomization through the extension study for reSURFACE 1 and reSURFACE 2 is shown in **Figure 1**

Table 1. Baseline demographics for patients entering extension

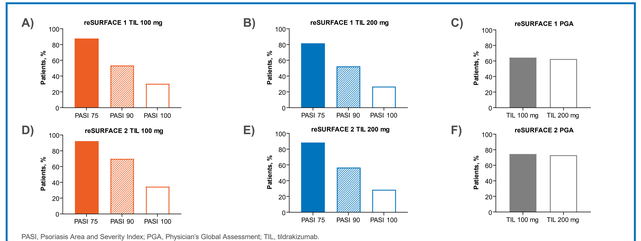
	reSURFACE 1		reSURFACE 2	
	TIL 100 mg (n = 239)	TIL 200 mg (n = 267)	TIL 100 mg (n = 382)	TIL 200 mg (n = 349)
Sex, male, n (%)	159 (66.5)	183 (68.5)	291 (76.2)	242 (69.3)
Age, mean ± SD, years	46.9 ± 13.0	47.1 ± 13.0	44.2 ± 13.2	45.6 ± 12.8
Race, White, n (%)	163 (68.2)	173 (64.8)	352 (92.1)	329 (94.3)
Baseline PASI score, mean ± SD	20 ± 7.6	21.3 ± 9.6	19.8 ± 7.6	19.3 ± 6.9
Weight, mean ± SD, kg	87.1 ± 24.4	87.8 ± 24.2	88.4 ± 21.4	89.0 ± 21.5
Body surface area, mean ± SD	30.2 ± 17.5	31.7 ± 19.6	32.6 ± 18.0	30.1 ± 15.8

PASI, Psoriasis Area and Severity Index; SD, standard deviation; TIL, tildrakizumab.

- The efficacy analysis was concluded at week 208 for reSURFACE 1 (extension week 144; 2210.8 total patient years) and week 196 for reSURFACE 2 (2768.3 total patient years)

Efficacy

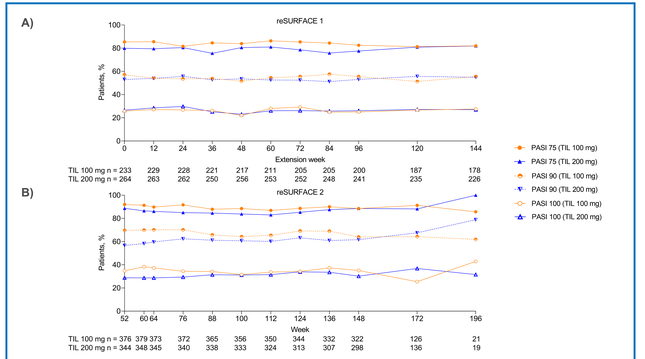
Figure 2. reSURFACE 1 week 64 results of PASI 75/90/100 responses for **A)** tildrakizumab 100 mg, **B)** tildrakizumab 200 mg, and **C)** PGA response; and reSURFACE 2 week 52 results of PASI 75/90/100 responses for **D)** tildrakizumab 100 mg, **E)** tildrakizumab 200 mg, and **F)** PGA response



PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; TIL, tildrakizumab.

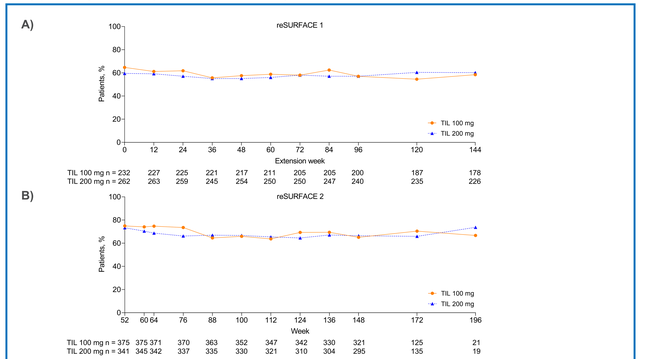
- The proportion of patients achieving PASI 75/90/100 responses and PGA responses ("clear" or "minimal" with a >2-grade reduction from baseline) during the base study period of 64 weeks (reSURFACE 1) or 52 weeks (reSURFACE 2) are shown in **Figure 2**

Figure 3. PASI 75/90/100 responses during the extension study period by tildrakizumab dose in **A)** reSURFACE 1, and **B)** reSURFACE 2



FAS population; missing data at a given visit were not imputed. n = number of patients with data at each visit.
FAS, full analysis set; PASI, Psoriasis Area and Severity Index; TIL, tildrakizumab.

Figure 4. PGA responses of 'clear' or 'minimal' with a grade ≥2 reduction from baseline during extension study period by dose in **A)** reSURFACE 1 and **B)** reSURFACE 2



FAS population; missing data at a given visit were not imputed. n = number of patients with data at each visit.
FAS, Full Analysis Set; PGA, Physician's Global Assessment; TIL, tildrakizumab.

- The proportions of patients who achieved a PGA response during the extension study period in reSURFACE 1 and reSURFACE 2 are presented in **Figure 4**

Safety

- Of the 506 patients who entered the extension period in reSURFACE 1, a total of 113 (22%) discontinued. In reSURFACE 2, a total of 153 (20.9%) of 731 patients discontinued
  - Most common causes of discontinuation were patient withdrawal (reSURFACE 1: 8%; reSURFACE 2: 7.5%), AEs (reSURFACE 1: 5%; reSURFACE 2: 3.0%), and loss to follow-up (reSURFACE 1: 4%; reSURFACE 2: 2.9%)
- The cumulative numbers of patients who reported prespecified AEs after up to 5 years of tildrakizumab treatment are shown in **Table 2**
- In reSURFACE 1, there were 2 deaths among patients who proceeded from the base study to the long-term extension: 1 patient receiving tildrakizumab 100 mg (metastatic carcinoma of the bladder with intracranial hemorrhage) and 1 patient receiving tildrakizumab 200 mg (suicide)
- In reSURFACE 2, there were 4 deaths among patients who proceeded into the extension: 3 patients receiving tildrakizumab 100 mg and 1 patient receiving tildrakizumab 200 mg

Table 2. Cumulative number of patients with AEs of interest after up to 5 years of treatment

	reSURFACE 1		reSURFACE 2		
AEs, n[a] (Exposure-adjusted rate)[b]	TIL 100 mg (n = 383; 1410.4 PY)	TIL 200 mg (n = 399; 1606.5 PY)	TIL 100 mg (n = 410; 1513.3 PY)	TIL 200 mg (n = 380; 1404.7 PY)	ETN[c] (n = 313; 153.4 PY)
Severe infections	13 (0.9)	17 (1.1)	17 (1.6)	14 (1.0)	3 (2.0)
Malignancies	18 (1.3)	11 (0.7)	10 (0.9)	12 (0.9)	4 (2.6)
Nonmelanoma skin cancer	6 (0.4)	5 (0.3)	3 (0.3)	5 (0.4)	2 (1.3)
Melanoma skin cancer	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	0
Confirmed extended MACE	7 (0.5)	9 (0.6)	7 (0.7)	10 (0.7)	1 (0.7)
Drug-related hypersensitivity reactions	2 (0.1)	1 (0.1)	2 (0.2)	3 (0.2)	0
Death	1 (0.1)	2 (0.1)	6 (0.6)	1 (0.1)	0

[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 unless otherwise noted.
[c]Etanercept exposure only occurred during parts 1 and 2, there was no exposure after week 28.
AE, adverse event; ETN, etanercept; MACE, major adverse cardiovascular event; PY, patient-year; TIL, tildrakizumab.

CONCLUSIONS

- Over 4 years of treatment with tildrakizumab, PASI and PGA response rates were high and durable for the tildrakizumab 100 and 200 mg doses in both reSURFACE 1 and reSURFACE 2
- Through up to 5 years of follow-up, both tildrakizumab doses were well tolerated with low rates of AEs of interest reported with long-term treatment in both reSURFACE 1 and reSURFACE 2. AE rates were comparable relative to etanercept-treated patients in reSURFACE 2

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

RGL has served as principal investigator for and is on the scientific advisory board or served as a speaker for AbbVie; Amgen; Boehringer Ingelheim; Celgene; Eli Lilly and Co.; Janssen; LEO Pharma; Merck & Co; Novartis; Pfizer; and Sun Pharmaceutical Industries, Inc. **JC** has received research/grant support from AbbVie; Amgen; Boehringer Ingelheim; Eli Lilly and Co.; Janssen; MC2 Therapeutics; Merck & Co.; Novartis; Pfizer; Regeneron; Sandoz; Sanofi; Sun Pharmaceutical Industries, Inc.; UCB; and Ventus Pharmaceuticals; has served as consultant for AbbVie; Amgen; Celgene; Dermira; Eli Lilly and Co.; Novartis; Sun Pharmaceutical Industries, Inc.; and UCB; and has worked on speakers bureau for AbbVie, Janssen, Eli Lilly and Co., Novartis, Regeneron, Sanofi, and UCB. **MG** has been an investigator, consultant, and/or speaker for AbbVie; Actelion Pharmaceuticals; Akros Pharma; Amgen; Arcutis Pharmaceuticals; Boehringer Ingelheim; Bristol-Myers Squibb; Celgene; Dermira; Eli Lilly and Co.; 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