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Safety, Immunogenicity, and Efficacy of Tildrakizumab in Patients With Chronic Plaque Psoriasis: Final Results From the reSURFACE 1 and reSURFACE 2 Long-Term Extension Studies

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Introduction & Objectives: Tildrakizumab, a monoclonal antibody targeting the interleukin-23 p19 subunit, is approved for the treatment of adults with moderate-to-severe plaque psoriasis. Final long-term safety, immunogenicity, and efficacy results are reported for tildrakizumab 100 mg (TIL100) and 200 mg (TIL200) from the completed reSURFACE 1 (NCT01722331) and reSURFACE 2 (NCT01729754) long-term extension studies (EXTs).

Materials & Methods: reSURFACE 1 and reSURFACE 2 were double-blinded, randomized, controlled Phase 3 trials in adults with moderate-to-severe chronic plaque psoriasis. Patients completing the base studies (64/52 weeks) with ≥50% improvement from baseline (BL) in Psoriasis Area and Severity Index (PASI) could enter the optional EXTs receiving the same TIL dose for up to an additional 192 weeks (Extension 1 [EXT 1]); patients completing EXT 1 could continue receiving TIL in EXT 2 (108 weeks) and then EXT 3 (48 weeks) until it became commercially available in local markets. Safety was assessed from frequencies of adverse events (AEs). Immunogenicity endpoints included frequency of antidrug antibodies (ADAs) and correlation of ADA with efficacy and safety. Efficacy endpoints in the EXTs included proportions of patients with ≥75%, ≥90%, and 100% improvement in PASI (PASI 75/90/100 response) among those with each response at the end of the base studies, and proportion of patients with Physician Global Assessment score of clear or minimal with a ≥2-grade reduction from base study BL (PGA 0/1) over time. Data are shown as observed.

Results: Among 506/730 patients entering the reSURFACE 1/reSURFACE 2 EXTs, 74.9%/77.0% completed EXT 1,

31.6%/7.1% completed EXT 2, and 15.4%/4.2% completed EXT 3 (**Table 1**); median treatment duration was 204/192 weeks.

Overall frequencies of treatment-related AEs (TRAEs), TRAEs leading to discontinuation, and serious TRAEs in the reSURFACE 1/reSURFACE 2 EXTs were 18.6%/26.0%, 2.2%/1.0%, and 3.8%/1.9% and similar between TIL100 and TIL200; malignancies, severe infections, and major adverse cardiovascular events were reported in 5.7%/3.0%, 5.5%/3.6%, and 2.8%/2.2% of patients (**Table 2**). Frequencies of AEs did not increase with long-term TIL100 or TIL200 treatment. Among 503/725 ADA-evaluable patients in the reSURFACE 1/reSURFACE 2 EXTs, 93.6%/80.8% had conclusive results: 79.9%/67.7% were ADA-negative, 9.1%/7.7% were treatment-emergent ADA-positive (neutralizing antibody [nAB] positive, 4.6%/1.8%), and 4.6%/5.4% were non–treatment-emergent ADA-positive (nAB positive, 1.2%/0.6%). There was no clear correlation between nAB frequency and efficacy or overall AE frequency among ADA-positive patients.

Of patients with PASI 75/90/100 responses at the end of the base studies who entered the EXTs, 94.1%/88.8%/68.6% receiving TIL100 and 92.1%/87.6%/78.6% receiving TIL200 had similar response at EXT study start in reSURFACE 1 and 96.5%/93.1%/84.0% and 93.7%/88.1%/79.8% in reSURFACE 2; 64.7% and 59.4% of patients in reSURFACE 1 and 74.1% and 70.8% in reSURFACE 2 had PGA 0/1 responses at EXT start. In both studies, the majority of patients in both dose arms maintained PASI 75/90/100 and PGA 0/1 responses throughout the EXTs for up to 368 weeks (**Figure 1; Figure 2**).

Conclusion: No new safety signals emerged after up to 368 weeks of tildrakizumab treatment in patients with plaque psoriasis. Efficacy of tildrakizumab was maintained for up to 368 weeks in the majority of patients at each time point.

Table 1. Disposition of patients in the extension studies

	reSURFACE 1			reSURFACE 2		
	TIL100 n = 239	TIL200 n = 267	Total N = 506	TIL100 n = 381	TIL200 n = 349	Total n = 730
Extension 1						
Completed, n (%)	171 (71.5)	208 (77.9)	379 (74.9)	290 (76.1)	272 (77.9)	562 (77.0)
Discontinued, n (%)	68 (28.5)	59 (22.1)	127 (25.1)	90 (23.6)	76 (21.8)	166 (22.7)
Reasons for discontinuation, n (%)						
AEs	19 (7.9)	8 (3.0)	27 (5.3)	14 (3.7)	11 (3.2)	25 (3.4)
Death	1 (0.4)	1 (0.4)	2 (0.4)	3 (0.8)	1 (0.3)	4 (0.5)
Lack of efficacy	6 (2.5)	5 (1.9)	11 (2.2)	10 (2.6)	11 (3.2)	21 (2.9)
Lost to follow-up	15 (6.3)	9 (3.4)	24 (4.7)	15 (3.9)	13 (3.7)	28 (3.8)
Noncompliance with study drug	0	1 (0.4)	1 (0.2)	2 (0.5)	2 (0.6)	4 (0.5)
Physician decision	5 (2.1)	5 (1.9)	10 (2.0)	8 (2.1)	11 (3.2)	19 (2.6)
Pregnancy	0	5 (1.9)	5 (1.0)	2 (0.5)	1 (0.3)	3 (0.4)
Progressive disease	0	0	0	0	2 (0.6)	2 (0.3)
Other protocol-specified criteria	0	0	0	1 (0.3)	0	1 (0.1)
Withdrawal by patient	22 (9.2)	25 (9.4)	47 (9.3)	35 (9.2)	24 (6.9)	59 (8.1)
Extension 2						
Total entered Extension 2	**n = 82**	**n = 108**	**N = 190**	**n = 77**	**n = 69**	**N = 146**
Completed, n (%)	70 (29.3)	90 (33.7)	160 (31.6)	31 (8.1)	21 (6.0)	52 (7.1)
Discontinued, n (%)	12 (5.0)	18 (6.7)	30 (5.9)	46 (12.1)	48 (13.8)	94 (12.9)
Reasons for discontinuation, n (%)						
AEs	2 (0.8)	2 (0.7)	4 (0.8)	2 (0.5)	0	2 (0.3)
Death	1 (0.4)	1 (0.4)	2 (0.4)	0	0	0
Lack of efficacy	0	0	0	4 (1.0)	1 (0.3)	5 (0.7)
Lost to follow-up	1 (0.4)	0	1 (0.2)	0	0	0
Physician decision	0	0	0	1 (0.3)	2 (0.6)	3 (0.4)
Study terminated by sponsor				12 (3.1)	27 (7.7)	39 (5.3)
Withdrawal by patient	4 (1.7)	10 (3.7)	14 (2.8)	10 (2.6)	8 (2.3)	18 (2.5)
Other protocol-specified criteria	4 (1.7)	5 (1.9)	9 (1.8)	17 (4.5)	10 (2.9)	27 (3.7)
Extension 3						
Total entered Extension 3	**n = 33**	**n = 45**	**N = 78**	**n = 20**	**n = 11**	**N = 31**
Completed, n (%)	33 (13.8)	45 (16.9)	78 (15.4)	20 (5.2)	11 (3.2)	31 (4.2)
Discontinued, n (%)	0	0	0	0	0	0

All patients entered a 20-week follow-up/washout period following the extension study treatment period to monitor safety/tolerability, PK, and ADA response. Patients returned for 2 visits during the follow up period occurring at 12 and 20 weeks after the patient's last visit during the treatment period. The follow-up period was not applicable for patients who switched to commercial drug at the discretion of the investigator. Patients who had already entered the follow-up period before the protocol amendment to accommodate Extensions 2 and 3 was implemented could resume study treatment after completing a minimum of 12 weeks of follow-up.

Extension 1 refers to the study period comprising the treatment visits from the end of the reSURFACE 1/reSURFACE 2 base studies to W192 in the extension studies; Extension 2 refers to additional treatment visits up to 108 weeks after completion of Extension 1; and Extension 3 refers to additional treatment visits up to 48 weeks after completion of Extension 2.

In reSURFACE 1, 197 patients in total entered Extension 2. Of these, 1 had unknown status due to early site closure and 6 switched to commercial drug without completion or discontinuation status; 190 have completion/discontinuation information available.

In reSURFACE 2, 249 patients in total entered Extension 2. Of these, 22 had unknown status due to early site closure and 81 switched to commercial drug without completion or discontinuation status; 146 have completion/discontinuation information available.

ADA, antidrug antibody; AE, adverse event; PK, pharmacokinetic; TIL100, tildrakizumab 100 mg; TIL200, tildrakizumab 200 mg; W, week.

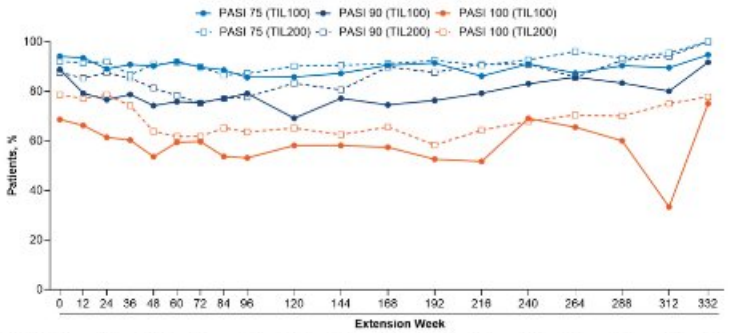
Table 2. Summary of AEs in the reSURFACE 1/reSURFACE 2 extension studies

Category, n (%)	reSURFACE 1			reSURFACE 2		
	TIL100 (n = 239)	TIL200 (n = 267)	Total (N = 506)	TIL100 (n = 381)	TIL200 (n = 349)	Total (N = 730)
≥1AE	216 (90.4)	231 (86.5)	447 (88.3)	321 (84.3)	307 (88.0)	628 (86.0)
Treatment-related AEs	44 (18.4)	50 (18.7)	94 (18.6)	91 (23.9)	99 (28.4)	190 (26.0)
SAEs	60 (25.1)	58 (21.7)	118 (23.3)	87 (22.8)	79 (22.6)	166 (22.7)
Treatment-related SAEs	12 (5.0)	7 (2.6)	19 (3.8)	8 (2.1)	6 (1.7)	14 (1.9)
Deaths	3 (1.3)	2 (0.7)	5 (1.0)	4 (1.0)	2 (0.6)	6 (0.8)
AEs leading to discontinuation	26 (10.9)	13 (4.9)	39 (7.7)	16 (4.2)	13 (3.7)	29 (4.0)
Treatment-related AEs leading to discontinuation	9 (3.8)	2 (0.7)	11 (2.2)	4 (1.0)	3 (0.9)	7 (1.0)
SAEs leading to discontinuation	23 (9.6)	7 (2.6)	30 (5.9)	7 (1.8)	8 (2.3)	15 (2.1)
Treatment-related SAEs leading to discontinuation	7 (2.9)	1 (0.4)	8 (1.6)	1 (0.3)	1 (0.3)	2 (0.3)
Tier 1 AEs						
Severe infections	12 (5.0)	16 (6.0)	28 (5.5)	15 (3.9)	11 (3.2)	26 (3.6)
Malignancies	19 (7.9)	10 (3.7)	29 (5.7)	9 (2.4)	13 (3.7)	22 (3.0)
Nonmelanoma skin cancer	1 (0.4)	1 (0.4)	2 (0.4)	5 (1.3)	4 (1.1)	9 (1.2)
Melanoma skin cancer	1 (0.4)	1 (0.4)	2 (0.4)	0	2 (0.6)	2 (0.3)
Confirmed extended MACE	6 (2.5)	8 (3.0)	14 (2.8)	7 (1.8)	9 (2.6)	16 (2.2)
Treatment-related hypersensitivity reactions	1 (0.4)	0	1 (0.2)	1 (0.3)	2 (0.6)	3 (0.4)

AE, adverse event; MACE, major adverse cardiovascular event; SAE, serious adverse event; TIL100, ± Idrakizumab 100 mg; TIL200, tildrakizumab 200 mg.

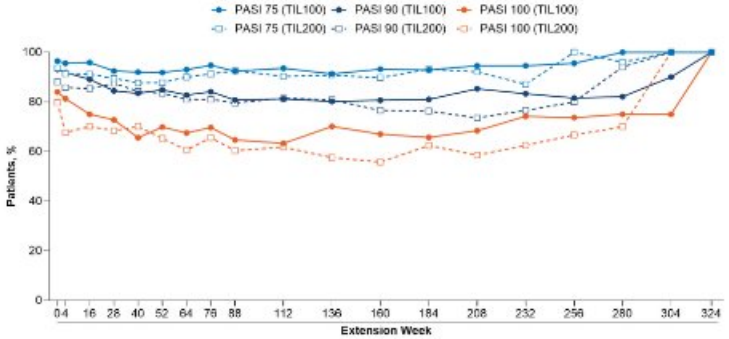
Figure 1. Percentages of PASI 75/90/100 responders at base study completion who maintained the response over time during the (A) reSURFACE 1 and (B) reSURFACE 2 extension studies

(A) reSURFACE 1



TIL100, n = 233	228	217	205	200	189	182	176	168	84	83	75	65	19	19
TIL200, n = 263	261	255	251	240	235	229	218	208	105	102	93	73	23	22

(B) reSURFACE 2



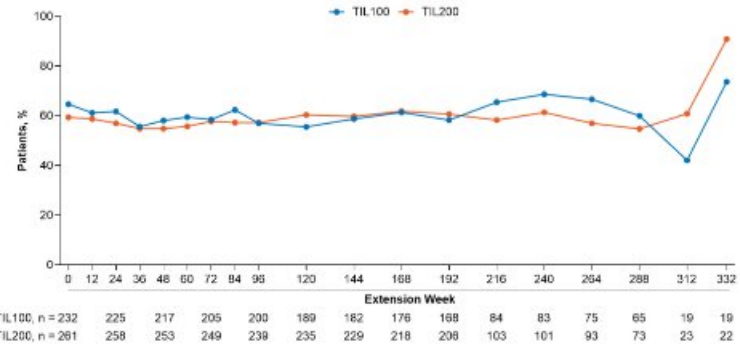
TIL100, n = 378	371	355	343	322	320	307	296	286	103	82	48	49	11	12
TIL200, n = 345	337	332	312	299	295	286	279	272	85	71	35	29	9	4

Percentages are calculated from the number of patients who had PASI 75/90/100 responses at completion of the reSURFACE1/reSURFACE 2 base studies (W64/52) and who remained in the extension study at the timepoints shown. Although patients were followed up for 368/332 weeks in the reSURFACE 1/reSURFACE 2 extension studies, timepoints beyond extension W332/324 are not shown because <10 patients remained in the studies.

BL, baseline; EXT, extension study; PASI 75/90/100, ≥75%/≥90%/100% improvement from baseline in Psoriasis Area and Severity Index; TIL100, tildrakizumab 100 mg; TIL200, tildrakizumab 200 mg; W, week.

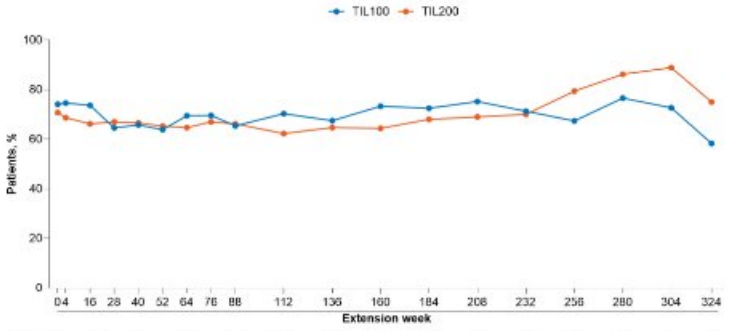
Figure 2. Percentages of patients with PGA 0/1 over time in the (A) reSURFACE 1 and (B) reSURFACE 2 extension studies

(A) reSURFACE 1



TIL100, n = 232	225	217	205	200	189	182	176	168	84	83	75	65	19	19
TIL200, n = 261	258	253	249	238	235	229	218	208	103	101	93	73	23	22

(B) reSURFACE 2



TIL100, n = 374	369	351	341	321	316	305	292	284	101	80	46	47	11	12
TIL200, n = 342	334	329	309	296	292	283	275	269	84	70	34	29	9	4

Although patients were followed up for 368/332 weeks in the reSURFACE 1/reSURFACE 2 extension studies, timepoints beyond extension W332/324 are not shown because <10 patients remained in the studies.

PGA 0/1, Physician Global Assessment score of clear or minimal with ≥2-grade improvement from baseline; TIL100, tildrakizumab 100 mg; TIL200, tildrakizumab 200 mg; W, week.