

Five-year efficacy and safety of tildrakizumab in patients with moderate-to-severe psoriasis who respond at week 28: pooled analyses of two randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2)

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Summary

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Conflicts of interest

Full details are given in Appendix 2.

Data availability statement

Data and other documents will be made available after publication, with no end date, to anyone who submits a reasonable request to the study sponsor.

Full author affiliations are given in Appendix 1.

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Background The phase III reSURFACE 1 and reSURFACE 2 (NCT01722331/NCT01729754) trials of the anti-interleukin-23p19 monoclonal antibody tildrakizumab (TIL) for psoriasis treatment are complete.

Objectives We present 5-year pooled data from reSURFACE 1 and reSURFACE 2.

Methods reSURFACE 1 and reSURFACE 2 were double-blind, randomized, controlled studies with optional long-term extensions. Adults with moderate-to-severe chronic plaque psoriasis were randomized 2 : 2 : 1 to TIL 100 mg (TIL 100) or 200 mg (TIL 200) or placebo at weeks 0 and 4, and every 12 weeks thereafter [reSURFACE 2 included an etanercept (ETN) arm]. Efficacy outcomes included proportions of patients achieving absolute and relative improvement from baseline Psoriasis Area and Severity Index (PASI) score through week 244 in TIL responders ($\geq 75\%$ improvement from baseline PASI; PASI 75 response) continuously receiving the same dose and ETN partial responders and nonresponders (PASI < 75 response) switched to TIL 200 at week 28. Safety was assessed from adverse events (AEs) in all patients as treated.

Results Efficacy analyses included 329 and 227 week 28 responders to TIL 100 and TIL 200, respectively, and 121 ETN partial responders/nonresponders switched to TIL 200 at week 28. Of TIL 100 or TIL 200 responders and ETN partial responders/nonresponders entering the extensions, 235/302, 176/213 and 85/107, respectively, were evaluated at week 244, and 88.7%, 92.5% and 81.3%, respectively, achieved PASI 75 response. Exposure-adjusted rates of serious AEs were 6.3 and 6.0 patients with events per 100 patient-years of TIL 100 and TIL 200, respectively.

Conclusions TIL treatment provided sustained disease control over 5 years in week 28 TIL responders and ETN partial responders/nonresponders, with a reassuring safety profile.

What's already known about this topic?

- Tildrakizumab (TIL) is approved for treatment of moderate-to-severe psoriasis, and 3-year data have been previously published.
- Long-term efficacy and safety data of biological therapies is crucial to inform clinical practice.

What does this study add?

- TIL is the first anti-interleukin-23p19 treatment for which 5-year efficacy and safety data are reported from two phase III studies, reSURFACE 1 and reSURFACE 2.

- These data provide evidence of sustained efficacy in TIL responders and in patients switched from etanercept to TIL at week 28, and a favourable long-term safety profile with total TIL exposure of over 5400 patient-years.

Long-term disease control and safety are key considerations in the treatment of chronic conditions such as psoriasis, and controlled data from long-term clinical studies are particularly valuable for guiding treatment decisions. Flexibility and the ability to optimize treatment for individual patients are also important in psoriasis treatment plans. Recent treatment guidelines from the British Association of Dermatologists and French Society of Dermatology favour absolute measures of disease severity, such as Psoriasis Area and Severity Index (PASI) score ≤ 3 or Physician's Global Assessment (PGA) of 'clear' (0) or 'nearly clear' (1), as the most relevant treatment goals in patients with severe baseline disease and those switching among therapies.^{1,2}

Growing evidence supports interleukin (IL)-23 as the master regulator of the psoriasis immune-inflammatory response.³ Tildrakizumab (TIL) is a humanized, IgG1 κ , monoclonal antibody specifically targeting IL-23p19, approved for the treatment of plaque psoriasis.^{4–8} The usual recommended dose is TIL 100 mg (TIL 100) at weeks 0 and 4, and every 12 weeks thereafter; in the European Union, TIL 200 mg (TIL 200) may be considered in patients with high disease burden.^{4–8} The phase III reSURFACE 1 (ClinicalTrials.gov NCT01722331) and reSURFACE 2 (ClinicalTrials.gov NCT01729754) trials assessed TIL efficacy and safety in patients with moderate-to-severe chronic plaque psoriasis. Primary results through week 28 and pooled results through week 148, including in-depth safety analysis, were previously published.^{4,9,10} This manuscript reports efficacy and safety through 5 years of treatment in reSURFACE 1 and reSURFACE 2, including the long-term extensions. Efficacy analyses include pooled patients who were responders to TIL, defined as $\geq 75\%$ improvement from baseline PASI score (PASI 75 response) at week 28, and reSURFACE 2 patients with partial response (PASI 50 < 75) or nonresponse (PASI < 50) to etanercept (ETN) at week 28 who switched to TIL 200.

Methods

Study design and participants

reSURFACE 1 and reSURFACE 2 were three-part, randomized, double-blind, placebo-controlled, parallel-group phase III trials; reSURFACE 2 included an active comparator (ETN) arm.^{4,10} Patients receiving TIL who completed the 64-week reSURFACE 1 and 52-week reSURFACE 2 base studies with $\geq 50\%$ improvement from baseline PASI score could enter the 192-week extension studies continuing the same dose (Figure 1).¹⁰ Study sites and base study dates have been previously described.⁴

Base study inclusion and exclusion criteria were previously described and are included in Methods S1 (see Supporting

Information).⁴ Briefly, eligible patients were ≥ 18 years of age, diagnosed with psoriasis ≥ 6 months before enrolment, had moderate-to-severe plaque psoriasis – defined as body surface area involvement $\geq 10\%$, PGA ≥ 3 and PASI score ≥ 12 – at entry, and were candidates for systemic therapy or phototherapy. The proportion of patients with previous biologic therapy was capped at 40%.

The study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The protocols were reviewed and approved by local institutional review boards or ethics panels, and all participants provided written informed consent.

Interventions

Treatment was previously described in detail.^{4,10} For part 1 (weeks 0–12), reSURFACE 1 patients were randomized 2 : 2 : 1 to receive TIL 100 or TIL 200 or placebo; reSURFACE 2 patients were randomized 2 : 2 : 1 : 2 to receive TIL 100 or TIL 200, placebo or ETN. Randomization was performed by region and stratified by bodyweight (≤ 90 or > 90 kg) and previous biologic therapy exposure. TIL 100 or TIL 200 was administered subcutaneously at baseline, week 4 and every 12 weeks thereafter. In part 2 (weeks 12–28), placebo-treated patients were rerandomized 1 : 1 to treatment with TIL 100 or TIL 200 at week 12, week 16 and every 12 weeks subsequently. In reSURFACE 2, ETN 50 mg was administered subcutaneously twice weekly in part 1 and once weekly in part 2; patients switched to TIL in part 3 received TIL 200 at week 32, week 36 and every 12 weeks thereafter. At week 28, patients who were responders or partial responders to TIL were rerandomized to continue the same treatment or receive a different dose of TIL or placebo for part 3 (weeks 28 to 64 or 52). Rerandomization at weeks 12 and 28 was performed by region and stratified by bodyweight.

Investigators, participants, study personnel and the analysis team were blinded to treatment allocation until all patients had completed part 3; after the base study database lock, patients in the extension studies received open-label TIL. Matching placebos were identical in appearance and packaging to TIL and ETN. Additional placebo doses were administered as needed to maintain masking.

Assessments

In TIL responders and partial or nonresponders to ETN at week 28, efficacy outcomes were proportions of patients achieving PASI 75 (part 1 co-primary outcome), PASI 90 and PASI 100 responses; absolute PASI scores < 5 , < 3 and < 1 ; and PGA 'clear' or 'minimal' with ≥ 2 -grade reduction from

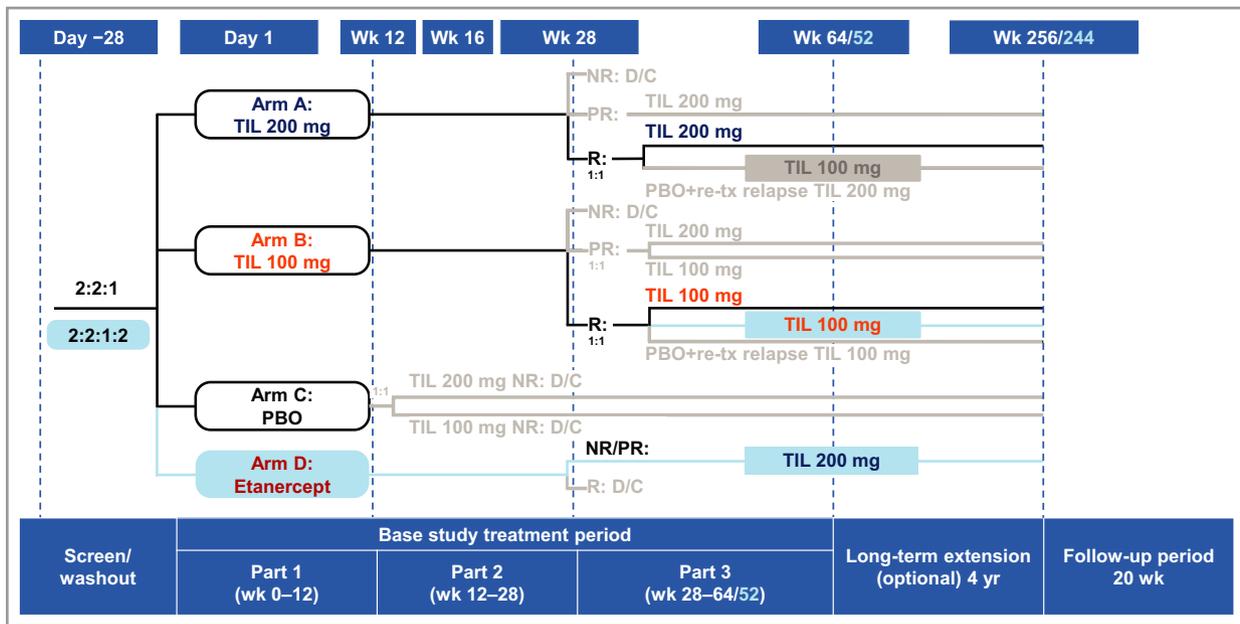


Figure 1 Study design. Light blue colour represents differences between reSURFACE 1 and reSURFACE 2. D/C, discontinued; NR, nonresponder; PBO, placebo; PR, partial responder; R, responder; re-tx, retreatment; TIL, tildrakizumab; wk, week; yr, year.

baseline (PGA 0/1; part 1 co-primary outcome) from week 28 to week 244.⁴ In part 3 and extension periods, PASI and PGA were evaluated at weeks 28, 32, 36, 40, 52, 60 and 64; every 12 weeks to week 148; and every 24 weeks thereafter.

Safety was assessed from exposure-adjusted incidence rates (EAIRs) of treatment-emergent adverse events (TEAEs). Pre-specified TEAEs of special interest (TEAE-SI) were severe infections, malignancies, nonmelanoma skin cancer (NMSC), melanoma, confirmed extended major adverse cardiovascular events (MACE) and drug-related hypersensitivity reactions as previously defined (Methods S1).^{4,10} AEs were assessed at all study visits.

Statistical analysis

Base study sample-size calculations and analysis methods were previously described.^{4,10} No formal hypothesis testing was performed for long-term follow-up results. Efficacy analyses were performed on the part 3 full analysis set, including all patients who entered and received at least one dose of study treatment in part 3. Pooled efficacy results from week 28 through the last common evaluation at week 244 are presented for TIL responders at week 28 who continuously received the same dose from part 1 into part 3, separately for TIL 100 and TIL 200, and for ETN partial responders and nonresponders at week 28 who switched to TIL 200. Placebo-treated patients, patients who discontinued before week 28, TIL partial responders or nonresponders, ETN responders and TIL responders at week 28 rerandomized to receive placebo or a different dose of TIL after week 28 were excluded from efficacy analyses.

The primary efficacy analysis used a multiple imputation approach for missing data as previously described;¹⁰ observed

cases and nonresponder imputation (NRI) were employed as sensitivity analyses (Methods S1). Assessments every 12 weeks after week 28 to week 148 and every 24 weeks thereafter are reported.¹⁰

Safety analyses were performed in the all-patients-as-treated population, including all patients who received at least one dose of the study drug based on the treatment received. Safety data from week 0 through 5 years were pooled between reSURFACE 1 (256 weeks) and reSURFACE 2 (244 weeks) and presented for patients who received TIL 100 or TIL 200 during any part of the study. MedDRA preferred terms for each AE were assigned to the treatment the patient was actively receiving when the AE occurred. Patients were counted in each assigned treatment group after starting a different treatment. Safety data are reported as EAIRs of patients with events per 100 patient-years (PYs) of exposure; EAIRs and 95% confidence intervals (CIs) were computed as previously described (Methods S1).¹⁰

Results

The reSURFACE 1 and reSURFACE 2 extension periods were completed on 17 May 2019 and 20 February 2019, respectively. Baseline demographic and disease characteristics in the safety analysis set were previously described^{4,10} (Table S1; see Supporting Information) and were similar among treatment arms.

Efficacy outcomes

As previously reported, 445 of 616 (72.2%) and 453 of 622 (72.8%) patients randomized to TIL 100 and TIL 200, respectively, were PASI 75 responders at week 28;⁴ 93 of 616 (15.1%)

and 64 of 622 (10.3%) patients receiving TIL 100 and TIL 200, respectively, discontinued treatment before part 3 due to nonresponse or other reasons (Figure 2). Among 329/227 week 28 TIL responders who continued receiving the same dose, 96.4%/96.5% of patients treated with TIL 100/TIL 200, respectively, completed part 3. Of patients who entered the extension periods, 80.1%/84.0% completed extension study treatment. Among ETN partial/nonresponders switched to TIL 200, 94.2% completed part 3 and 81.3% who entered the extension period completed treatment through week 244. During the extension periods, the most frequent reason for discontinuation was patient withdrawal. Few patients discontinued due to lack of efficacy or AEs (Figure 2).

The analyses outlined below and shown in Figures 3–5 exclude 93 patients randomized to TIL 100 and 64 randomized to TIL 200 who discontinued before week 28 or were nonresponders (PASI < 50 response) at week 28; 154 patients randomized to TIL 100 and 229 randomized to TIL 200 who were rerandomized to a different dose at week 28; and 40 patients randomized to TIL 100 and 102 randomized to TIL 200 who were partial responders (PASI 50 < 75 response) at week 28 and continued receiving the same dose. Missing data were handled with multiple imputation.

The proportions (95% CI) of TIL 100 responders achieving PASI 75/90/100 were 99.7% (98.3–100)/70.8% (65.6–75.7)/28.6% (23.8–33.8) at week 28 and 88.7% (84.6–92.1)/65.9% (60.3–71.2)/32.8% (27.5–38.4) at week 244 (Figure 3a). The proportions of TIL 200 responders achieving PASI 75/90/100 were 100% (98.4–100)/73.1% (66.9–78.8)/36.6% (30.3–43.2) at week 28 and 92.5% (88.1–95.7)/69.5% (62.8–75.6)/40.8% (34.2–47.8) at week 244 (Figure 3b).

Similarly, the proportions of TIL 100 responders achieving absolute PASI scores < 5/< 3/< 1 were 96.4% (93.7–98.1)/85.1% (80.8–88.8)/50.8% (45.2–56.3) at week 28 and 88.7% (84.6–92.1)/78.8% (73.8–83.3)/47.7% (41.9–53.5) at week 244 (Figure 4a). The proportions of TIL 200 responders achieving absolute PASI scores < 5/< 3/< 1 were 96.5% (93.2–98.5)/86.8% (81.7–90.9)/55.1% (48.3–61.7) at week 28 and 90.6% (85.9–94.2)/82.6% (76.9–87.5)/57.7% (50.8–64.5) at week 244 (Figure 4b). Efficacy outcomes and sensitivity analyses are shown in Table S2 and Figures S1 and S2 (see Supporting Information).

Median absolute PASI score through week 244 is shown in Figure 5a, and median percentage change from baseline PASI score through week 244 in Figure 5b; approximately 75% or more of patients who achieved PASI 75 response at each measurement also achieved PASI 90 response (Figure 5c, d). The proportions (95% CI) of TIL 100 and TIL 200 responders achieving PGA 0/1 were 82.7% (78.1–86.6) and 84.1% (78.7–88.6), respectively, at week 28 and 68.5% (63.0–73.7) and 74.2% (67.8–79.9), respectively, at week 244 (Figure 6; efficacy outcomes and sensitivity analyses are shown in Table S2 and Figure S3; see Supporting Information).

Among ETN partial responders or nonresponders switched to TIL 200, the proportions (95% CI) achieving PASI 75/90/100 responses at week 244 were 81.3% (72.6–88.2)/49.5%

(39.7–59.4)/21.5% (14.1–30.5) (Figure 3c); PASI scores < 5/< 3/< 1 were achieved by 14.9% (9.1–22.5)/0/0 of patients at week 28 and 85.0% (76.9–91.2)/66.4% (56.6–75.2)/36.4% (27.4–46.3) at week 244 (Figure 4c). Efficacy outcomes and sensitivity analyses are shown in Table S2 and Figures S1 and S2. Median absolute PASI score and percentage change from baseline PASI score are shown in Figure 5a, b); at each measurement after week 52, the majority of patients who achieved PASI 75 response also achieved PASI 90 response (Figure 5e). The proportion (95% CI) of ETN partial responders and nonresponders achieving PGA 0/1 was 12.4% (7.1–19.6) at week 28 and 57.0% (47.1–66.5) at week 244 (Figure 6; efficacy outcomes and sensitivity analyses are shown in Table S2 and Figure S3).

Safety outcomes

Exposure-adjusted incidence rates of treatment-emergent adverse events

Throughout base study parts 1–3 and extension studies (total exposure to TIL 100 and TIL 200 of 2688.4 and 2753.5 PYs, respectively), the EAIRs of patients with TEAEs per 100 PYs were 27.2 for TIL 100 and 28.1 for TIL 200 (Table 1); pooled data for all base study treatments are shown in Table S3 (see Supporting Information). The most frequent TEAE was nasopharyngitis, at 10.5 per 100 PYs of TIL 100 and 10.7 per 100 PYs of TIL 200 treatment; Table 2 shows TEAEs reported in $\geq 5\%$ of any analysis group. The EAIRs of serious AEs were 6.3 and 6.0 per 100 PYs of exposure to TIL 100 and TIL 200, respectively; the majority were not considered drug-related (Table 1). Forty-eight patients receiving TIL 100 (1.8 per 100 PYs) and 38 (1.4 per 100 PYs) receiving TIL 200 discontinued treatment due to AEs (Table 1).

In addition to the nine deaths previously reported,^{9,10} five patients died between week 148 and week 256. The TEAEs resulting in death during this period were chronic cardiac failure in a patient receiving TIL 100; metastatic carcinoma of the bladder and intracranial haemorrhage in a patient receiving TIL 100; acute myocardial infarction in a patient receiving TIL 200; and two completed suicides, one each in patients receiving TIL 100 and TIL 200 (details in Table S4; see Supporting Information). One additional suicide in a patient treated with TIL 100 was recorded after week 256. All patients who completed suicide had a history of psychiatric comorbidities and/or were receiving concomitant psychiatric medication (Table S4). The total EAIR of completed suicide for the pooled base and extension periods was 0.04 per 100 PYs of TIL treatment.

Treatment-emergent adverse events of special interest

The EAIRs of TEAE-SI were generally comparable between patients treated with TIL 100 and TIL 200 (Table 3). Frequency of severe infections was 1.2 per 100 PYs of TIL 100 and 1.3 per 100 PYs of TIL 200; the most common were diverticulitis, pneumonia, cellulitis and appendicitis (Table S5;

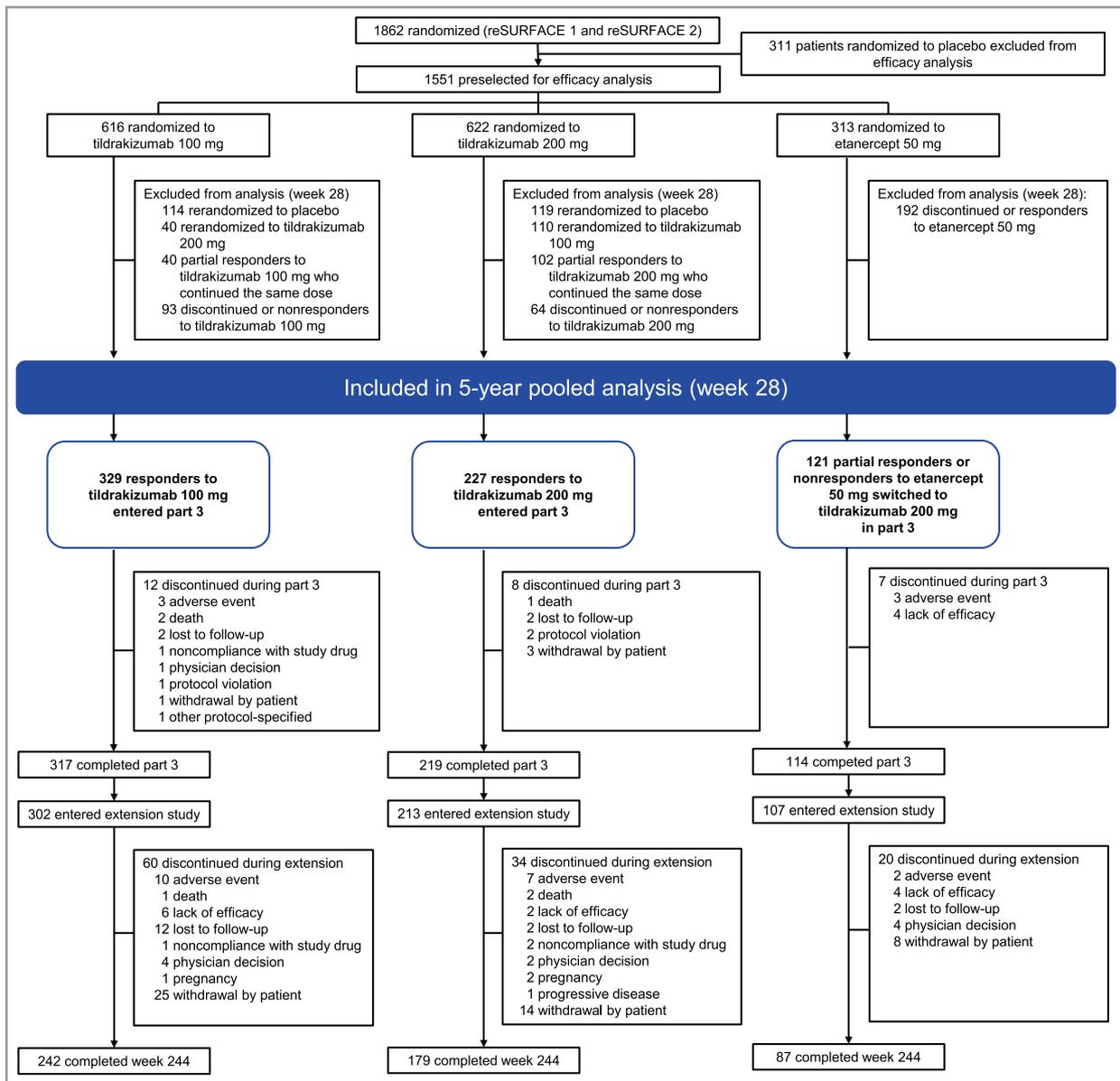


Figure 2 Patient disposition through week 244.

see Supporting Information). Malignancies other than NMSC, most frequently rectal adenocarcinoma and malignant melanoma in situ (Table S6; see Supporting Information), occurred in 20 patients receiving TIL 100 (0.7 per 100 PYs) and 17 (0.6 per 100 PYs) receiving TIL 200. Twelve patients receiving TIL 100 (0.4 per 100 PYs) and 11 receiving TIL 200 (0.4 per 100 PYs) developed NMSC, most often basal cell carcinoma (Table S6). Confirmed extended MACE, most frequently acute myocardial infarction and coronary artery disease (Table S7; see Supporting Information), occurred in 14 patients receiving TIL 100 (0.5 per 100 PYs) and 20 receiving TIL 200 (0.7 per 100 PYs). Frequencies of severe infections, malignancies and MACE did not increase appreciably over time (Tables S8 and S9; see Supporting Information).

Candida infections were uncommon; skin or nail candidiasis occurred in 0.19 and 0.29 and mucocutaneous candidiasis in

0.33 and 0.33 patients per 100 PYs of exposure to TIL 100 and TIL 200, respectively (Table S10; see Supporting Information). *Aspergillus* infection occurred in one patient receiving TIL 100. No *Candida* or *Aspergillus* infection was considered severe. One case of suspected new-onset Crohn disease in a patient receiving TIL 100 (0.04 events per 100 PYs) was previously reported.¹⁰ The patient had a prior history of diverticulitis and no previous biologic treatment for psoriasis; the event was considered mild and did not lead to treatment discontinuation.

Discussion

These analyses present final results from 5 years of continuous TIL treatment of week 28 responders – the longest follow-up investigation to date of an anti-IL-23p19 antibody, with > 5400 PYs of total TIL exposure. Over 80% of patients entering

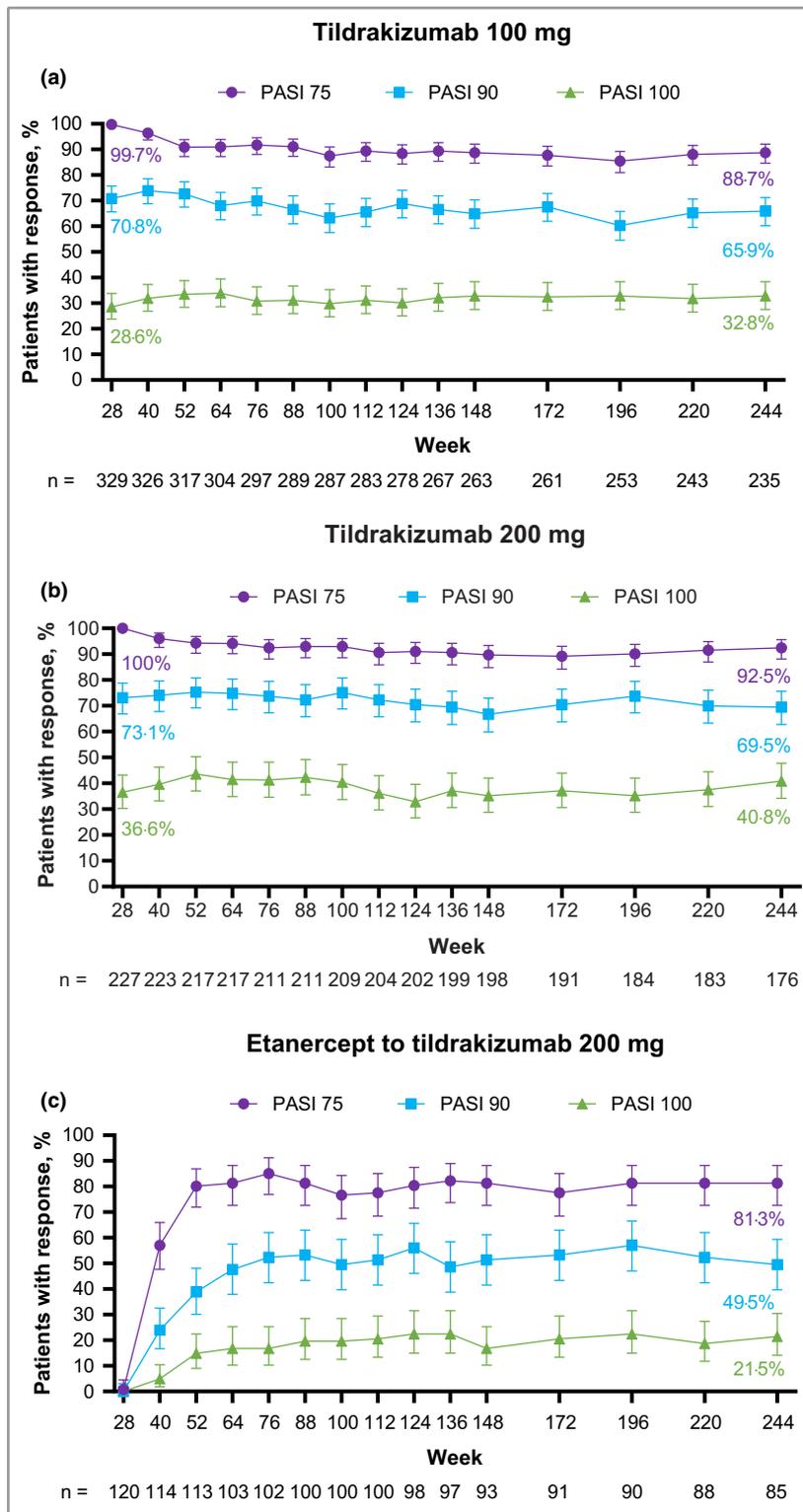


Figure 3 Proportions of TIL 100 responders (a), TIL 200 responders (b) and etanercept partial responders and nonresponders (c) achieving PASI 75, PASI 90 and PASI 100 responses from week 28 through week 244. Missing data were handled with multiple imputation. Numbers of patients with data at each timepoint are shown below each graph. Error bars show the 95% confidence interval. PASI 50/75/90/100 response, 50%/75%/90%/100% improvement from baseline Psoriasis Area and Severity Index score; TIL 100/200, tildrakizumab 100/200 mg.

the extensions completed treatment through week 244. Among TIL responders, a large proportion maintained efficacy through week 244. More than 75% of patients continuously

treated with TIL achieved PASI < 3 and > 65% achieved PGA 0/1 at week 244, consistent with evolving guidance to use absolute treatment goals in clinical practice.^{1,2} Partial or

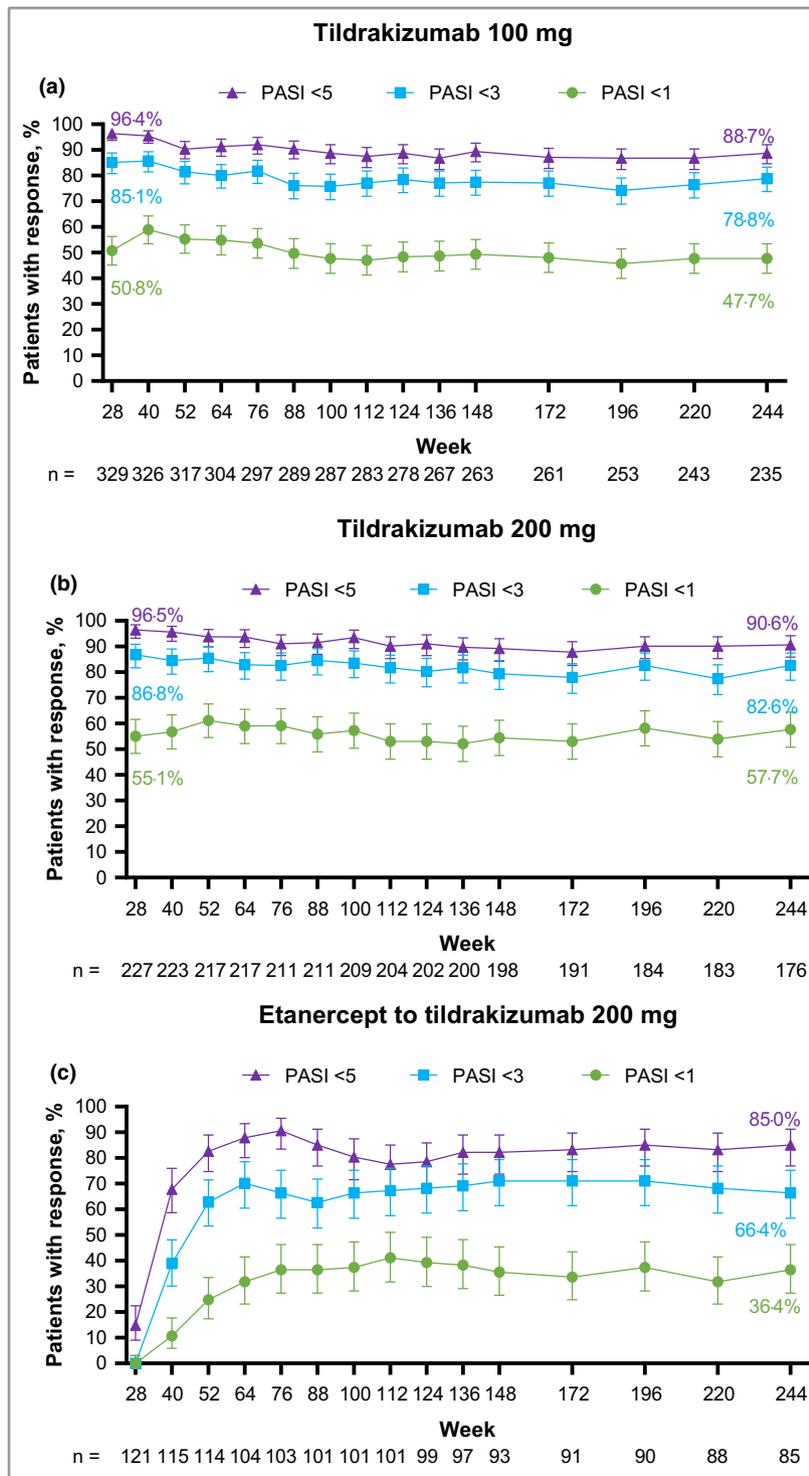


Figure 4 Proportions of TIL 100 responders (a), TIL 200 responders (b) and etanercept partial responders and nonresponders (c) achieving PASI scores < 5, < 3 and < 1 from week 28 through week 244. Missing data were handled with multiple imputation. Numbers of patients with data at each timepoint are shown below each graph. Error bars show the 95% confidence interval. PASI, Psoriasis Area and Severity Index; PASI 50/75/90/100 response, 50%/75%/90%/100% improvement from baseline PASI score; TIL 100/200, tildrakizumab 100/200 mg.

nonresponders switched from ETN at week 28 had week 244 PASI < 3 and PGA 0/1 rates of 66% and 57%, respectively.

Patients underwent long-term treatment with two different TIL doses, allowing investigation of dose effects on safety;

there were no apparent dose-dependent safety signals and no new or unexpected AEs. Safety data were generally comparable with the 3-year analysis and results from treatment for up to 4 years with guselkumab and 2 years with risankizumab,

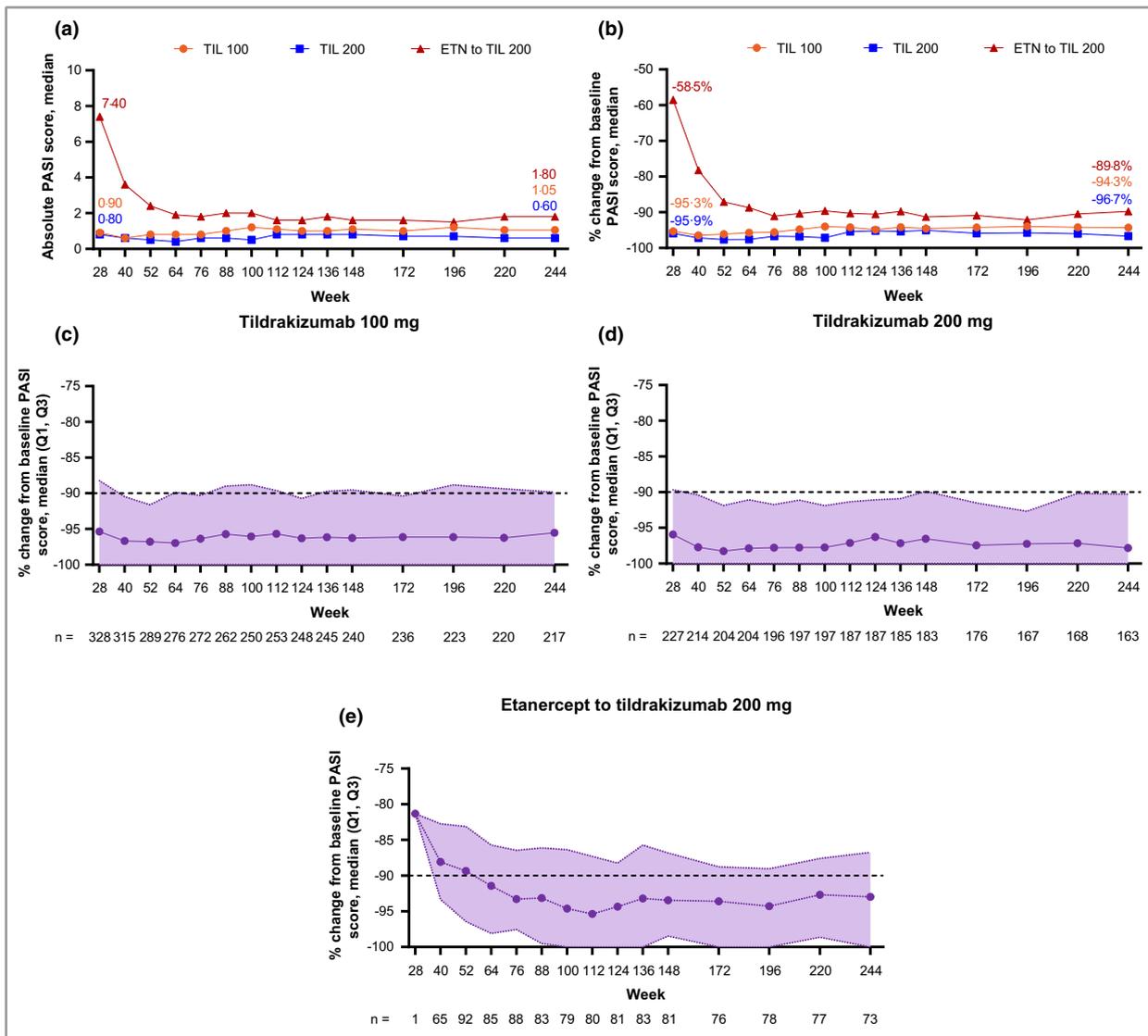


Figure 5 Median absolute PASI score (a) and median percentage change from baseline PASI score (b) in all patients; percentage change from baseline PASI in patients who achieved PASI 75 response at each measurement among TIL 100 responders (c), TIL 200 responders (d) and ETN partial responders and nonresponders switched to TIL 200 (e). Missing data were handled with multiple imputation. In panels C–E, the purple dots and line represent the median, and the purple shading represents the interquartile range of percentage change from baseline PASI score in patients who achieved PASI 75 response at each measurement. The dashed line represents the PASI 90 response. The numbers of patients achieving PASI 75 response at each timepoint are shown below the graphs. ETN, etanercept; ETN to TIL 200, ETN partial responders and nonresponders switched to TIL 200 mg; PASI, Psoriasis Area and Severity Index; PASI 75/90 response, 75%/90% improvement from baseline PASI score; Q, quartile; TIL 100/200, responders who continuously received tildrakizumab 100/200 mg into part 3.

supporting overall safety of IL-23p19 inhibitors.^{11–13} TIL safety findings in patients with elevated risk for AE-SI, such as patients with metabolic syndrome^{14,15} and elderly patients,¹⁶ do not differ significantly from data presented here; long-term analyses are ongoing. Safety concerns with anti-IL-17 agents include candidiasis, inflammatory bowel disease and suicidal ideation (brodalumab only).¹⁷ In reSURFACE 1 and reSURFACE 2, there were no severe candidiasis cases and only one suspected case of new-onset Crohn disease (a condition more prevalent in patients with psoriasis vs. the general population¹⁸) over 5 years of treatment. The EAIR of completed

suicide was consistent with overall suicide rates in patients with psoriasis from a recent meta-analysis,¹⁹ and all patients who completed suicide had prior history of treatment for psychiatric comorbidities and/or drug addiction (Table S4).

Long-term incidence of AE-SIs was generally comparable with results from the psoriasis reference population captured in the Psoriasis Longitudinal Assessment and Registry (PSOLAR). The cumulative incidence for TIL 100/TIL 200 vs. PSOLAR was 0.5/0.7 vs. 0.22 per 100 PYs for adjudicated MACE, 0.7/0.6 vs. 0.55 per 100 PYs for malignancy excluding NMSC and 1.2/1.3 vs. 1.45 per 100 PYs for severe or

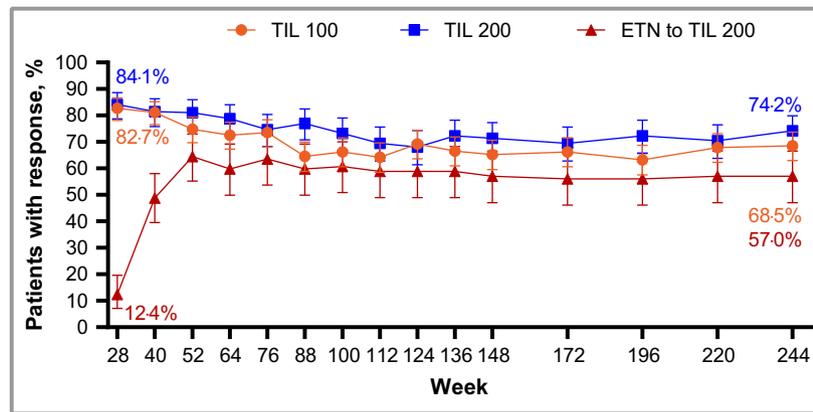


Figure 6 Proportion of patients with Physician's Global Assessment 'clear' (0) or 'minimal' (1) with ≥ 2 -grade reduction from baseline from week 28 through week 244. Missing data were handled with multiple imputation. Error bars show the 95% confidence interval. ETN, etanercept; ETN to TIL 200, ETN partial responders and nonresponders switched to TIL 200 mg; TIL 100/200, responders who continuously received tildrakizumab 100/200 mg into part 3.

Table 1 Summary of adverse events (AEs) through weeks 256/244

	TIL 100, N = 872 ^a	TIL 200, N = 928 ^a
Total follow-up, PYs	2688.4	2753.5
Any TEAE	732	775
	27.2 (25.3–29.3)	28.1 (26.2–30.2)
Drug-related TEAEs	249	271
	9.3 (8.1–10.5)	9.8 (8.7–11.1)
Any SAE	170	165
	6.3 (5.4–7.3)	6.0 (5.1–7.0)
Drug-related SAEs	21	15
	0.8 (0.5–1.2)	0.5 (0.3–0.9)
Deaths	9	5
	0.3 (0.2–0.6)	0.2 (0.1–0.4)
TEAEs leading to discontinuation	48	38
	1.8 (1.3–2.4)	1.4 (1.0–1.9)
Drug-related AEs leading to discontinuation	18	9
	0.7 (0.4–1.1)	0.3 (0.1–0.6)
SAEs leading to discontinuation	29	23
	1.1 (0.7–1.5)	0.8 (0.5–1.3)
Drug-related SAEs leading to discontinuation	9	5
	0.3 (0.2–0.6)	0.2 (0.1–0.4)

SAE, serious AE; TEAE, treatment-emergent AE; TIL 100/200, tildrakizumab 100/200 mg. ^aData shown as n followed by patients with events per 100 patient-years (PYs) of exposure (95% confidence interval).

serious infections.^{20–22} The PSOLAR reports included MACE in biologic-treated patients only and did not include extended MACE and nonserious infections that required intravenous antibiotics; furthermore, as observational studies they may have been subject to selection bias and less stringent follow-up.^{20–22}

The main study limitation is the use of a responder population with no active-controlled arm from week 28 forward, as per the study design. The proportions of patients achieving

PASI 75 response at week 28 with NRI were previously reported;⁴ the responder population is clinically relevant for long-term follow-up because biologic-treated patients who do not achieve primary PASI 75 or other response thresholds generally change treatment, whereas secondary treatment failure in primary responders remains a concern.²³ Because TIL was the first anti-IL-23p19 agent to enter phase III trials, efficacy and safety in TIL responders were emphasized during the extension phases. Therefore, the study protocol did not continue the ETN responder cohort as an active-controlled arm during the extensions. These restrictions resulted in relatively small study populations. Missing data and loss to follow-up are inevitable in long-term studies, and multiple imputation was employed to minimize resulting positive or negative bias. There is no consensus on reporting this type of long-term data; resulting heterogeneity among studies precludes direct efficacy comparison, which can be addressed by meta-analysis.^{24–26} However, multiple imputation is considered more appropriate compared with NRI for reducing uncertainty when reporting long-term data and may prevent underestimation of response.^{27,28}

Patient-reported outcomes, antidrug antibody data and serum TIL levels were not recorded in the extensions, and only the first year of treatment was fully blinded. There was no safety control population, as short-term safety data for placebo (12 weeks) and ETN (28 weeks) cannot be extrapolated for comparison with data from up to 5 years of TIL exposure; this highlights the importance of pharmacovigilance registries in determining long-term safety. However, the different doses of TIL allow some comparison of safety results, and no dose-related differences in frequency of severe infections or malignancies were noted.

In summary, this first report of 5-year data for an anti-IL-23p19 agent shows sustained disease control in a large proportion of TIL responders and ETN partial and nonresponders switched to TIL at week 28, with a reassuring safety profile over 5 years.

Table 2 Numbers and exposure-adjusted incidence rates of treatment-emergent adverse events occurring in $\geq 5\%$ of patients in one or more treatment arms through weeks 256/244

	TIL 100, N = 872 ^a	TIL 200, N = 928 ^a
Total follow-up, PYs	2688.4	2753.5
Nasopharyngitis	281	296
	10.5 (9.3–11.7)	10.7 (9.6–12.0)
Upper respiratory tract infection	102	127
	3.8 (3.1–4.6)	4.6 (3.8–5.5)
Hypertension	81	92
	3.0 (2.4–3.7)	3.3 (2.7–4.1)
Influenza	64	86
	2.4 (1.8–3.0)	3.1 (2.5–3.9)
Arthralgia	81	83
	3.0 (2.4–3.7)	3.0 (2.4–3.7)
Back pain	65	74
	2.4 (1.9–3.1)	2.7 (2.1–3.4)
Headache	61	71
	2.3 (1.7–2.9)	2.6 (2.0–3.3)
Cough	57	67
	2.1 (1.6–2.7)	2.4 (1.9–3.1)
Diarrhoea	60	57
	2.2 (1.7–2.9)	2.1 (1.6–2.7)
Bronchitis	48	61
	1.8 (1.3–2.4)	2.2 (1.7–2.8)
Sinusitis	58	45
	2.2 (1.6–2.8)	1.6 (1.2–2.2)
Urinary tract infection	56	48
	2.1 (1.6–2.7)	1.7 (1.3–2.3)
Gastroenteritis	47	52
	1.7 (1.3–2.3)	1.9 (1.4–2.5)
Oropharyngeal pain	33	41
	1.2 (0.8–1.7)	1.5 (1.1–2.0)
Pruritus	30	32
	1.1 (0.8–1.6)	1.2 (0.8–1.6)
Nausea	27	33
	1.0 (0.7–1.5)	1.2 (0.8–1.7)
Psoriasis	28	30
	1.0 (0.7–1.5)	1.1 (0.7–1.6)
Injection-site erythema	9	12
	0.3 (0.2–0.6)	0.4 (0.2–0.8)
Injection-site reaction	5	5
	0.2 (0.1–0.4)	0.2 (0.1–0.4)

TIL 100/200, tildrakizumab 100/200 mg. ^aData shown as n followed by patients with events per 100 patient-years (PYs) of exposure (95% confidence interval). Includes events that occurred in $> 5\%$ of patients treated with placebo or etanercept during the base studies.

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Table 3 Treatment-emergent adverse events of special interest through weeks 256/244

	TIL 100, N = 872 ^a	TIL 200, N = 928a
Total follow-up, PYs	2688.4	2753.5
Severe infection	33	37
	1.2 (0.8–1.7)	1.3 (0.9–1.9)
Malignancy excluding NMSC	20	17
	0.7 (0.5–1.1)	0.6 (0.4–1.0)
NMSC	12	11
	0.4 (0.2–0.8)	0.4 (0.2–0.7)
Melanoma	2	3
	0.1 (0–0.3)	0.1 (0–0.3)
Confirmed extended MACE	14	20
	0.5 (0.3–0.9)	0.7 (0.4–1.1)
Injection-site reaction ^b	33	41
	1.2 (0.8–1.7)	1.5 (1.1–2.0)
Drug-related hypersensitivity reaction	7	4
	0.3 (0.1–0.5)	0.1 (0–0.4)

MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; TIL 100/200, tildrakizumab 100/200 mg. ^aData shown as n followed by patients with events per 100 patient-years (PYs) of exposure (95% confidence interval). ^bNot recorded during the extension studies.

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Appendix 2 Conflicts of interest

D.T. has received honoraria as an advisor, speaker and/or investigator from AbbVie, Ammirall, Amgen, Biogen-Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly, Galapagos, Janssen-Cilag, LEO Pharma, Novartis, Pfizer, Regeneron, Roche-Possay, Samsung, Sandoz, Sanofi and UCB. S.P. has been a consultant and/or speaker for AbbVie, Ammirall, Celgene, Eli Lilly, Janssen, LEO Pharma, Merck Sharp & Dohme, Novartis, Pfizer, Sandoz and UCB. R.B.W. has received research grants from AbbVie, Ammirall, Amgen, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer and UCB; and has received consulting fees from AbbVie, Ammirall, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi, Xenoport and UCB. A.K.G. has been an investigator for Sun Pharmaceutical Industries, Inc. W.C. reports nothing to disclose. Z.D. has received grants as an investigator from Merck and Sun Pharmaceutical Industries, Inc. P.F. is a consultant, investigator, speaker and/or advisor for and/or received travel grants from 3M/iNova/Valeant, Abbott/AbbVie, Amgen, Arcutis, Aslan, Biogen-Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celtaxsys, Cutanea, Dermira, Eli Lilly, Galderma, GSK/Stiefel, Hexima, Janssen, LEO Pharma/Peplin, Novartis, Regeneron, Reistone, Sanofi Genzyme, Schering-Plough/MSD, Sun Pharmaceutical Industries, Inc., UCB and Wyeth/Pfizer. A.I. has received honoraria as a member of an advisory board for AbbVie, Celgene K.K., Eli Lilly Japan K.K., Janssen Pharmaceutical K.K., Maruho Co. Ltd, Novartis Pharma K.K. and Sun Pharma Japan Ltd. R.G.L. 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, Janssen, LEO Pharma, Merck, Novartis, Pfizer and Sun Pharmaceutical Industries, Inc. A.A. has received honoraria and/or research grants from AbbVie, Celgene, Eisai, Eli Lilly Japan, Janssen, Kyowa Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe Pharma, Sun Pharma, Taiho Pharma, Torii Pharmaceutical and UCB. M.Y. has been a consultant for AbbVie; a consultant and speaker for Amgen, Eli Lilly, Janssen, Novartis, Regeneron, Sanofi and Sun Pharmaceutical Industries, Inc.; received clinical research funding from AbbVie, Amgen (Celgene), Bristol-Myers Squibb, ChemoCentryx, Eli Lilly, Galderma, Janssen, LEO Pharma, Menlo Therapeutics, Sun Pharmaceutical Industries, Inc. and UCB. M.F. and I.P.C. are employees of Ammirall SA. A.M.M. is an employee of Sun Pharmaceutical

Industries, Inc.; and has individual shares in Johnson and Johnson, and as part of a retirement account/mutual funds. S.J.R. is an employee of Sun Pharmaceutical Industries, Inc. K.R. has served as an advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Affibody, Ammirall, Amgen, Biogen-Idec, Boehringer Ingelheim, Celgene, Covagen, Eli Lilly, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Medac, Merck Sharp & Dohme, Miltenyi, Novartis, Ocean Pharma, Pfizer, Samsung Bioepis, Sanofi, Takeda, UCB, Valeant and Xenoport.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Methods S1 Full inclusion and exclusion criteria; Outcomes; Statistical analysis.

Table S1 Baseline demographics and disease characteristics.

Table S2 Efficacy outcomes at weeks 28, 52 and 244 using multiple imputation, observed cases and nonresponder imputation methodology.

Table S3 Pooled exposure-adjusted rates of adverse events and prespecified adverse events of special interest in the reSURFACE 1 and reSURFACE 2 base studies.

Table S4 Details of deaths after week 148 through week 256.

Table S5 Details of severe infections.

Table S6 Details of malignancies.

Table S7 Details of confirmed extended major adverse cardiovascular events (MACE).

Table S8 Year-by-year exposure-adjusted rates of adverse events and prespecified adverse events of special interest following exposure to tildrakizumab 100 mg.

Table S9 Year-by-year exposure-adjusted rates of adverse events and prespecified adverse events of special interest following exposure to tildrakizumab 200 mg.

Table S10 Details of *Candida* infections.

Figure S1 Sensitivity analyses for Psoriasis Area and Severity Index (PASI) 75, PASI 90 and PASI 100 response rates.

Figure S2 Sensitivity analyses for Psoriasis Area and Severity Index (PASI) score < 5, PASI score < 3 and PASI score < 1.

Figure S3 Sensitivity analyses for Physician Global Assessment 'clear' or 'minimal' with ≥ 2 grade reduction from baseline.