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Safety of Tildrakizumab for Moderate-to-Severe Plaque Psoriasis: Pooled Analysis of Three Randomised Controlled Trials

Running Head: Pooled analysis of tildrakizumab for psoriasis

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Summary

Background: Short-term IL-23p19 inhibition by tildrakizumab improves plaque psoriasis and appears well-tolerated.

Objectives: Safety/tolerability were assessed for up to 64 weeks of tildrakizumab therapy using pooled data from 3 randomised controlled trials for moderate-to-severe psoriasis.

Methods: Data pools for the placebo-controlled (up to 16 weeks) and full-trial periods (up to 64 weeks) were analysed (N=2081).

Results: In the placebo-controlled period, frequencies of treatment-emergent adverse events (TEAEs; range=47.9%-54.0%), serious TEAEs (range=1.4%-2.3%), discontinuations due to AEs (range=0.6%-1.9%), major adverse cardiovascular events (MACE; range=0.0%-0.1%), and severe infections (range=0.0%-0.3%) were comparable among tildrakizumab 100 mg, tildrakizumab 200 mg, placebo, and etanercept. In the full-trial period, exposure-adjusted rates (patients/100-patient-years) for TEAEs, serious TEAEs, and discontinuations due to AEs with tildrakizumab 100 mg and 200 mg were lower than or comparable to placebo, and lower than etanercept. Exposure-adjusted rates of MACE (range=0.0-0.5) and severe infections (range=0.9-2.0) were comparable among groups. No TEAEs of inflammatory bowel disease or suicide were reported. *Candida* skin infections were infrequent at frequencies of 0.1%, 0.3%, 0.0%, and 0.0% for the tildrakizumab 100 mg, tildrakizumab 200 mg, placebo, and ETN groups, respectively, in the placebo-controlled period, and exposure-adjusted rates of 0.2, 0.7, 0.0, and 0.0, respectively, in the full-trial period. Oral candidiasis was also infrequent.

Conclusions: Up to 64 weeks of tildrakizumab was well-tolerated, with low rates of serious TEAEs, discontinuations due to AEs, and AEs of clinical interest.

Keywords

tildrakizumab; chronic plaque psoriasis; IL-23; etanercept; adverse events; infection; MACE; malignancy

- What is already known about this topic?
    - Tildrakizumab improves moderate-to-severe plaque psoriasis and appears to be well-tolerated with short-term use.
- What does this study add?

- Pooled analysis of 3 randomised controlled trials consolidates the safety and tolerability in a larger group of patients for up to 64 weeks of tildrakizumab treatment.

Introduction

Targeting of cytokines involved in psoriasis pathogenesis has been a focus of therapy. Initially, TNF-α blockers became a successful treatment option, although these medications can be associated with infections and other side effects.[1-3] The importance of the IL-23/T helper(Th)17 pathway in psoriasis has fueled the development of IL-23 inhibitors.[4-9] IL-23 is elevated in psoriasis lesions[10] and downregulation of IL-23 mRNA expression in lesions is associated with successful clinical responses to treatment.[11,12] Furthermore, IL-23 drives activation of human Th17 cells, which subsequently promote chronic inflammation and produce cytokines with downstream effects characteristic of psoriasis, such as keratinocyte activation and hyperproliferation.[13,14]

Tildrakizumab is a high-affinity, humanised, IgG1κ monoclonal antibody directed against the p19 subunit of IL-23. One phase 2 and two large phase 3 randomised controlled trials (RCTs) of tildrakizumab have been conducted in patients with moderate-to-severe chronic plaque psoriasis.[6,9] Tildrakizumab appeared well-tolerated in all three trials, with low frequencies of serious adverse events (AEs) and discontinuations due to AEs.

Dose-associated risk of *Candida albicans* infections and inflammatory bowel disease have been reported with IL-17 blockers,[15-17] but not with the IL-23 inhibitor guselkumab or tildrakizumab.[4,6] This suggests that IL-23-independent IL-17A production may be preserved during anti-IL-23 therapy and thus protect against development of these specific side effects. The present analysis further assessed the safety and tolerability of tildrakizumab for up to 64 weeks of use in a large group of patients using pooled data from the three previously reported RCTs.[6,9] In addition to candidiasis and inflammatory bowel disease, other important safety outcomes such as major adverse cardiovascular events (MACE) and malignancy, which are possibly increased in patients with psoriasis versus the general population, were assessed.[18-21]

Patients and Methods

Trial designs

Pooled data from 3 multicentre, international RCTs, P05495 (Phase 2; NCT01225731), reSURFACE 1 (Phase 3; NCT01722331), and reSURFACE 2 (Phase 3; NCT01729754) were included in this analysis. Trial details and primary results have been previously described.[6,9] Patients in all 3 trials had moderate-to-severe plaque psoriasis defined as ≥10% body surface area, ≥3 Physician's Global Assessment, and Psoriasis Area and Severity Index (PASI) ≥12. Exclusion criteria related to safety outcomes are listed in the **Supplementary Methods**.

In the P05495 trial, patients in Part 1 (weeks 1–16) received subcutaneous tildrakizumab 5 mg, 25 mg, 100 mg, 200 mg, or placebo at weeks 0 and 4 (**Supplemental Figure**). In Part 2 (weeks 16–52), patients were re-randomised to various tildrakizumab doses based on responder status. In the reSURFACE 1 and 2 trials, patients in Part 1 (weeks 1–12) received subcutaneous tildrakizumab 100 mg, 200 mg, or placebo at weeks 0 and 4 (**Supplemental Figure**). In reSURFACE 2, etanercept (ETN) 50 mg administered twice-weekly during Part 1 was an additional treatment arm. Patients receiving placebo in Part 1 of reSURFACE 1 and 2 were re-randomised to tildrakizumab 100 mg or 200 mg and received tildrakizumab at weeks 12, 16, 28, and every subsequent 12 weeks. Patients receiving tildrakizumab in Part 1 continued their originally randomised treatment and received a dose of study medication at week 16, and the patients in reSURFACE 2 who received ETN in Part 1 continued their ETN treatment, but administered once weekly. Patients in Part 3 (weeks 28–64 in reSURFACE 1 and weeks 28–52 in reSURFACE 2) were re-randomised to tildrakizumab 100 mg or 200 mg (or placebo in reSURFACE 1) based on responder (PASI ≥75) and partial responder (PASI ≥50 and PASI <75) status and received treatment every 12 weeks. Responders in the ETN arm in reSURFACE 2 were discontinued at week 28; partial (PASI ≥50 and PASI <75) and non-responders (PASI <50) were assigned to tildrakizumab 200 mg. Each trial had a 20-week follow-up period after treatment completion/discontinuation.

Safety assessments

A serious AE was any AE that resulted in death, was life-threatening, required hospitalisation or prolongation of existing inpatient hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, was a cancer, was associated with an

overdose, or was considered another important medical event.[22] Confirmed major cardiovascular adverse events (MACE) included non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths that were confirmed as “cardiovascular” or “sudden”. All deaths and serious cardiovascular events were adjudicated by an external clinical adjudication committee. Severe infections were those that met the regulatory definition of a serious adverse event or required IV antibiotics. Pre-specified events of clinical interest for the pooled analyses included severe infections, malignancies, non-melanoma skin cancer, melanoma skin cancer, MACE, injection site reactions, and drug-related hypersensitivity reactions.

Data analysis

Data pools of treatment-emergent adverse events (TEAEs) for the placebo-controlled period and full-trial period (52 weeks for P05495 and reSURFACE 2; 64 weeks for reSURFACE 1) were analysed. In the full-trial period pool, patients who received multiple treatments were counted in each treatment received after adjustment for exposure. For patients who dropped out during the trial and entered the follow-up period, AEs occurring during the follow-up were included and were attributed to the last treatment received. Frequencies (patients with events/number of patients exposed) were calculated for safety outcomes in the placebo-controlled period. Exposure-adjusted rates (patients with events/100 patient-years) were also calculated for specific AEs in the placebo-controlled period and for safety outcomes in the full-trial period. Differences and 95% confidence intervals (CI) in frequencies between tildrakizumab treatments and placebo for the pre-specified events of clinical interest in the placebo-controlled period were calculated based on the Miettinen & Nurminen method with no strata information included.

Results

Patients and exposure

A total of 2081 patients were treated with tildrakizumab 100 mg (n=705), tildrakizumab 200 mg (n=708), placebo (n=355), or ETN (n=313) and were included in the pooled analysis. Of the 2081 treated patients, 2000 patients (96.1%) completed Part 1 and entered into Part 2 of the studies. Baseline demographics and disease characteristics of randomised patients were similar among the treatment groups (**Table 1**). The mean (range) duration of exposure during the full-trial period was 48 (4–76) weeks for tildrakizumab 100 mg, 47 (4–76) weeks for tildrakizumab 200 mg, and 19 (4–40) weeks for placebo. The mean (range) duration of exposure with ETN was 11.4 (0.5–12.0) weeks for patients who received treatment twice-weekly during Part 1 and

15.4 (0.5–17.0) weeks for patients who received treatment once-weekly during Part 2. The total exposure was 998 patient-years for tildrakizumab 100 mg, 929 patient-years for tildrakizumab 200 mg, 219 patient-years for placebo, and 153 patient-years for ETN.

Overall safety

In the placebo-controlled period, frequencies (patients/number of patients exposed) of TEAEs for tildrakizumab 100 mg, tildrakizumab 200 mg, placebo, and ETN were 48.2%, 47.9%, 53.8%, and 54.0%, respectively (**Table 2**). The most common TEAE in all treatment groups was nasopharyngitis (**Figure 1**). AEs related to the injection site were numerically higher in the ETN group compared with the tildrakizumab groups or placebo (**Figure 1**). Exposure-adjusted rates during the placebo-controlled period were consistent with the frequency data, confirming the higher rates for injection site reactions with ETN compared with tildrakizumab treatment or placebo (**Supplemental Table 1**).

In the full-trial period, exposure-adjusted rates (patients/100 patient-years) for TEAEs for tildrakizumab 100 mg, tildrakizumab 200 mg, placebo, and ETN were 77.0, 79.3, 153.5, and 148.6, respectively (**Table 2**). The highest exposure-adjusted rates for treatment-related AEs, serious TEAEs, and discontinuations due to AEs were observed in the ETN group, whereas the rates with tildrakizumab treatment were lower than or comparable to placebo (**Table 2**). Similar to the placebo-controlled period, in the full-trial period the most common TEAE in all treatment groups was nasopharyngitis, and AEs related to injection site were highest in the ETN group.

Seven deaths, all unrelated to treatment per investigator and study Sponsor assessment, occurred during or after the trials. All deaths and serious cardiovascular events were adjudicated by an external clinical adjudication committee. Additional details of these cases can be found in **Supplemental Table 2**.

Prespecified AEs of clinical interest

Frequencies of confirmed MACE, malignancies, non-melanoma skin cancer, drug-related hypersensitivity events, and severe infections in the placebo-controlled period were low, ranging from 0.0–0.3% among the groups (**Table 3**). There were no events of melanoma skin cancer in any treatment group in the placebo-controlled period. The frequency of injection site reactions was higher in the ETN group (17.9%) compared with tildrakizumab 100 mg (3.4%), tildrakizumab 200 mg (4.0%), and placebo (2.3%). The two drug-related hypersensitivity reactions in patients with tildrakizumab treatment were assessed as due to concomitant medications. There were no statistically significant differences between tildrakizumab treatment

and placebo in the frequencies of any of the prespecified AEs (**Table 3**).

Exposure-adjusted rates of confirmed MACE in the full-trial period ranged from 0.0–0.5, exposure-adjusted rates of malignancies, non-melanoma skin cancer, and severe infections were low, ranging from 0.9–2.6 among the groups (**Table 3**). Two patients (both tildrakizumab 100 mg) developed melanoma skin cancer in the full-trial period. Both cases were determined to be melanoma *in situ*. With the exception of malignant neoplastic processes involving the skin, the only malignancy reported more than once in patients receiving tildrakizumab was pancreatic cancer (2 cases, both tildrakizumab 200 mg). The exposure-adjusted rate of injection site reactions was higher in the ETN group (40.4) compared with tildrakizumab 100 mg (3.5), tildrakizumab 200 mg (4.6), and placebo (5.0).

Infections

In the placebo-controlled period, frequencies of infections were comparable for tildrakizumab 100 mg and 200 mg (22.7% and 21.9%, respectively) and placebo (22.5%); all were comparable with ETN (23.6%). In the full-trial period, exposure-adjusted rates for infections with tildrakizumab 100 mg and 200 mg (48.9 and 52.6, respectively) were lower than with placebo and ETN (79.5 and 86.0, respectively). In all, 33 severe infections were identified (**Table 4**).

One patient, a 58-year old Asian male (birthplace unknown), had bone tuberculosis, which led to treatment discontinuation (tildrakizumab 200 mg). The patient reported occasional travel to Asia for business, but no other risk factors were noted. The original single-step Mantoux test in this patient was negative. After treatment, the TB resolved with no further sequelae. One sepsis event (tildrakizumab 200 mg) occurred 7 months after ending tildrakizumab treatment. *Candida* skin infections were infrequent in all treatment groups in the placebo-controlled period at frequencies of 0.1%, 0.3%, 0.0%, and 0.0% for the tildrakizumab 100 mg, tildrakizumab 200 mg, placebo, and ETN groups, respectively; exposure-adjusted rates for *Candida* skin infections in the full-trial period were 0.2, 0.7, 0.0, and 0.0, respectively. Oral candidiasis was also infrequent, occurring at frequencies of 0.1%, 0.3%, 0.0%, and 0.0% for the tildrakizumab 100 mg, tildrakizumab 200 mg, placebo, and ETN groups, respectively, during the placebo-controlled period and exposure-adjusted rates of 0.2, 0.7, 0.0, and 0.0, respectively, during the full-trial period.

Other AEs of interest

No TEAEs of new-onset or exacerbation of pre-existing inflammatory bowel disease or multiple sclerosis were reported during the trials. No suicides were reported. One suicide attempt was reported in a patient who was receiving tildrakizumab 200 mg and who was on antipsychotic therapy for a known history of schizophrenia. The event was considered by the investigator to be unrelated to treatment.

Discussion

This pooled analysis of 3 RCTs demonstrates that up to 64 weeks of tildrakizumab is well-tolerated in a large group of patients with moderate-to-severe psoriasis. Frequencies and exposure-adjusted rates of TEAEs, treatment-related AEs, serious AEs, and discontinuations due to AEs with tildrakizumab treatment were lower than or comparable to placebo.

Frequencies and exposure-adjusted rates of MACE with tildrakizumab treatment were low and comparable to placebo, indicating no increased risk of MACE. Analysis of MACE in the pooled analysis was selected as a prespecified AE of interest because patients with psoriasis are at increased risk for cardiovascular events,[18-20] and initial reports during the development of briakinumab, an IL-12/23 inhibitor, suggested an imbalance of MACE between briakinumab and placebo.[23] The concerns regarding increased MACE contributed to the withdrawal of the briakinumab application from the US Food and Drug Administration.[24] However, a combined analysis of trials of the IL-12/23 inhibitor ustekinumab did not reveal an increased risk of MACE compared with the general population or in patients with psoriasis.[25] Pooled analysis of 10 trials of secukinumab, an IL-17A inhibitor, also did not find an increased risk of MACE.[17] Furthermore, a systematic review and meta-analysis of 38 RCTs found no indication of increased MACE risk versus placebo with the licensed dose of any biologic for the treatment of moderate-to-severe psoriasis, including biologics that inhibit IL-23 or IL-17 (e.g., ustekinumab, secukinumab, and ixekizumab).[26] To date, no pooled analyses investigating the risk of MACE with the IL-23 inhibitor guselkumab have been published.

Patients with psoriasis appear to have an increased risk of malignancies, including non-melanoma skin cancer.[21] In the current pooled analysis, frequencies and exposure-adjusted rates of malignancies, non-melanoma skin cancer, and melanoma skin cancer with tildrakizumab treatment were similar to placebo, indicating no increased risk of these events with tildrakizumab. There were 2 cases of pancreatic cancer in patients treated with tildrakizumab 200 mg.

The risk of infection is always a concern when a treatment inhibits a molecule in the immune system pathway. Infection frequency with tildrakizumab treatment during the placebo-

controlled period was comparable with placebo, and exposure-adjusted rates during the full-trial period were lower with tildrakizumab treatment compared with placebo.

Worsening of inflammatory bowel disease[15] and increased frequency of *Candida* infections[16,17] have been noted during treatment with IL-17 inhibitors. In the current analysis, no new or worsening events of inflammatory bowel disease or suicide were associated with tildrakizumab treatment. The frequency and exposure-adjusted rates of *Candida* infections with tildrakizumab were low and comparable with placebo.

During the short duration of the placebo-controlled period, the frequencies of TEAEs, serious AEs, and discontinuations due to AEs were comparable among the tildrakizumab doses and ETN. The frequency of treatment-related AEs was higher with ETN versus tildrakizumab or placebo, mainly driven by injection site-related AEs. During the full-trial period, the exposure-adjusted rates of TEAEs, treatment-related AEs, serious AEs, and discontinuations due to AEs were all numerically higher with ETN versus the tildrakizumab doses. However, aside from injection site reactions, the rates of prespecified AEs (e.g., MACE, severe infections, malignancies, etc.) were comparable among the tildrakizumab doses and ETN. Injection site reactions were notably higher with ETN.

The current analysis is limited by the short placebo exposure compared with tildrakizumab treatment, per the trial protocols. Furthermore, the number of patients receiving placebo and ETN was approximately half the number of patients receiving each tildrakizumab dose. Longer term follow-up studies are needed to fully determine the safety of tildrakizumab in regard to MACE and malignancies. Nevertheless, up to 64 weeks of tildrakizumab treatment was well-tolerated, with low rates of serious TEAEs, discontinuations due to AEs, and AEs of clinical interest. There was no evidence of increased risk for AEs of interest associated with IL-17 inhibitors within the limits of cross-trial comparison. Analysis of data from long-term extension trials will provide further knowledge regarding the safety and tolerability of tildrakizumab.

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Figure Legends

Figure 1. Treatment-emergent adverse events in ≥2% of patients in at least one treatment group during the placebo-controlled period (all patients as treated). AE, adverse event; ETN, etanercept; TIL, tildrakizumab; URTI, upper respiratory tract infection.

Table 1. Baseline demographics and disease characteristics for the randomised pooled study population

Characteristic	TIL 100 mg (n=705)	TIL 200 mg (n=708)	Placebo (n=357)	ETN 50 mg (n=313)
Men, %	71	73	70	71
Age, mean y (SD)	46 (13)	46 (13)	47 (13)	46 (14)
Race				
White, %	81	80	78	92
Asian, %	13	15	16	3
Weight, median, (interquartile range [Q3-Q1])	86.0 (26.2)	85.8 (26.8)	85.5 (27.9)	85.7 (28.3)
Baseline PASI, median, (interquartile range [Q3-Q1])	17.7 (8.4)	17.6 (9.0)	17.6 (7.4)	18.4 (9.3)
Baseline BSA %, median, (interquartile range [Q3-Q1])	26.0 (24.0)	26.0 (23.0)	26.0 (21.0)	28.0 (23.0)

History of psoriatic arthritis, yes, %	17	17	15	13
Prior exposure to biologics for psoriasis, yes, %	18	18	19	12
Prior phototherapy, yes, %	32	31	31	44
Prior conventional systemic therapy*, yes, %	38	40	39	45

BSA, body surface area; ETN, etanercept; PASI, Psoriasis Area and Severity Index; TIL, tildrakizumab
*e.g., methotrexate, cyclosporine.

Table 2. Summary of adverse events in the placebo-controlled and full-trial periods (all patients as treated)

	Placebo-Controlled Period, n (%)				**Full-trial period, Exposure-Adjusted Rate (Patients/100 Patient Years [95% CI])**			
	TIL 100 mg (n=705)	**TIL 200 mg (n=708)**	**Placebo (n=355)**	**ETN 50 mg (n=313)**	**TIL 100 mg (n=1083)**	**TIL 200 mg (n=1041)**	**Placebo (n=588)**	**ETN 50 mg (n=313)**
TEAE	340 (48.2)	339 (47.9)	191 (53.8)	169 (54.0)	77.0 (74.0, 79.9)	79.3 (76.1, 82.4)	153.5 (142.5, 164.4)	148.6 (137.8, 158.5)
Treatment-related AE	104 (14.8)	99 (14.0)	47 (13.2)	92 (29.4)	23.3 (20.7, 26.1)	25.2 (22.4, 28.2)	37.9 (30.6, 46.2)	73.0 (62.2, 84.4)

Serious AE	10 (1.4)	16 (2.3)	6 (1.7)	7 (2.2)	5.8 (4.4, 7.5)	7.2 (5.6, 9.1)	6.4 (3.5, 10.6)	13.0 (8.1, 19.8)
Treatment-related serious AE	0	3 (0.4)	0	2 (0.6)	0.3 (0.1, 0.9)	1.0 (0.4, 1.8)	0.9 (0.1, 3.3)	3.3 (1.1, 7.5)
Discontinued due to TEAE	4 (0.6)	9 (1.3)	4 (1.1)	6 (1.9)	2.2 (1.4, 3.3)	2.2 (1.3, 3.3)	2.3 (0.7, 5.3)	5.9 (2.7, 11.0)
Discontinued due to treatment-related AE	1 (0.1)	3 (0.4)	2 (0.6)	4 (1.3)	0.8 (0.3, 1.6)	0.9 (0.4, 1.7)	0.9 (0.1, 3.3)	2.6 (0.7, 6.6)

AE, adverse event; ETN, etanercept; TEAE, treatment-emergent adverse event; TIL, tildrakizumab.

Table 3. Adverse events of clinical interest in the placebo-controlled and full-trial periods (all patients as treated)

	Placebo-Controlled Period, n (%)				**Full-Trial Period, Exposure-Adjusted Rate (Patients with Events/100 Patient Years)**			
	TIL 100 mg	**TIL 200 mg**	**Placebo**	**ETN 50 mg**	**TIL 100 mg**	**TIL 200 mg**	**Placebo**	**ETN 50 mg**

	(n=705)	(n=708)	(n=355)	(n=313)	(n=1083)	(n=1041)	(n=588)	(n=313)
Confirmed MACE*	1 (0.1)	0	0	0	0.4	0.3	0.5	0.0
Difference vs. placebo, estimate (95% CI)	0.1 (–0.9, 0.8)	0.0 (–1.1 0.5)	–	–	–	–	–	–
P value vs. placebo	–	–	–	–	–	–	–	–
Severe infections	1 (0.1)	2 (0.3)	1 (0.3)	0	1.1	1.6	0.9	2.0
Difference vs. placebo, estimate (95% CI)	–0.1 (–1.4, 0.6)	0.0 (–1.3, 0.8)	–	–	–	–	–	–
P value vs. placebo	0.62	1.00	–	–	–	–	–	–
Malignancies	2 (0.3)	1 (0.1)	0	1 (0.3)	1.7	1.2	0.9	2.6
Difference vs. placebo, estimate (95% CI)	0.3 (–0.8, 1.0)	0.1 (–0.9, 0.8)	–	–	–	–	–	–
P value vs. placebo	0.32	0.48	–	–	–	–	–	–
Non-melanoma skin cancer	2 (0.3)	1 (0.1)	0	1 (0.3)	1.1	0.9	0.9	1.3
Difference vs. placebo, estimate (95% CI)	0.3 (–0.8, 1.0)	0.1 (–0.9, 0.8)	–	–	–	–	–	–

P value vs. placebo	0.32	0.48	–	–	–	–	–	–
Melanoma skin cancer	0	0	0	0	0.2	0.0	0.0	0.0
Difference vs. placebo, estimate (95% CI)	0.0 (–1.1, 0.5)	0.0 (–1.1, 0.5)	–	–	–	–	–	–
P value vs. placebo	>0.99	>0.99	–	–	–	–	–	–
Injection site reactions	24 (3.4)	28 (4.0)	8 (2.3)	56 (17.9)	3.5	4.6	5.0	40.4
Difference vs. placebo, estimate (95% CI)	1.2 (–1.2, 3.1)	1.7 (–0.7, 3.8)	–	–	–	–	–	–
P value vs. placebo	0.30	0.15	–	–	–	–	–	–
Drug-related hypersensitivity reactions	1 (0.1)	1 (0.1)	1 (0.3)	0	0.5	0.2	0.5	0.0
Difference vs. placebo, estimate (95% CI)	–0.1 (–1.4, 0.6)	–0.1 (–1.4, 0.5)	–	–	–	–	–	–
P value vs. placebo	0.62	0.62	–	–	–	–	–	–

ETN, etanercept; MACE, major cardiovascular adverse event; TIL, tildrakizumab.

*Included non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths that were confirmed as “cardiovascular” or “sudden”. MACE was a prespecified tier 2 analysis and *p* values were not calculated. Extended MACE was a prespecified tier 1 analysis and no significant difference versus placebo was observed.

Table 4. Severe infection events identified during the full-trial period.

		Treatment at Onset of Infection, Number of Events			
		TIL 100 mg (n=1083)	**TIL 200 mg (n=1041)**	**Placebo (n=588)**	**ETN 50 mg (n=313)**
Total patient-years exposure		998	928	219	153
Body System	**Infection**				
Respiratory	Pneumonia	0	1	0	0
	Epiglottitis	1	1	0	0
	Sinusitis	3	0	0	0
Skin	Cellulitis	1	3	2	1
	Soft tissue infection	0	1	0	0
	Wound infection	1	1	0	0
	Skin ulcer	0	0	1	0
	Erysipelas	1	0	0	0
	Herpes zoster	0	1	0	1
Gastrointestinal	Appendicitis	2	0	0	0
	Diverticulitis	1	3	0	0
	Gastroenteritis	1	1	0	0
	Gastroenteritis salmonella	0	1	0	0
Urinary tract	Urosepsis	0	0	0	1
	Pyelonephritis	0	1	0	0
Other	Bone tuberculosis	0	1	0	0
	Sepsis	0	1	0	0

ETN, etanercept; TIL, tildrakizumab.