Efficacy and safety of tildrakizumab, a high-affinity anti–interleukin-23p19 monoclonal antibody, in patients with active psoriatic arthritis

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BACKGROUND

- Psoriatic arthritis (PsA) is a progressive, chronic inflammatory arthritis with an estimated prevalence of 0.2%–0.3% globally[1-4]
- There is an unmet need for therapeutics that maximally address all of the manifestations of PsA and have an acceptable safety profile[2,5]
- Tildrakizumab is an anti–interleukin (IL)-23p19 monoclonal antibody approved in the US, Europe, Australia, and Japan for treatment of plaque psoriasis[6,7]
- A randomized, double-blind, multidose, placebo-controlled, phase 2b study (NCT02980692) to evaluate the efficacy and safety of tildrakizumab for the treatment of PsA was recently completed

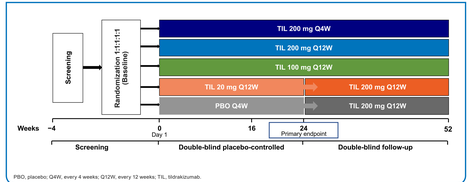
OBJECTIVE

- To evaluate the efficacy and safety of tildrakizumab through 52 weeks in patients with PsA

METHODS

- Part 1 of the study was the double-blind, placebo-controlled period (weeks 0–24) (**Figure 1**)
- At week 24, patients in the placebo and tildrakizumab 20 mg every 12 weeks (Q12W) arms switched to tildrakizumab 200 mg Q12W; all treatments continued in Part 2 (weeks 25–52, double-blind follow-up) (**Figure 1**)

Figure 1. Study design



PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab.

- All patients were administered study drug or placebo every 4 weeks to maintain blinding throughout the study, with placebo given between tildrakizumab doses for patients receiving dosing Q12W
- Randomized patients were stratified by prior anti–tumor necrosis factor (TNF)-α use (yes/no; capped at 30% of total patients) and baseline body weight (≤90 kg/>90 kg)
- Patients who failed to show minimal response to treatment (<10% improvement from baseline in swollen and tender joint counts) at week 16 were allowed to adjust background medications (methotrexate [MTX], leflunomide, or oral corticosteroids) according to the maximum permitted dosing

Inclusion criteria

- Patients ≥18 years old with a diagnosis of PsA (Classification of Psoriatic Arthritis) criteria for ≥6 months[8] and with ≥3 tender and ≥3 swollen joints as evaluated by an independent assessor
- Criteria for permitted background medications:
  - Stable use of nonsteroidal anti-inflammatory drugs (including as needed use)
  - Use of MTX (≤25 mg per week) or leflunomide ≤20 mg per day for ≥3 months and on a stable dose for ≥8 weeks prior to start of treatment with study drug
  - Stable use of oral corticosteroids (prednisone ≤10 mg per day) for ≥4 weeks prior to start of treatment with study drug
  - Ability to maintain current background treatment for the first 24 weeks of the study

Exclusion criteria

- Patients with prior use of the following therapies for psoriasis and/or PsA were excluded:
  - More than 1 biologic treatment or any prior use of anti–IL-17, IL-23, or IL-12/IL-23 p40 biologic therapies for psoriasis/PsA (eg, secukinumab, ustekinumab, ixekizumab, brodalumab, or investigational drugs)
  - Anti-TNF therapy (etanercept within 4 weeks, infliximab within 8 weeks, all others within 3 months prior to study drug treatment)
  - B-cell and T-cell depleting agents (within 12 months of screening); biologic therapies within the longer of 5 half-lives or 3 months prior to study drug treatment
  - Apremilast or other approved or investigational medications for treatment of PsA within the longer of 5 half-lives or 30 days of initiating tildrakizumab
- Presence of major chronic inflammatory or connective tissue disease other than PsA (eg, rheumatoid arthritis), concurrent uncontrolled systemic disease, history of hepatitis B/C or human immunodeficiency virus infections, or history of malignancies within past 5 years
- Presence of prespecified abnormal laboratory parameters at screening
- Use of nonpermitted drugs (including high potency opioid analgesics, parenteral corticosteroids, or live vaccines) within 28 days of start of treatment

Efficacy assessments

- The proportion of patients with ACR20 (primary endpoint), ACR50, and ACR70 responses (≥20%, ≥50% and ≥70% improvement, respectively, in American College of Rheumatology criteria for signs and symptoms of psoriatic arthritis) was assessed at week 24
- The proportion of patients achieving 75%/90%/100% improvements in PASI (PASI 75/90/100) was assessed only for patients with moderate to severe psoriasis, defined as ≥3% BSA affected at baseline
- The proportion of patients with disease activity scores 28-C-reactive protein (DAS28-CRP) <3.2 was also assessed through week 52

Safety assessments

- Safety assessments included treatment-emergent adverse event (TEAE) monitoring (Medical Dictionary of Regulatory Activities v20.1)

Statistical analyses

- Efficacy and safety were analyzed on the full analysis set, defined as all randomized patients who received ≥1 dose of study drug or placebo
- The Cochran-Mantel-Haenszel test was used for statistical analysis of response rates for ACR20/50/70 and PASI 75/90/100 between tildrakizumab arms vs placebo, stratified by prior anti–TNF-α therapy use and baseline body weight
- Two-sided 95% confidence intervals and P-values were calculated for each tildrakizumab treatment arm vs placebo
- Patients who withdrew from the study early or had incomplete data were classified as nonresponders for efficacy endpoints
- For ACR20 at week 24, patients with missing responses/lack of efficacy at week 16 who received modifications to background medications were imputed as nonresponders

RESULTS

Efficacy

- Overall, 391 of 500 screened patients met the inclusion criteria, with 77–79 per treatment arm (**Table 1**)

Table 1. Demographics and baseline clinical disease characteristics

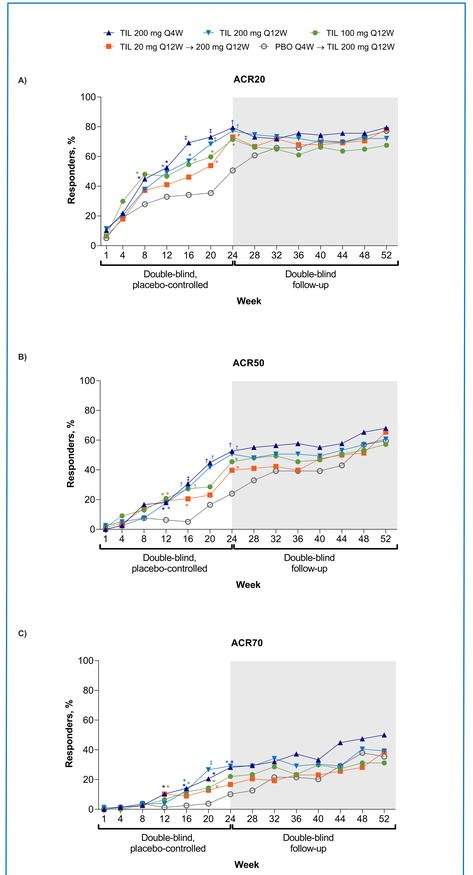
	TIL 200 mg Q4W (n = 78)	TIL 200 mg Q12 (n = 79)	TIL 100 mg Q12W (n = 77)	TIL 20 →200 mg Q12W (n = 79)	PBO →200 mg Q12W (n = 79)
Demographics					
Age, years, mean ± SD	50.1 ± 13.3	49.3 ± 11.2	49.2 ± 11.9	47.2 ± 13.4	48.1 ± 13.3
Female, n (%)	46 (59.0)	37 (46.8)	47 (61.0)	41 (52.6)	44 (55.7)
Race, n (%)					
White	76 (97.4)	78 (98.7)	75 (97.4)	75 (96.2)	74 (93.7)
Black or African American	0	0	1 (1.3)	1 (1.3)	3 (3.8)
Other	2 (2.6)	1 (1.3)	1 (1.3)	2 (2.6)	2 (2.5)
Weight, kg, mean ± SD	85.1 ± 19.7	87.2 ± 19.5	83.7 ± 18.9	85.2 ± 18.1	85.3 ± 20.2
BMI, kg/m², mean ± SD	30.1 ± 6.5	30.2 ± 6.5	29.5 ± 6.8	29.4 ± 5.2	29.5 ± 6.0
Baseline disease characteristics					
Duration of PsA, years, median (range)	4.3 (0.1–42.8)	4.1 (0.0–32.1)	5.1 (0.1–34.5)	4.3 (0.1–35.7)	4.0 (0.3–28.8)
Prior anti–TNF-α therapy, n (%)[a]	18 (22.8)	17 (21.8)	19 (23.8)	19 (24.4)	18 (23.7)
Swollen joint count, median (range)	8.0 (3–35)	7.0 (3–45)	8.0 (0–38)	8.0 (3–38)	8.0 (3–42)
Tender joint count, median (range)	13.5 (3–64)	15.0 (4–63)	19.0 (3–59)	14.0 (4–54)	15.0 (3–64)
PtGA, mean ± SD	57.8 ± 18.3	61.1 ± 20.7	60.3 ± 20.2	61.9 ± 17.4	65.2 ± 18.1
PGA, mean ± SD	54.0 ± 16.1	55.4 ± 16.2	57.3 ± 17.3	59.4 ± 14.4	59.5 ± 15.6
Patient pain assessment, mean ± SD	55.4 ± 19.1	59.6 ± 23.5	59.2 ± 22.1	60.9 ± 19.7	64.2 ± 20.4
LEI, median (IQR)[b]	3.0 (2.0)	2.0 (2.0)	3.0 (3.0)	3.0 (2.0)	2.0 (2.0)
LDI, median (IQR)[b]	21.8 (27.0)	28.3 (55.0)	32.1 (72.5)	28.6 (48.9)	34.0 (133.5)
BSA, (%), median (range)	5.0 (0–85)	4.0 (0–56)	8.0 (0–90)	4.0 (0–70)	3.0 (0–80)
BSA ≥3%, n (%)	53 (67.9)	44 (55.7)	55 (71.4)	41 (52.6)	42 (53.2)
PASI, median (IQR)[c]	3.6 (10.2)	3.9 (7.7)	7.0 (10.1)	4.0 (10.2)	2.4 (5.9)
HAQ-DI score, median (range)	1.1 (0.0–2.9)	1.0 (0.0–2.5)	1.1 (0.0–2.8)	1.0 (0.0–2.4)	1.3 (0.0–2.5)
hsCRP, mg/L, median (range)	3.3 (0.3–156.5)	3.7 (0.3–85.0)	4.9 (0.1–155.9)	5.2 (0.2–67.4)	5.7 (0.2–124.0)
ESR, mm/h, median (range)[d]	15.0 (0–84)	16.0 (0–92)	19.0 (2–90)	20.0 (0–86)	22.5 (0–90)

[a]For prior anti–TNF-α therapy, total patients analyzed (N) = 79, 78, 80, 79, and 76 for TIL 200 mg Q4W, TIL 200 mg Q12W, TIL 100 mg, TIL 20 mg, and PBO.
[b]For patients with baseline scores ≥1; N = 48, 43, 51, 55, and 43 for LEI; N = 27, 21, 21, 19, and 25 for LDI.
[c]For analysis of baseline PASI, all patients were analyzed, regardless of % BSA involved; N = 75, 79, 76, 75, and 75 for TIL 200 mg Q4W, TIL 200 mg Q12W, TIL 100 mg, TIL 20 mg, and PBO.
[d]Total patients analyzed (n) = 71, 69, 70, 68, 62, respectively.
Shown for randomized patients who received ≥1 dose of study drug.
BMI, body mass index; BSA, body surface area; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-Reactive Protein; HAQ-DI, health assessment questionnaire disability index; IQR, interquartile range; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; PASI, Psoriasis Area and Severity Index; PBO, placebo; PGA, physician global assessment of disease activity; PtA, psoriatic arthritis; PtGA, patient global assessment of disease activity; Q4W, every 4 weeks; Q12W, every 12 weeks; SD, standard deviation; TIL, tildrakizumab; TNF, tumor necrosis factor.

- A total of 331 (84.7%) patients completed Part 1 and 315 (80.6%) completed Part 2
- By week 52, a total of 76 (19.4%) patients discontinued, most commonly due to lack of efficacy (9.5%) or withdrawn consent (3.3%)
- Concomitant use of other antirheumatic medications in the total study population included leflunomide only (3.8%), leflunomide + prednisone/prednisolone (0.3%), MTX only (51.4%), MTX + prednisone/prednisolone (5.1%), sulfasalazine only (0.3%), prednisolone only (2.1%), sulfasalazine + leflunomide (0.3%)
- Of the 391 patients randomized to treatment, 53%–71% of patients had moderate to severe psoriasis (BSA ≥3% at baseline, 41–55 per treatment arm)

- At week 24, there was a significantly greater proportion of ACR20, ACR50, and ACR70 responders among tildrakizumab treatment arms vs placebo except for tildrakizumab 20 mg Q12W and tildrakizumab 100 mg Q12W arms for ACR70 (**Figure 2**)
- ACR20, ACR50, and ACR70 response rates continued to increase through week 52, including in the patients who switched from placebo or tildrakizumab 20 mg Q12W to tildrakizumab 200 mg Q12W (**Figure 2**)

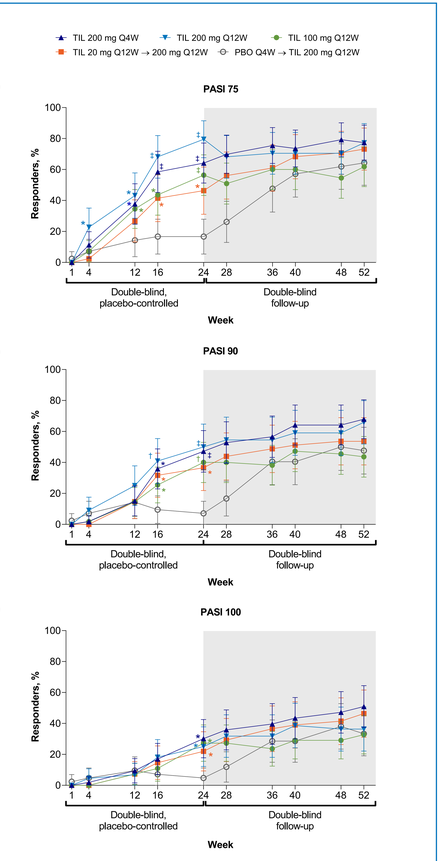
Figure 2. Response rates for **A)** ACR20, **B)** ACR50, and **C)** ACR70 across treatments and timepoints



*P <0.05; †P <0.001; ‡P <0.0001 vs PBO.
Missing responses were imputed as nonresponses.
ACR, American College of Rheumatology; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab.

- At week 24, there was a significantly greater proportion of PASI 75, PASI 90, and PASI 100 responders among patients receiving any dose of tildrakizumab compared with those receiving placebo (**Figure 3**)
  - The proportion of responses in placebo-treated patients were low across all PASI outcomes
- After 24 weeks, responses continued to increase and were sustained through week 52, including in patients switching from placebo to tildrakizumab 200 mg Q12W or from tildrakizumab 20 to 200 mg Q12W after week 24 (**Figure 3**)

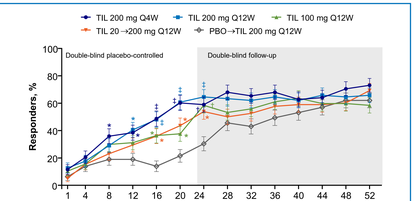
Figure 3. Response rates for **A)** PASI 75, **B)** PASI 90, and **C)** PASI 100 across treatments and time points



Response rates calculated in patients with BSA ≥3% at baseline. Error bars represent 95% CI. Missing responses were imputed as nonresponses. P-values are based on Cochran-Mantel-Haenszel test (with prior anti-TNF use and baseline weight as stratification factors).
*P <0.05; †P <0.001; ‡P <0.0001 vs PBO.
BSA, body surface area; CI, confidence interval; PASI, Psoriasis Area and Severity Index; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab; TNF, tumor necrosis factor.

- By week 24, DAS28-CRP response rates significantly increased across all tildrakizumab treatment arms (**Figure 4**); and continued to increase after week 24 and were sustained through week 52, including in the placebo to tildrakizumab 200 mg Q12W arm

Figure 4. DAS28-CRP response rates across treatments and timepoints



TIL 200 mg Q4W n/N =	9/78	16/78	28/78	30/78	38/78	47/78	46/78 (59%)	53/78	51/78	53/78	49/78	50/78	55/78	57/78 (73%)
TIL 200 mg Q12W n/N =	15/79	14/79	23/79	32/79	38/79	48/79	51/79 (65%)	50/79	49/79	51/79	49/78	52/79	51/79	52/79 (66%)
TIL 100 mg Q12W n/N =	8/77	12/77	23/77	24/77	28/77	29/77	45/77 (58%)	41/77	43/77	47/77	49/77	46/77	46/77	46/77 (58%)
TIL 20 →200 mg Q12W n/N =	4/78	12/78	18/78	23/78	28/78	34/78	42/78 (54%)	39/78	41/78	45/78	46/78	46/78	47/78	54/78 (69%)
PBO →TIL 200 mg Q12W n/N =	5/79	11/79	15/79	15/79	11/79	17/79	24/79 (30%)	36/79	34/79	39/79	43/79	40/79	49/79	49/79 (62%)

Missing responses were imputed as nonresponses. Error bars represent standard error of the mean.
*P <0.05; †P <0.001; ‡P <0.0001 vs PBO.
PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab.

Safety

- From baseline–week 52, incidence of AEs was similar across all treatment arms (**Table 2**)
- The most frequent were nasopharyngitis (1.3%–9.0%, Part 1; 2.5%–9.0%, Part 2) and upper respiratory tract infection (1.3%–5.1%, Part 1; 0%–5.1%, Part 2)
  - Most TEAEs, including infections, were mild
- There was 1 case each of pyelonephritis and urinary tract infection (both during weeks 0–24 in the 100 mg Q12W arm) and there was 1 case of chronic tonsillitis (during weeks 0–24 in the tildrakizumab 20 to 200 mg Q12W arm)
- One malignancy occurred (intraductal proliferative breast lesion in the tildrakizumab 20 to 200 mg Q12W arm)
- There were no reports of systemic candidiasis, uveitis, inflammatory bowel disease, major adverse cardiac events, or death (**Table 2**)

Table 2. Summary of cumulative safety from baseline through week 52

	TIL 200 mg Q4W (n = 78)	TIL 200 mg Q12W (n = 79)	TIL 100 mg Q12W (n = 77)	TIL 20→ 200 mg Q12W (n = 79)	PBO→TIL 200 mg Q12W (n = 79)
Treatment Emergent Adverse Events (TEAE)	51 (65.4)	50 (63.3)	53 (68.8)	51 (65.4)	47 (59.5)
Serious TEAEs	2 (2.6)	2 (2.5)	2 (2.6)	4 (5.1)	3 (3.8)
Discontinuations due to TEAEs	0	1 (1.3)	0	0	0
Deaths due to TEAEs	0	0	0	0	0
AE of special interest	0	0	1 (1.3)	1 (1.3)	0
AE of clinical interest	0	0	1 (1.3)	2 (2.6)	1 (1.3)

Shown as (%) for patients who received ≥1 dose of study medication.
AE, adverse event; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; TEAE, treatment-emergent AE; TIL, tildrakizumab.

CONCLUSIONS

- By week 24, all tildrakizumab dose arms were significantly more efficacious than placebo in treating articular manifestations of psoriatic arthritis, as assessed by ACR20, ACR50, ACR70, and DAS28-CRP, with responses further increasing through week 52 for patients switching from placebo to tildrakizumab 200 mg Q12W
- There were also significantly more tildrakizumab-treated patients who achieved PASI 75, PASI 90, and PASI 100 responses compared with placebo-treated patients by week 24
- These findings demonstrate that tildrakizumab improved joint and skin manifestations of PsA through week 52 and was well tolerated among patients in all groups

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