Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Phase 2b Study to Demonstrate the Safety and Efficacy 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 0.3%–1% globally[1,2]
- There is an unmet need for therapeutics that address all of the manifestations of PsA and have an acceptable safety profile[2,3]
- Tildrakizumab is an anti–interleukin (IL)-23p19 monoclonal antibody approved in the US, Europe, and Australia for treatment of moderate to severe plaque psoriasis[4,5]
- A randomized, double-blind, multiple-dose, placebo-controlled, phase 2b study (NCT02980692) to evaluate the efficacy and safety of tildrakizumab for the treatment of PsA was recently completed

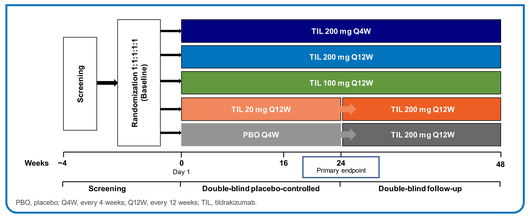
OBJECTIVE

- To evaluate the efficacy and safety of tildrakizumab in patients with active PsA at 24 weeks from the interim analysis of the randomized, double-blind, placebo-controlled, multiple-dose, phase 2b trial

METHODS

- Study design is summarized in **Figure 1**

Figure 1. Study design



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

- Placebo was given every 4 weeks (Q4W) to patients receiving tildrakizumab every 12 weeks (Q12W) to maintain blinding
- Patients were stratified by prior anti-tumor necrosis factor (TNF)-α use (yes/no; prior use capped at 30% of total patients) and baseline body weight (≤90 kg/>90kg)
- 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 daily dose

Inclusion criteria

- Patients ≥18 years old with a diagnosis of PsA (Classification of Psoriatic Arthritis [CASPAR] criteria)[6] for ≥6 months, 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 medications 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)
  - Etanercept, infliximab and all other anti-TNF therapies within 4 weeks, 8 weeks, and 3 months, respectively
  - B-cell and T-cell depleting agents within 12 months of screening; other biologic therapies within the longer of 5 half-lives or 3 months of initiating tildrakizumab
  - 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 noncutaneous or in situ cervical/breast/total malignancies <5 years in the past
- Presence of prespecified abnormal laboratory parameters, use of nonpermitted drugs (including high-potency opioid analgesics, parenteral corticosteroids, and live vaccines) within 28 days of start of treatment

Efficacy assessments

- The proportion of patients at week 24 with ≥20%, ≥50% and ≥70% improvement in American College of Rheumatology criteria (ACR20/50/70)
- The proportion of patients achieving ≥75%, ≥90%, and 100% improvement in Psoriasis Area and Severity Index (PASI 75/90/100); in patients with measurable psoriasis, defined as BSA ≥3% at baseline
- Improvements in sixty-six swollen and 68 tender joint counts (SJC, TJC)
- Patient-rated present pain level due to arthritis (improvements in visual analog scale [0–100 mm])
- Leeds enthesitis index (improvements in LEI)

Safety assessments

- Treatment-emergent AEs (TEAEs) were monitored (coded by Medical Dictionary of Regulatory Activities v20.1) and laboratory assessments were performed throughout the study
- Analyses were based on the actual treatment received; missing safety data were not replaced

RESULTS

- In total, 391/500 patients screened met inclusion criteria
- Patient demographics and baseline disease characteristics were consistent across treatment arms (**Table 1**)

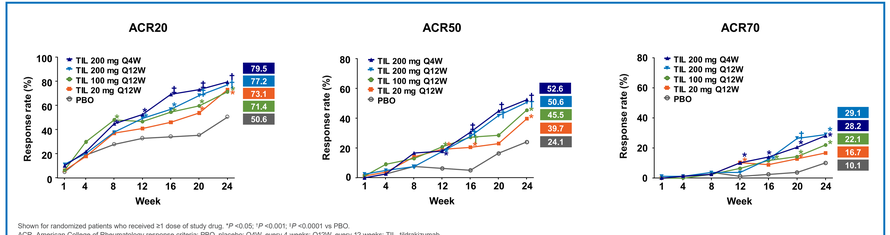
Table 1. Demographics and baseline clinical disease characteristics

	TIL 200 mg Q4W (n = 78)	TIL 200 mg Q12W (n = 79)	TIL 100 mg Q12W (n = 77)	TIL 20 mg Q12W (n = 78)	PBO (n = 79)
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	87.1 ± 19.5	83.6 ± 18.9	85.1 ± 18.1	85.3 ± 20.2
BMI, kg/m^2, mean ± SD	30.1 ± 6.5	30.2 ± 6.5	29.5 ± 6.8	29.4 ± 5.2	29.5 ± 6.0
Duration of PsA, years, mean ± SD	6.9 ± 7.3	6.8 ± 6.3	6.3 ± 7.2	6.6 ± 6.7	7.3 ± 8.0
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, mean ± SD	10.4 ± 7.4	10.0 ± 8.0	11.0 ± 8.2	9.4 ± 6.4	11.8 ± 9.8
Tender joint count, mean ± SD	16.6 ± 11.9	19.5 ± 13.9	21.3 ± 14.8	19.0 ± 13.0	19.7 ± 14.7
Patient GADA, mean ± SD	57.8 ± 18.3	61.1 ± 20.7	60.3 ± 20.2	61.9 ± 17.4	65.2 ± 18.1
Physician GADA, 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
Enthesitis (LEI >0), n (%)	48 (61.5)	43 (54.4)	51 (66.2)	55 (70.5)	43 (54.4)
Enthesitis score (LEI >0), mean ± SD	3.1 ± 1.7	2.8 ± 1.7	3.2 ± 1.8	3.1 ± 1.7	2.8 ± 1.8
BSA, (%), mean ± SD	11.9 ± 16.0	9.0 ± 12.4	12.8 ± 16.0	10.4 ± 14.1	8.2 ± 12.2
BSA ≥3%, n (%)	53 (67.9)	44 (55.7)	54 (70.1)	41 (52.6)	42 (53.2)
PASI, mean ± SD[b]	7.6 ± 9.8	6.2 ± 7.4	8.8 ± 9.5	6.6 ± 7.0	5.0 ± 6.5
HAQ score, mean ± SD	1.0 ± 0.6	1.0 ± 0.6	1.0 ± 0.7	1.1 ± 0.6	1.2 ± 0.6

[a]For prior anti–TNF-α therapy, total patients analyzed (N) = 79, 78, 80, 78, and 76 for TIL 200 mg Q4W, TIL 200 mg Q12W, TIL 100 mg, TIL 20 mg, and PBO.
[b]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.
Shown for randomized patients who received ≥1 dose of study drug.
BMI, body mass index; BSA, body surface area; GADA, global assessment of disease activity; HAQ, health assessment questionnaire disability index; LEI, Leeds Enthesitis Index; PASI, Psoriasis Area and Severity Index; PBO, placebo; PsA, psoriatic arthritis; Q4W, every 4 weeks; Q12W, every 12 weeks; SD, standard deviation; TIL, tildrakizumab; TNF, tumor necrosis factor.

- 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%)
- At week 24, there was a significantly greater proportion of ACR20, ACR50, and ACR70 responders among all tildrakizumab treatment arms vs placebo except for tildrakizumab 20 mg Q12W for ACR70 (**Figure 2**)

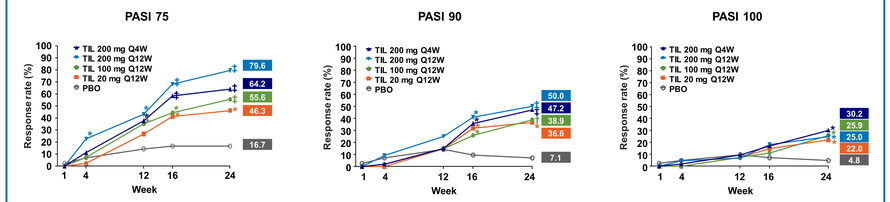
Figure 2. Proportion of patients achieving ACR20, ACR50, and ACR70 responses by treatment and timepoint



Shown for randomized patients who received ≥1 dose of study drug. *P <0.05; †P <0.001; ‡P <0.0001 vs PBO.
ACR, American College of Rheumatology response criteria; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab.

- At week 24, among patients with ≥3% BSA involvement at baseline, there was a significantly greater proportion of PASI 75, PASI 90, and PASI 100 responders among those 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

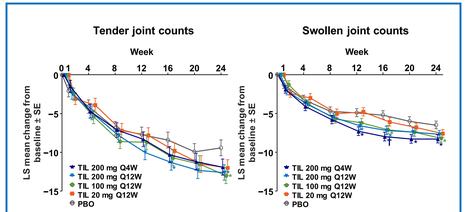
Figure 3. Proportion of patients achieving PASI 75, PASI 90, and PASI 100 responses by treatment and timepoint



Response rates calculated in patients with BSA ≥3% at baseline, missing responses were imputed as nonresponses.
*P <0.05; †P <0.001; ‡P <0.0001 vs PBO.
BSA, body surface area; PASI, Psoriasis Area and Severity Index; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab.

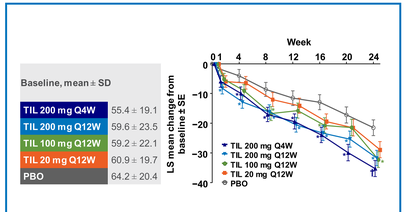
- Tildrakizumab 100 and 200 mg Q12W significantly reduced tender joint counts vs placebo (**Figure 4**)
- Tildrakizumab 100 mg Q12W and 200 mg Q4W significantly reduced swollen joint counts vs placebo (**Figure 4**)
- All tildrakizumab arms improved patient pain from baseline (*P* <0.05 vs placebo except tildrakizumab 20 Q12W, **Figure 5**)

Figure 4. Mean change in tender and swollen joint counts by treatment and timepoint



Shown for randomized patients who received ≥1 dose of study drug; values at week 0 represent baseline.
*P <0.05; †P <0.001 vs PBO.
LS, least squares; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; SE, standard error; TIL, tildrakizumab.

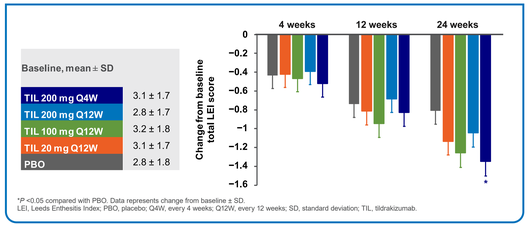
Figure 5. Mean change in patient pain by treatment and timepoint



Shown for randomized patients who received ≥1 dose of study drug; values at week 0 represent baseline.
*P <0.05; †P <0.001 vs PBO.
LS, least squares; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; SE, standard error; TIL, tildrakizumab.

- Tildrakizumab 200 Q4W significantly improved LEI by 71.2% (*P* <0.05, **Figure 6**)

Figure 6. Enthesitis by treatment and timepoint



*P <0.05 compared with PBO. Data represents change from baseline ± SD.
LEI, Leeds Enthesitis Index; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; SD, standard deviation; TIL, tildrakizumab.

- No deaths or discontinuations due to TEAEs were reported (**Table 2**)

Table 2. Summary of safety at week 24

	Any TIL arm (n = 312)	PBO (n = 79)
Any TEAE	156 (50.0)	34 (43.0)
Any serious TEAEs	7 (2.2)	2 (2.5)
Any TEAE related to treatment	35 (11.2)	10 (12.7)
Discontinuation due to TEAEs	0	0
Serious infections	1 (0.3)[a]	0
Major adverse cardiac events	0	0
Malignancy	0	0
Deaths due to TEAEs	0	0

[a]Chronic tonsillitis.
Data are shown as n (%) for randomized patients who received ≥1 dose of study drug.
PBO, placebo; TEAE, treatment-emergent adverse event; TIL, tildrakizumab.

- The most commonly reported TEAEs were nasopharyngitis (17 [5.4%] tildrakizumab-treated vs 5 [6.3%] placebo-treated), headache (15 [4.8%] vs 2 [2.5%]), and hypertension (11 [3.5 %] vs 4 [5.1%]), respectively
- There were no significant elevations in laboratory parameters that led to a serious TEAE designation
- At 24 weeks, there were no reports of candidiasis, inflammatory bowel disease, major adverse cardiac events, significantly increased liver enzymes, malignancies, or suicidal ideation

CONCLUSIONS

- By week 24, all 4 dose categories of tildrakizumab were significantly more efficacious than placebo in treatment of joint and skin manifestations of PsA
- There was a clear separation in ACR20 improvements from baseline between tildrakizumab and placebo as early as 8 weeks
- Shortening the dosing interval from Q12W to Q4W for the 200-mg dose did not result in a measurable increase in skin or joint response scores
- Tildrakizumab was well tolerated with low rates of TEAEs reported

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