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Real-World Effectiveness and Safety of Tildrakizumab in Patients With Moderate-to-Severe Psoriasis: Week 28 Interim Analysis of a Phase 4 Study

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ABSTRACT

Background: Tildrakizumab is an anti–interleukin-23 p19 monoclonal antibody approved for the treatment of adults with moderate-to-severe plaque psoriasis. This analysis evaluated real-world effectiveness and safety of tildrakizumab for 28 weeks.

Methods: In this Phase 4 study (NCT03718299), adults with moderate-to-severe plaque psoriasis received tildrakizumab 100 mg subcutaneously at week 0, week 4, and every 12 weeks thereafter. Clinical improvement was assessed from Psoriasis Area and Severity Index (PASI) score change from baseline; disease activity from body surface area (BSA) percentage affected, static Physician's Global Assessment (sPGA), and sPGA x BSA; and safety from adverse events (AEs).

Results: At week 28, 52/55 enrolled patients were assessed. Mean (standard deviation [SD]) PASI score decreased significantly (P<0.001) from 11.6 (7.1) at baseline to 1.8 (3.0; 82.1% improvement) at week 28; 55.8% of patients achieved PASI 90 response. From baseline to week 28, mean (SD) BSA decreased significantly from 14.5% (11.5%) to 2.9% (6.4%), sPGA from 3.2 (0.6) to 1.2 (0.9), and BSA x sPGA from 47.0 (41.5) to 6.8 (20.3; all P<0.001). Serious AEs were infrequent. No treatment-emergent AEs were considered related to tildrakizumab.

Conclusions: Real-world tildrakizumab treatment significantly improved clinical status and reduced disease activity, with no new safety concerns.

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INTRODUCTION

Plaque psoriasis is a chronic, inflammatory skin disorder spanning a patient's lifetime and hence requires long-term management.[1] Psoriasis is a multisystem disease that remarkably impacts patients' physical health and is associated with an increased incidence of comorbid conditions, including cardiovascular disease, Crohn's disease, type 2 diabetes, obesity, and lymphoma.[1-3] Psoriasis and its symptoms also have a considerable impact on patients' quality of life.[2]

Interleukin (IL)-23 is a key pro-inflammatory cytokine mediating psoriatic inflammation and tissue damage and is thus a target of plaque psoriasis therapy.[4,5] The p19 subunit of IL-23 is unique to this cytokine, while the p40 subunit is also present in IL-12.[4] Tildrakizumab, a high affinity, anti–IL-23 p19 monoclonal antibody, selectively binds to the p19 subunit, blocking its interaction with the IL-23 receptor. It is approved by the US Food and Drug Administration for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[6,7]

The efficacy and safety of tildrakizumab in patients with moderate-to-severe plaque psoriasis were assessed in 2 Phase 3, multinational, randomized clinical trials, reSURFACE 1 (NCT01722331) and reSURFACE 2 (NCT01729754).[7-9] In the 64-week reSURFACE 1 trial, patients received a subcutaneous injection of tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo at baseline, week 4, and every 12 weeks thereafter. In the 52-week reSURFACE 2 trial, patients received a subcutaneous injection of tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo on the same schedule as in reSURFACE 1, with etanercept 50 mg (twice weekly to week 12, then weekly to week 28) as an active comparator. In both trials, at week 12, higher proportions of patients receiving tildrakizumab 100 mg achieved ≥75% and ≥90% improvement from baseline in Psoriasis Area and Severity Index (PASI) score (PASI 75 and PASI 90 response, respectively) and Physician Global Assessment (PGA) score of "clear" or "minimal" compared with patients receiving placebo.[7] Frequencies of adverse events (AEs) were favorable and similar among tildrakizumab treatment arms in

both trials.[7] Patients receiving tildrakizumab who successfully completed the reSURFACE 1 or reSURFACE 2 base study with at least a PASI 50 response were eligible to enroll in an optional extension study and receive the same dose of tildrakizumab for an additional 4 years. In pooled data analyses from reSURFACE 1 and reSURFACE 2, long-term treatment with tildrakizumab in patients who achieved a PASI 75 response at week 28 was associated with sustained disease control and a favorable safety profile for up to 5 years of total treatment.[9]

Although the efficacy and safety of tildrakizumab are well established in the clinical trial setting, little published real-world evidence is available from clinical practice settings. This manuscript reports the effectiveness of tildrakizumab in terms of clinical improvement and residual disease activity, as well as safety of tildrakizumab, from the week 28 interim analysis of a 64-week Phase 4 study in real-world practice.

MATERIALS AND METHODS

Study Design and Population

This Phase 4, open-label, real-world study was conducted at 2 sites in the United States, initiated in July 2019, and registered at www.ClinicalTrials.gov (record #NCT03718299). Eligible patients were immunocompetent, aged ≥18 years, had moderate-to-severe plaque psoriasis that was diagnosed at least 6 months prior to study entry, had ≥3% of their total body surface area (BSA) affected by psoriasis, and were candidates for phototherapy or systemic therapy. Patients were excluded from the study if they had erythrodermic psoriasis; only pustular, guttate, or inverse psoriasis; or evidence of skin conditions other than psoriasis that would interfere with study-related evaluations of psoriasis. Patients with prior or concomitant treatment with any biological agent other than tildrakizumab within 1 week prior to baseline, any new investigational drug within 12 weeks prior to baseline, or new treatment for psoriasis not used consistently prior to screening were also excluded. The study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by a central Institutional Review Board, and all patients were required to provide written informed consent prior to study initiation.

Treatment and Assessments

All patients received tildrakizumab 100 mg by subcutaneous injection at week 0, week 4, and every 12 weeks thereafter through week 52. The interim analysis was performed after all patients had the opportunity to complete treatment up to week 28. The investigator assessed patients' PASI scores at baseline and weeks 4, 16, and 28. The percentage of BSA affected and the static PGA (sPGA) were assessed by the investigator at baseline, every 4 weeks up to week 16, and at week 28. For the percentage of BSA affected, investigators could use the estimate that 1% BSA is equivalent to the area of the patient's closed hand. To determine sPGA, first, the psoriasis plaque attributes of induration, erythema, and scaling were rated on individual 6-point scales (0 = no evidence to 5 = severe), with each attribute averaged over the patient's entire body. Final sPGA was then obtained based on another 6-point scale (0 = clear, except for residual discoloration, to 5 = severe, lesions have individual induration, erythema, and scaling scores of at least 5).[10]

Safety was evaluated from AEs, which were reported spontaneously by patients or elicited by investigators during questioning and examination of a patient at any time during the study. AE data collected included date of onset, location (within/not within the affected region), severity (mild, moderate, severe), and relationship to treatment (not related, unlikely, possibly, probably, definitely).

Outcomes

The primary endpoint of the study, improvement in quality of life as measured by change from baseline in the total Psychological General Well-Being Index score, is reported elsewhere.[11] In this interim analysis, clinical improvement during tildrakizumab treatment through week 28 was evaluated from improvement from baseline in PASI score and the proportions of patients achieving 75%/90%/100% improvement from baseline PASI score (PASI 75/90/100 responses, respectively). Disease activity was evaluated from the percentage of BSA affected, sPGA, and sPGA x BSA over time.

Safety was assessed based on the incidence and severity of treatment-emergent AEs (TEAEs) and treatment-emergent serious AEs through week 28.

Statistical Analysis

Sample Size

A sample size of 60 patients screened was selected to provide adequate estimates; no formal sample size calculations were performed. Following screening, 55 patients were enrolled in the study.

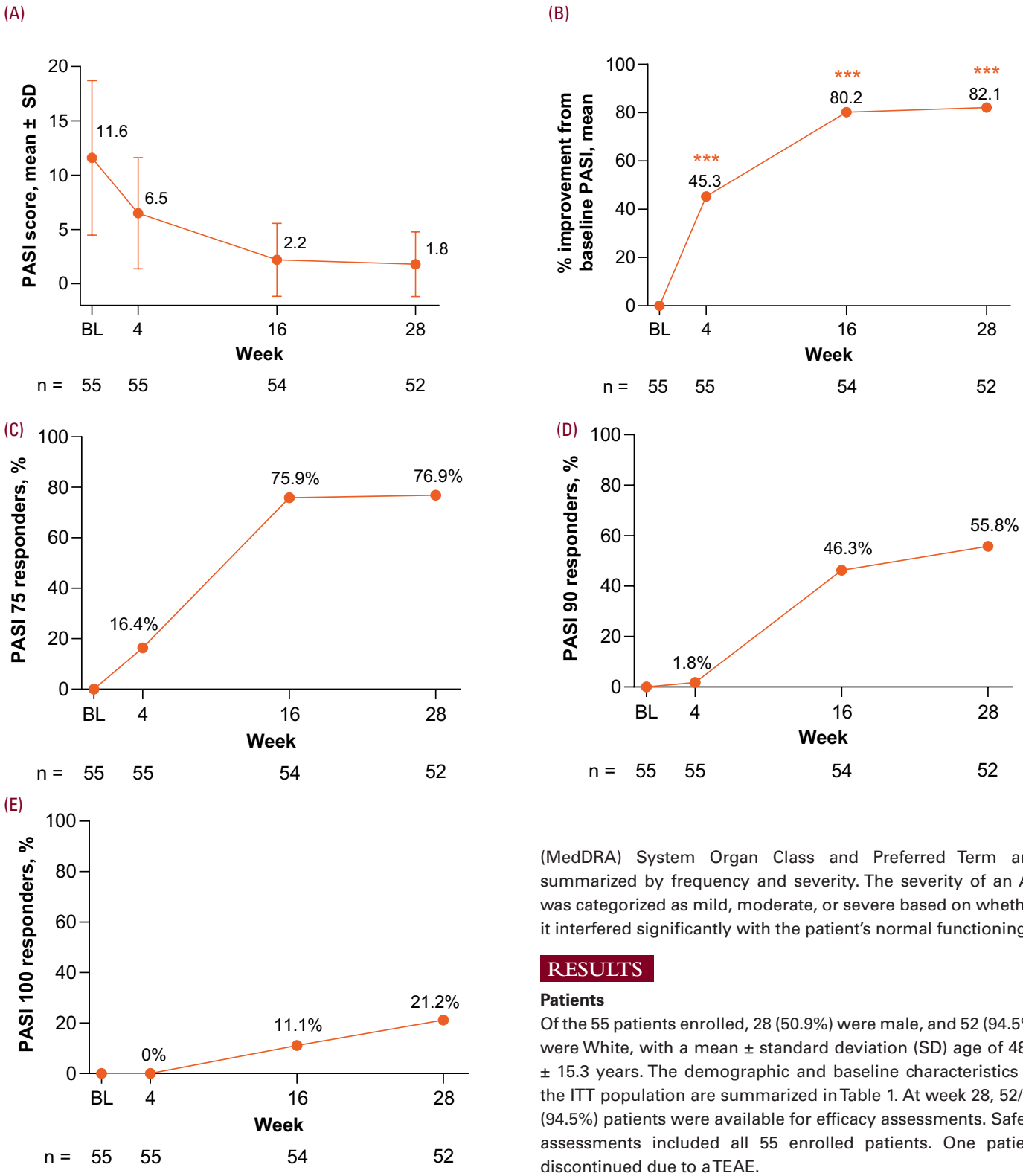
Effectiveness Analyses

Effectiveness was analyzed in the intention-to-treat (ITT) population, which consisted of all enrolled patients assigned to receive study medication. Descriptive statistics were calculated for the absolute values and percentage changes from baseline in PASI score, BSA, sPGA, and sPGA x BSA; the PASI 75/90/100 response rates were also summarized with descriptive statistics. Changes from baseline were analyzed using Student's t-test. Missing data were not imputed.

Safety Analyses

Safety analyses included all enrolled patients who received at least 1 dose of study treatment (safety population). The TEAEs were classified by Medical Dictionary for Regulatory Activities

FIGURE 1. Real-world treatment effectiveness through week 28 by PASI score. (A) Absolute PASI score, (B) Percentage improvement from baseline PASI score, (C) PASI 75 response rate, (D) PASI 90 response rate, and (E) PASI 100 response rate.



(MedDRA) System Organ Class and Preferred Term and summarized by frequency and severity. The severity of an AE was categorized as mild, moderate, or severe based on whether it interfered significantly with the patient's normal functioning.

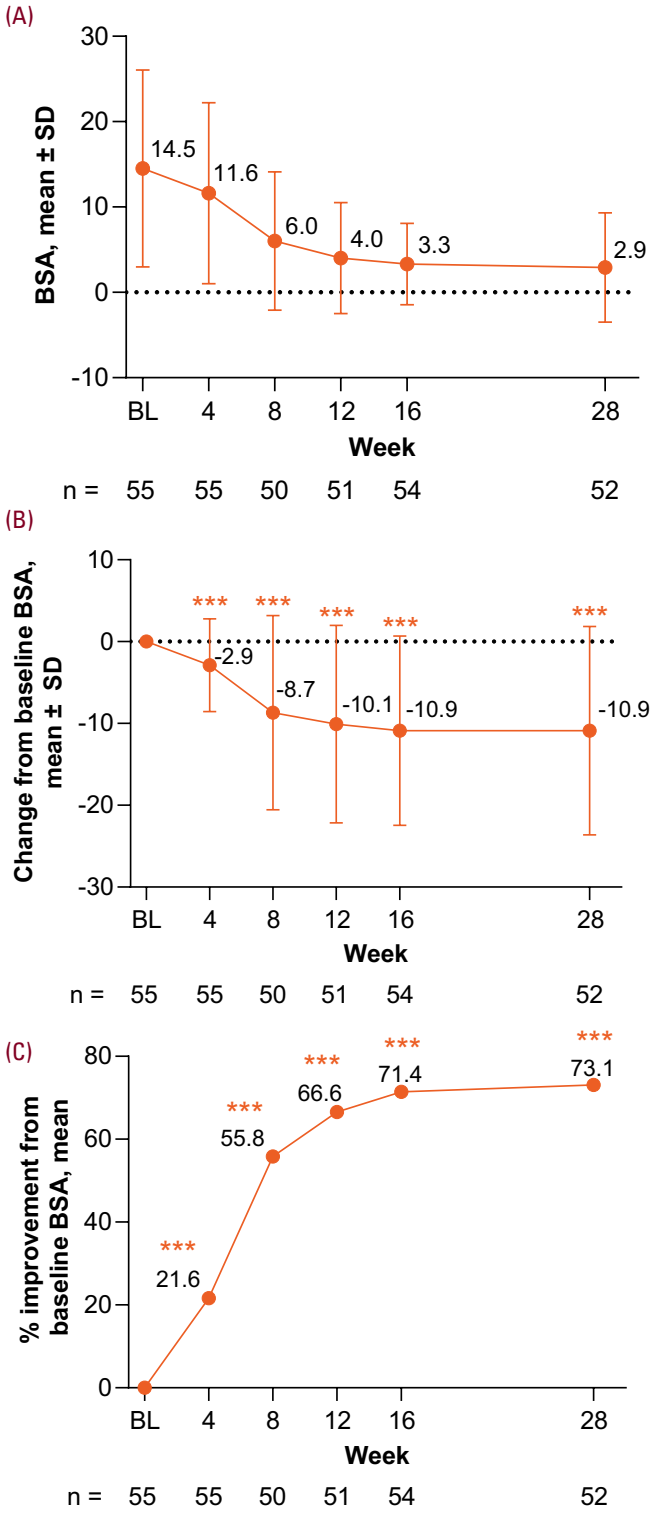
RESULTS

Patients

Of the 55 patients enrolled, 28 (50.9%) were male, and 52 (94.5%) were White, with a mean ± standard deviation (SD) age of 48.6 ± 15.3 years. The demographic and baseline characteristics of the ITT population are summarized in Table 1. At week 28, 52/55 (94.5%) patients were available for efficacy assessments. Safety assessments included all 55 enrolled patients. One patient discontinued due to a TEAE.

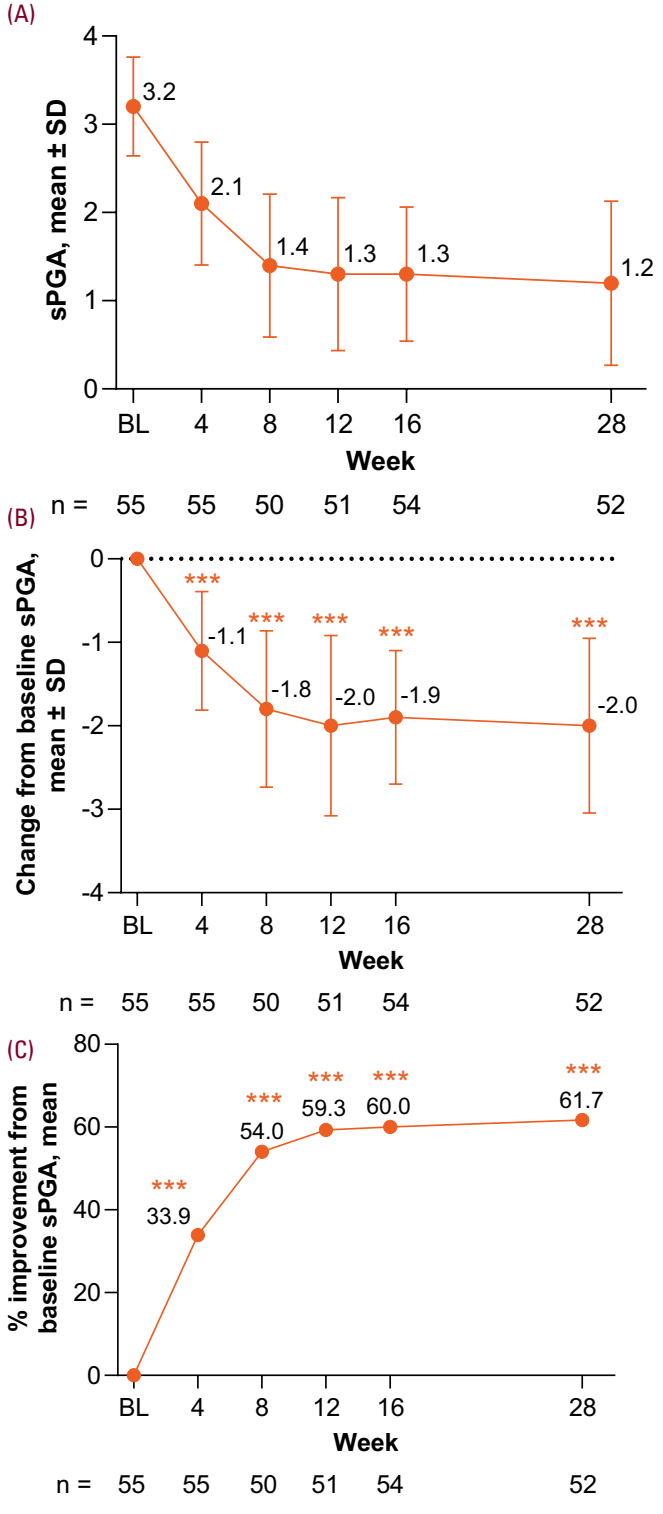
ITT population.
Data in panel A are shown as the mean; error bars represent the SD.
***P <0.001. n value reports number of patients assessed.
BL, baseline; ITT, intention-to-treat; PASI, Psoriasis Area and Severity Index; PASI 75/90/100 response, 75%/90%/100% improvement from baseline PASI score; SD, standard deviation.

FIGURE 2. Real-world treatment effectiveness through week 28 by BSA. (A) BSA, (B) Absolute change from baseline in BSA, and (C) Percentage improvement from baseline BSA.



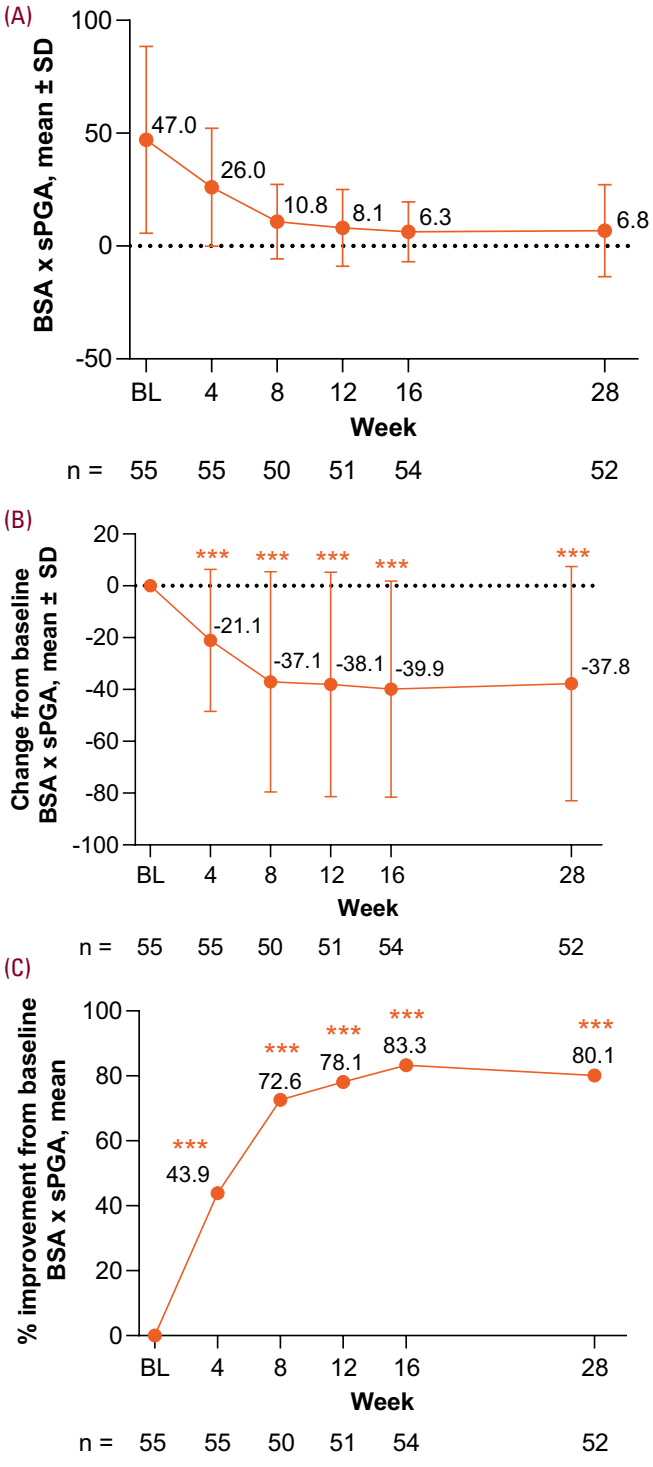
ITT population.
Data shown as the mean; error bars in panels A and B represent the SD.
Mean change from baseline at each visit in Panel B may not correspond to the difference between the mean at each visit and the mean at baseline in Panel A due to the different numbers of patients assessed at each visit.
***P<0.001. n value reports number of patients assessed.
BL, baseline; BSA, body surface area; ITT, intention-to-treat; SD, standard deviation.

FIGURE 3. Real-world treatment effectiveness through week 28 by sPGA. (A) sPGA, (B) Absolute change from baseline, and (C) Percentage improvement from baseline sPGA.



ITT population.
Data shown as the mean ± SD in panels A and B; error bars represent the SD.
Mean change from baseline at each visit in Panel B may not correspond to the difference between the mean at each visit and the mean at baseline in Panel A due to the different numbers of patients assessed at each visit.
***P <0.001. n value reports number of patients assessed.
BL, baseline; ITT, intention-to-treat; SD, standard deviation; sPGA, static Physician Global Assessment.

FIGURE 4. Real-world treatment effectiveness through week 28 by calculated BSA x sPGA. (A) BSA x sPGA, (B) Absolute change from baseline, and (C) Percentage improvement from baseline BSA x sPGA.



ITT population.
Data shown as the mean ± SD in panel A and B; error bars represent the SD.
Mean change from baseline at each visit in Panel B may not correspond to the difference between the mean at each visit and the mean at baseline in Panel A due to the different numbers of patients assessed at each visit.
***P<0.001. n value reports number of patients assessed.
BL, baseline; BSA, body surface area; ITT, intention-to-treat; SD, standard deviation; sPGA, static Physician Global Assessment.

TABLE 1.

Demographics and Baseline Characteristics of the ITT Population	Tildrakizumab (N = 55)
Sex	
Male	28 (50.9)
Age, years, mean ± SD	48.6 ± 15.29
Race	
American Indian or Alaska Native	0 (0.0)
Asian	1 (1.8)
Black or African American	2 (3.6)
Native Hawaiian or Pacific Islander	0 (0.0)
White	52 (94.5)
Other	0 (0.0)
Not reported	0 (0.0)
Ethnicity	
Hispanic or Latino	5 (9.1)
Not Hispanic or Latino	50 (90.9)
Not reported	0 (0.0)
BSA, mean ± SD	14.5 ± 11.5
PASI, mean ± SD	11.6 ± 7.1
sPGA, mean ± SD	3.2 ± 0.6
BSA x sPGA, mean ± SD	47.0 ± 41.5

All data are n (%) unless otherwise noted.
BSA, body surface area; ITT, intention-to-treat; PASI, Psoriasis Area and Severity Index; SD, standard deviation; sPGA, static Physician Global Assessment.

Effectiveness

Patients experienced significant improvement in disease severity by multiple measures as early as week 4, with further improvements by week 28. The PASI score decreased from a mean ± SD of 11.6 ± 7.1 (median, 10.5; range, 2.7 to 33.8) at baseline to 6.5 ± 5.1 at week 4 (mean percent improvement, 45.3%; P<0.001) and to 1.8 ± 3.0 at week 28 (mean percent improvement, 82.1%; P<0.001; Figure 1A–B). At week 28, the PASI 75 response rate was 76.9%, the PASI 90 response rate was 55.8%, and the PASI 100 response rate was 21.2% (Figure 1C–E).

Mean ± SD BSA decreased from 14.5 ± 11.5 at baseline to 11.6 ± 10.6 at week 4 (mean percent improvement, 21.6%) and further decreased to 2.9 ± 6.4 by week 28 (mean percent improvement, 73.1%; both P<0.001; Figure 2A–C). The mean ± SD sPGA was 3.2 ± 0.6 at baseline and decreased to 2.1 ± 0.7 by week 4 (mean percent improvement, 33.9%; P<0.001) and to 1.2 ± 0.9 by week 28 (mean percent improvement, 61.7%; P<0.001; Figure 3A–C). The mean (± SD) calculated sPGA x BSA decreased from 47.0 ± 41.5 at baseline to 26.0 ± 26.2 at week 4 (mean percent improvement, 43.9%; P<0.001) and to 6.8 ± 20.3 at week 28 (mean percent improvement, 80.1%; P<0.001; Figure 4A–C).

TABLE 2.

TEAEs Through Week 28	
Evaluation	**Tildrakizumab (N = 55)**
Any TEAE	31 (56.4)
Treatment-related TEAEs	0
Serious TEAEs	3 (5.5)
TEAEs leading to treatment discontinuation	1 (1.8)
Most frequent TEAEs (>3% of patients)	
Gastrointestinal disorders	6 (10.9)
Large intestine polyp	2 (3.6)
General disorders and administration site conditions	2 (3.6)
Infections and infestations	8 (14.5)
Nasopharyngitis	2 (3.6)
Upper respiratory tract infection	2 (3.6)
Metabolism and nutrition disorders	2 (3.6)
Musculoskeletal and connective tissue disorders	6 (10.9)
Arthralgia	2 (3.6)
Neoplasms*	3 (5.5)
Skin papilloma	2 (3.6)
Nervous system disorders	4 (7.3)
Skin and subcutaneous tissue disorders	11 (20.0)
Dermatitis	3 (5.5)
Eczema	2 (3.6)
Psoriasis	7 (12.7)
Vascular disorders	5 (9.1)
Hypertension	5 (9.1)

Data shown as n (%) of patients with event in the safety population reported according to MedDRA System Organ Class and preferred term.
*Includes benign, malignant, and unspecified (including cysts and polyps).
MedDRA, Medical Dictionary for Regulatory Activities;TEAE, treatment-emergent adverse event.

Safety

Tildrakizumab treatment was generally well tolerated. TEAEs reported through week 28 are summarized in Table 2. TEAEs occurred in 31 (56.4%) patients; the most frequently reported were skin and subcutaneous tissue disorders (20.0%), infections and infestations (14.5%), musculoskeletal and connective tissue disorders (10.9%), and gastrointestinal disorders (10.9%). No TEAEs of tuberculosis, opportunistic infections, or inflammatory bowel disease occurred in this study. Serious TEAEs occurred in 3 (5.5%) patients (COVID-19 infection, cerebrovascular accident, immunoglobulin A nephropathy; n = 1 each). No TEAEs were considered related to tildrakizumab treatment. One AE of transitional cell carcinoma (1.8%) before week 28 led to discontinuation after week 28.

DISCUSSION

This week 28 interim analysis of data from a 64-week, Phase 4 trial provides insights into the effectiveness and safety of tildrakizumab treatment in community practice patients with moderate-to-severe plaque psoriasis. Significant clinical improvement from baseline was observed at week 28 based on PASI response thresholds, with low disease activity based on absolute PASI score, BSA, sPGA, and BSA x sPGA. No new safety concerns were identified.

Both clinical improvement and disease activity are important indicators of treatment effectiveness. Improvement is desirable to patients, especially those with a large disease burden at baseline; however, a patient with high baseline disease severity who experiences 90% improvement may still have clinically significant disease after treatment. Conversely, a patient with moderate disease severity at baseline may have very acceptable low disease severity after treatment despite not achieving response thresholds such as the PASI 90. The results of our study emphasize that real-world tildrakizumab treatment is effective in terms of both clinical improvement and disease activity.

There is a knowledge gap regarding the real-world effectiveness of biologic therapies for plaque psoriasis compared with the efficacy and safety observed in clinical trials. Randomized clinical trials enroll select patient populations with stringent inclusion and exclusion criteria. In contrast, real-world studies provide valuable insights from a patient-centric perspective and allow physicians and the greater medical community to see the effects of treatments from a far more generalizable context.[12] The results of this real-world analysis are consistent with those of the Phase 3 reSURFACE 1 and reSURFACE 2 clinical trials. In reSURFACE 1 and reSURFACE 2, 77% and 73%, respectively, of patients treated with tildrakizumab 100 mg for 28 weeks achieved PASI 75 response; 49% and 55%, respectively, achieved PASI 90 response.[7] The mean (SD) pooled PASI scores at baseline, week 12, and week 28 were 20.2 (7.7), 5.7 (7.0), and 4.6 (6.6), respectively. In addition, the overall frequencies of TEAEs were generally similar between the Phase 3 trials and the present study.[7]

AEs reported in the current analysis are consistent with the safety profile of tildrakizumab in clinical practice, with common TEAEs including nasopharyngitis and upper respiratory tract infection.[5]

LIMITATIONS

Limitations of this interim analysis include the lack of a comparator study arm, a relatively short duration of follow-up, and a limited number of patients

CONCLUSION

This interim analysis provides information on the effectiveness and safety of tildrakizumab treatment beyond clinical trials, demonstrating the impact of treatment on clinical outcomes in patients with moderate-to-severe plaque psoriasis in the real-world setting. The full 1-year results are expected to provide further insight into the safety and effectiveness of tildrakizumab in clinical practice.

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.

DISCLOSURES

JH has been a speaker, advisor, and consultant for AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Boehringer Ingelheim, and Novartis; an advisor for Galderma, Mayne, Regeneron, and Sanofi; an advisor and consultant for Ortho Dermatologics; and a speaker and advisor for Sun Pharma, Incyte, LEO Pharma, and Beiersdorf. JGV reports nothing to disclose. BS is an employee of Sun Pharmaceutical Industries, Inc. NB is an advisor, consultant, and investigator for AbbVie, Almirall, Arcutis, Beiersdorf, Biofrontera, Bristol Myers Squibb, Boehringer Ingelheim, Cara, Dermavant, Eli Lilly, EPI Health, Ferndale, Galderma, Genentech, InCyte, ISDIN, Johnson & Johnson, LaRoche-Posay, LEO Pharma, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, Sun Pharma, and Verrica.

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