Received: 14 October 2020 | Accepted: 21 January 2021

DOI: 10.1111/1346-8138.15789

THE JOURNAL OF DERMATOLOGY

ORIGINAL ARTICLE

Efficacy and safety of tildrakizumab in Japanese patients with moderate to severe plaque psoriasis: Results from a 64-week phase 3 study (reSURFACE 1)

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Funding information
Merck Sharp & Dohme; Sun Pharmaceutical Industries, Inc.

Abstract

Tildrakizumab is a high-affinity, humanized immunoglobulin G1κ, anti-interleukin-23p19 monoclonal antibody recently approved in Japan for treatment of plaque psoriasis. We report results from Japanese patients treated with tildrakizumab in the multinational, randomized, double-blind, placebo-controlled reSURFACE 1 study (clinicaltrials.gov NCT01722331). Adults with moderate to severe plaque psoriasis were randomized (2:2:1) to receive subcutaneous tildrakizumab 100 or 200 mg or placebo every 12 weeks. Placebo recipients were rerandomized to tildrakizumab 100 or 200 mg at week 12. The global study coprimary endpoints were the proportions of patients achieving 75% improvement from baseline Psoriasis Area and Severity Index (PASI 75) and Physician Global Assessment (PGA) response (0/1 with ≥2 grade reduction from baseline) at week 12. Analyses included 158 Japanese patients randomized to tildrakizumab 100 (n = 64) or 200 mg (n = 62) or placebo (n = 32). Japanese patients had higher mean baseline body surface area involvement and PASI versus all reSURFACE 1 patients. At week 12, significantly more Japanese patients receiving tildrakizumab 100 and 200 mg versus placebo achieved PASI 75 (54.7% and 54.8% vs 6.3%, respectively, both nominal $p < 0.001$) and PGA 0/1 response (54.7% and 56.5% vs 9.4%, respectively, both nominal $P < 0.001$). Response rates increased over time with maximal efficacy after 22-28 weeks; >80% of patients achieving PASI 75 or PASI 90 at week 28 and continuing tildrakizumab treatment at the same dose maintained response at week 64. From baseline to week 28, absolute PASI decreased from >12 in all patients to ≤2 in >40% and ≤3 in >50% of patients receiving tildrakizumab. Tildrakizumab was generally well tolerated with an adverse event profile similar to that of placebo. Tildrakizumab treatment was associated with durable efficacy in Japanese patients with moderate to severe plaque psoriasis despite greater baseline disease severity versus the global reSURFACE 1 population.

KEYWORDS
antibodies, humanized, interleukin-23 subunit p19, Japanese, monoclonal, psoriasis, randomized controlled trial, tildrakizumab

1 | INTRODUCTION

Psoriasis is a chronic immune-mediated disease that has prevalence of 1% to 5% in most western countries but a lower prevalence in Asia, Latin America, and Africa.[1] In Japan, the estimated prevalence of psoriasis is 0.34%, and of these patients, approximately 97% are diagnosed with plaque psoriasis.[2] Biologic therapy is recommended by the Japanese Dermatological Association for patients with plaque-type psoriasis who have not adequately responded to standard systemic therapies, including phototherapy, and have >10% body surface area (BSA) involvement, or who have refractory skin or joint symptoms intractable to standard systemic therapies and significantly impaired quality of life (QoL).[3] As of the 2009–2012 survey of the Japanese Society for Psoriasis Research, 33.3% of Japanese patients with psoriasis used systemic therapy, including 11.4% receiving infliximab, 10.9% receiving adalimumab, and 6.2% receiving ustekinumab.[4] Japanese patients report that the most important attribute for biologic treatment for psoriasis is sustained efficacy after drug withdrawal, followed by dosing convenience, copayment amount, long-term efficacy, and early onset of efficacy.[5]

Interleukin 23 (IL-23) is a key mediator of psoriasis through the differentiation, proliferation, and survival of Th17 cells.[6] Tildrakizumab is a high-affinity, humanized, immunoglobulin G1κ, anti–IL-23p19 monoclonal antibody.[6] Tildrakizumab was previously approved in the USA, the EU, and Australia for treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy and is approved in Japan to treat plaque psoriasis in adult patients who have inadequate response to conventional therapies as of 29 June 2020.[7-10] In the global phase 3 reSURFACE 1 study (clinicaltrials.gov NCT01722331), patients treated with tildrakizumab at weeks 0, 4, and subsequently every 12 weeks, achieved 75% reduction from baseline in Psoriasis Area and Severity Index (PASI 75) and Physician's Global Assessment of 0 or 1 with ≥2 grade improvement from baseline (PGA 0/1) at significantly higher rates relative to placebo-treated patients.[6] Tildrakizumab was well tolerated in the global clinical development program, with low frequencies of serious adverse events (SAEs) and adverse events (AEs) leading to study discontinuation.[6,11] In an effort to understand the efficacy and safety of tildrakizumab among Japanese with plaque psoriasis, this subgroup analysis explores outcomes with tildrakizumab in Japanese patients enrolled in reSURFACE 1 during the 64-week base study period.

2 | METHODS

2.1 | Study design

reSURFACE 1 was a three-part, double-blind, randomized, placebo-controlled, 64-week phase 3 study conducted at 118 study sites in five countries, including 45 sites in Japan.[6] The study protocol was reviewed and approved by independent ethics committees at each study site and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided informed consent in accordance with International Conference on Harmonisation-E6 Guideline for Good Clinical Practice and local country and/or cultural practices as applicable.[6]

2.2 | Patients

Detailed patient inclusion and exclusion criteria were previously reported.[6]

Briefly, eligible patients were aged ≥18 years with moderate to severe chronic (for ≥6 months) plaque psoriasis, defined as BSA involvement ≥10%, PGA ≥3, and PASI ≥12 at baseline, and were candidates for phototherapy or systemic therapy.[6] Key exclusion criteria were predominantly nonplaque forms of psoriasis, severe psoriatic arthritis well controlled on current therapy, and anticipated need for topical therapy, phototherapy, or systemic therapy for psoriasis during the trial.

2.3 | Treatments

In part 1 (weeks 0–12), patients were randomized 2:2:1 to receive tildrakizumab 100 mg, tildrakizumab 200 mg, or placebo by subcutaneous injection at weeks 0 and 4. In part 2 (weeks 12–28), patients receiving tildrakizumab continued to receive the same dose every 12 weeks. Patients randomized to placebo treatment were rerandomized to receive tildrakizumab 100 or 200 mg at weeks 12 and 16 and administered every 12 weeks thereafter. In part 3 (weeks 28–64), patients originally randomized to tildrakizumab treatment who achieved PASI 75 were rerandomized to continue receiving tildrakizumab at the same dose or to placebo treatment through week 64. Patients rerandomized to placebo resumed tildrakizumab treatment at their previous dose on relapse. All patients received placebo or tildrakizumab injections every 4 weeks to maintain the blind. Patients randomized to receive tildrakizumab 200 mg in part 1 with a partial response to treatment (PASI 50 but not PASI 75) at week 28 continued to receive tildrakizumab 200 mg. Patients with partial response to tildrakizumab 100 mg at week 28 were rerandomized to treatment with either tildrakizumab 100 or 200 mg to assess the value of dose escalation. Patients rerandomized from placebo to tildrakizumab treatment at week 12 who achieved PASI 50 at week 28 continued to receive tildrakizumab at the same dose through week 64. Patients who did not achieve PASI 50 at week 28 discontinued the study.

2.4 | Assessments

Changes from baseline in PASI and PGA were assessed at weeks 4, 8, 12, 16, 22, 28, 32, and every 4 weeks thereafter until week 64. The Dermatology Life Quality Index (DLQI) was administered at baseline, and change was monitored at weeks 12, 28, 40, 52, and 64. Adverse events were monitored throughout the study and for up to 20 weeks after the last study visit.

2.5 | Outcomes

The prespecified coprimary efficacy outcomes for the global reSURFACE 1 study were the proportion of patients with PASI 75 response at week 12 and the proportion of patients with PGA score of "clear" or "minimal" (PGA 0/1), with at least a 2-grade reduction from baseline (PGA 0/1 response) at week 12. Key secondary efficacy outcomes were the proportions of patients achieving 90% or 100% reductions from baseline in PASI (PASI 90 and PASI 100) at week 12. Other secondary efficacy outcomes included the proportions of patients achieving PASI 75, PASI 90, and PASI 100 at week 28 and the proportions of patients with DLQI of 0 or 1 (DLQI 0/1) at weeks 12 and 28. Exploratory efficacy outcomes included the proportions of patients who maintained PASI 75 and PASI 90 from week 28 through week 64, achieved improvement in PASI score distribution from baseline to week 28, and the percent change in PASI from baseline to week 28 stratified by baseline PASI ≥40 versus <40.

Safety assessments included monitoring of AEs, SAEs, AE-related discontinuations, prespecified AEs of special interest (Tier 1), laboratory tests, and vital signs. Tier 1 AEs included serious infections, malignancies (excluding carcinoma in situ of the cervix), nonmelanoma skin cancer, melanoma, confirmed extended major adverse cardiac events (MACE), and drug-related hypersensitivity reactions (e.g. anaphylaxis, urticaria, and angioedema).

2.6 | Statistical analysis

The full analysis set (FAS) was the primary population for efficacy analyses. For parts 1 and 2, the FAS included all patients who received ≥1 dose of part 1 or part 2 study medication based on the assigned treatment. For part 3, the FAS included all patients who entered part 3 and received ≥1 dose of part 3 study medication based on the assigned treatment. The all subjects as treated (ASAT) analysis set was the primary population for safety and tolerability analyses. For parts 1 and 2, the ASAT analysis set included all randomized patients who received ≥1 dose of part 1 or part 2 study medication based on the treatment received. For part 3, the ASAT analysis set included all randomized patients who received ≥1 dose of part 3 study medication based on the treatment received. Baseline characteristics were summarized using descriptive statistics.

Coprimary and secondary efficacy endpoints were analyzed using a Cochran–Mantel–Haenszel test stratified by body weight and prior exposure to biologic therapy for psoriasis. Patients with missing data for the coprimary and secondary endpoints were treated as nonresponders (i.e. nonresponder imputation). The proportions of patients achieving endpoints over time shown in Figures 2–3 are shown as observed (i.e. missing data were not imputed). The distribution of PASI scores and responses stratified by baseline PASI score are presented descriptively. Comparisons between treatment arms within the Japanese patient subgroup were not adjusted for multiplicity, and nominal *P* values are presented. The numbers and frequencies of AEs were summarized descriptively for study parts 1, 2, and 3.

3 | RESULTS

3.1 | Patients

Of 772 patients enrolled in the reSURFACE 1 base study from December 2012 to October 2015, 158 were Japanese with 64 randomized to tildrakizumab 100 mg, 62 to tildrakizumab 200 mg, and 32 to placebo (Figure 1). Of these, 142 Japanese patients (89.9%) completed study treatment through week 64, and 120 entered the long-term extension phase. The baseline demographics of the Japanese and the overall reSURFACE populations are summarized in Table 1. The majority of Japanese patients were male (78.5%), with mean ± standard deviation (SD) age 48.2 ± 11.9 years, values that were generally similar to the overall population. However, there were some differences in baseline characteristics between Japanese patients and the overall reSURFACE 1 population. In particular, Japanese patients had higher baseline BSA involvement (42.9% vs 30.2%) and mean PASI score (25.7 vs 20.1), lower mean weight (69.7 vs 88.5 kg), and were less likely to have received prior biologics for psoriasis (5.1% vs 22.9%) compared with the overall reSURFACE 1 population.

3.2 | Efficacy

The results for the primary and key secondary endpoints prespecified in the global study are summarized in Table 2. For the first coprimary endpoint, significantly more patients receiving tildrakizumab 100 mg (54.7%) or tildrakizumab 200 mg (54.8%) achieved PASI 75 compared with placebo at week 12 (6.3%, nominal $P < 0.001$ for both doses vs placebo). For the second coprimary endpoint, significantly larger proportions of patients achieved PGA 0/1 response at week 12 following treatment with tildrakizumab 100 mg (54.7%) or tildrakizumab 200 mg (56.5%) compared with placebo treatment (9.4%, both nominal $P < 0.001$ vs placebo).

For the key secondary efficacy endpoints, proportions of patients achieving PASI 90 at week 12 were significantly larger among patients treated with tildrakizumab 100 (26.6%, nominal $P = 0.005$) or 200 mg (35.5%, nominal $P < 0.001$) compared with placebo (3.1%). Additionally, at week 12, 6.3% of patients receiving tildrakizumab 100 mg and 9.7% receiving tildrakizumab 200 mg achieved PASI 100 compared with 3.1% receiving placebo, but this difference did not reach statistical significance (both nominal $P > 0.05$).

Among patients receiving tildrakizumab 100 or 200 mg from baseline, proportions achieving PASI 75, PASI 90, and PASI 100 increased from week 12 to week 28 and proportions achieving PGA 0/1 response at week 28 were numerically higher relative to week 12. PASI 75 response rates at 28 weeks were 65.0% and 73.3%, respectively, for tildrakizumab 100 and 200 mg, while the PGA

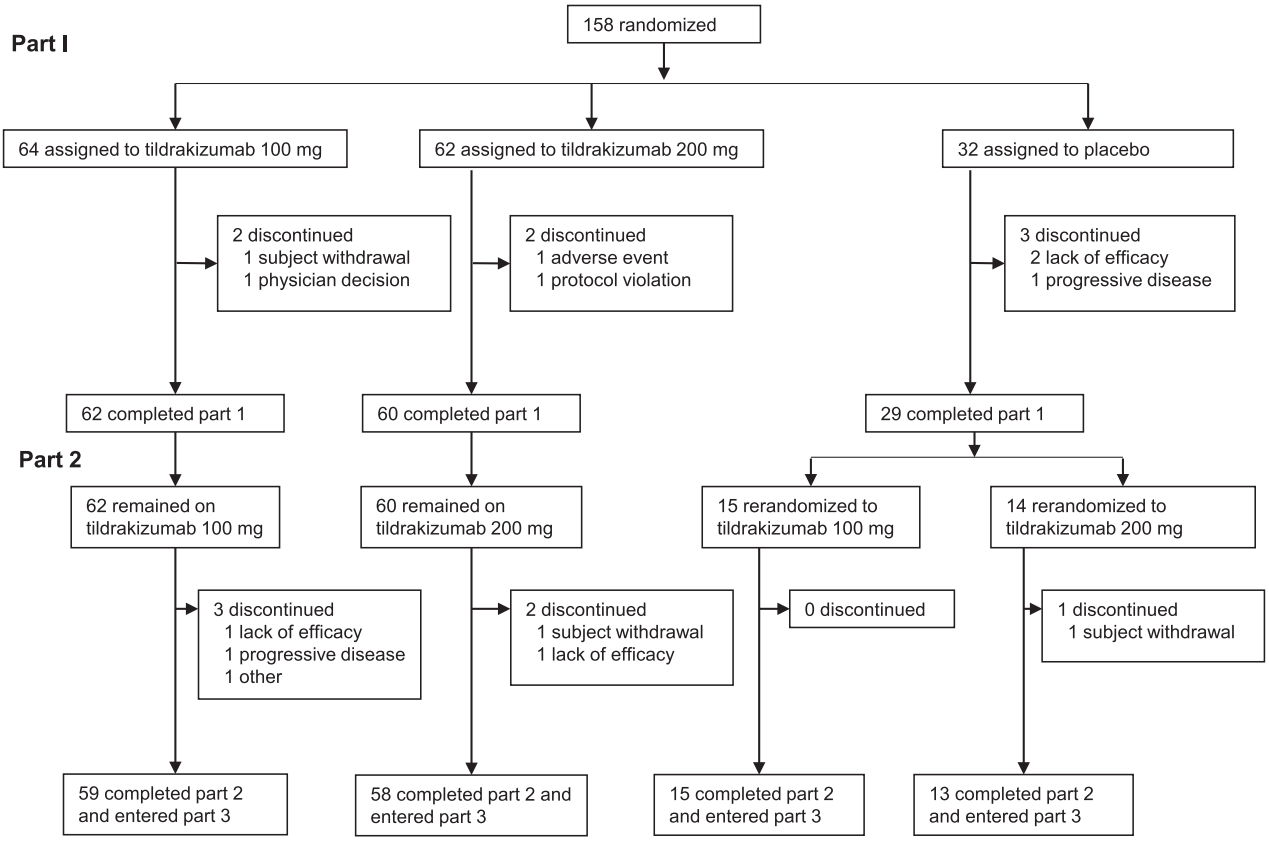

FIGURE 1 Patient disposition

0/1 response rates were 61.7% and 65.0%. At week 28, PASI 90 response rates were 51.7% and 46.7%, and PASI 100 response rates were 11.7% and 25.0%, respectively, for the 100- and 200-mg dose groups (Table 3).

PASI 75 and PGA 0/1 responses over time through week 28 are illustrated in Figure 2a,b, respectively. Over time, progressively more patients randomized to tildrakizumab achieved PASI 75 responses, with maximal efficacy observed between weeks 22 and 28 (Figure 2a). Relatively higher proportions of patients who were originally assigned to receive placebo and rerandomized to receive tildrakizumab at week 12 achieved similar PASI 75 responses (80.0%–92.3%) compared with those receiving continuous tildrakizumab (65.0%–73.3%) by week 28. Similarly, PGA 0/1 responses in both the original tildrakizumab cohorts and the rerandomized groups increased rapidly and were maximized by weeks 22 to 28. Likewise, the proportion of PASI 90 and PASI 100 responders increased over time with maximal response rates seen between weeks 22 and 28 for patients receiving continuous tildrakizumab and placebo-treated patients who were crossed over to tildrakizumab (Figure 2c,d).

At week 12, there was a significantly greater proportion of patients in the tildrakizumab 200 mg arm versus placebo with DLQI 0/1 (41.9% vs 9.4%, $P = 0.001$; Table 4). For those receiving tildrakizumab 100 mg, the proportion of patients with DLQI 0/1 at week 12 was higher versus placebo (22.2% vs 9.4%), but the difference was not statistically significant ($P = 0.110$). However, when assessed as change in DLQI from baseline relative to placebo, the tildrakizumab 100 and 200 mg arms were both associated with significantly greater improvements versus placebo at week 12 (−8.0 and −8.4 points, respectively, both $P < 0.001$). By week 28, the proportions of patients with DLQI 0/1 were higher relative to week 12 among patients treated with tildrakizumab 100 or 200 mg (Table 4). Among patients who continuously received tildrakizumab 100 and 200 mg after week 12, the proportions with DLQI 0/1 were 80.0% (16/20) and 69.6% (16/23), respectively, at week 40, 85.0% (17/20) and 69.6% (16/23), respectively, at week 52, and 65.0% (13/20) and 65.2% (15/23), respectively, at week 64.

Among patients with PASI 75 at week 28 who continued treatment with tildrakizumab at the same dose, 18/20 (90.0%) receiving tildrakizumab 100 mg and 20/23 (87.0%) receiving tildrakizumab 200 mg maintained PASI 75 at week 64 (Figure 3a). Of patients with PASI 90 at week 28, 14/17 (82.4%) patients receiving tildrakizumab 100 mg and 12/13 (92.3%) receiving tildrakizumab 200 mg maintained PASI 90 at week 64 (Figure 3b). The distribution of PASI scores at baseline, week 28, and week 64 following treatment with tildrakizumab 100 or 200 mg is shown in Figure 4. At baseline, all patients receiving tildrakizumab had PASI scores above the threshold for enrollment (i.e. PASI ≥12). At week 28, PASI was <2 in 46.7%, <3 in 53.3%, and <5 in 61.7% of patients treated with tildrakizumab 100 mg (Figure 4a). Among patients receiving tildrakizumab 200 mg, 41.7% had PASI <2, 51.7% had PASI <3, and 68.3% had PASI <5 at week 28 (Figure 4b). In patients treated with tildrakizumab 100 mg who were responders or partial responders

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TABLE 1 Patient demographics and baseline characteristics of Japanese patients who entered the reSURFACE 1 long-term extension study

	Japanese reSURFACE 1			Overall reSURFACE 1		
Patient characteristics	**TIL 100 mg (n = 64)**	**TIL 200 mg (n = 62)**	**Placebo (n = 32)**	**TIL 100 mg (n = 309)**	**TIL 200 mg (n = 308)**	**Placebo (n = 155)**
Sex, male, n (%)	48 (75)	52 (84)	24 (75)	207 (67)	226 (73)	100 (65)
Age, years	46.3 ± 11.9	49.0 ± 11.6	50.5 ± 12.6	46.4 ± 13.1	46.9 ± 13.2	47.9 ± 13.6
Weight, kg	68.4 ± 14.7	71.4 ± 13.1	69.2 ± 14.0	88.5 ± 23.9	88.9 ± 24.1	87.5 ± 26.0
BMI, kg/m^2	24.6 ± 4.63	25.1 ± 4.38	24.7 ± 3.64	30.3 ± 7.26	30.4 ± 7.67	30.4 ± 8.63
Baseline disease characteristics						
BSA, %	44.8 ± 20.2	41.6 ± 21.6	41.3 ± 21.1	29.7 ± 17.4	30.9 ± 17.8	29.6 ± 17.3
PASI	26.4 ± 10.3	25.6 ± 12.0	24.3 ± 9.5	20.0 ± 7.9	20.7 ± 8.5	19.3 ± 7.1
PGA, n (%)						
3	32 (50.0)	29 (46.8)	18 (56.3)	206 (66.7)	202 (65.6)	111 (71.6)
4	31 (48.4)	29 (46.8)	13 (40.6)	95 (30.7)	95 (30.8)	41 (26.5)
5	1 (1.6)	4 (6.5)	1 (3.1)	7 (2.3)	11 (3.6)	2 (1.3)
PsA, yes, n (%)	13 (20.3)	13 (21.0)	6 (18.8)	54 (17.5)	60 (19.5)	19 (12.3)
Total cholesterol, mg/dl	199.6 ± 40.8	192.9 ± 30.9	194.7 ± 34.3	194.7 ± 40.0	194.2 ± 40.0	189.8 ± 39.2
LDL cholesterol, mg/dl	107.3 ± 28.00	111.1 ± 25.18	110.6 ± 29.27	108.7 ± 33.05	110.6 ± 32.67	107.7 ± 33.18
HDL cholesterol, mg/dl	60.4 ± 15.02	56.5 ± 15.37	59.9 ± 16.63	55.5 ± 16.03	53.4 ± 14.91	54.9 ± 17.52
Triglycerides, mg/dl	160.8 ± 152.2	126.5 ± 61.1	120.8 ± 76.2	158.7 ± 112.3	151.6 ± 79.4	136.8 ± 76.9
Fasting glucose, mg/dl	97.6 ± 31.9	98.2 ± 19.1	96.5 ± 16.9	102.4 ± 33.9	101.2 ± 29.6	102.6 ± 33.3
Nonfasting glucose, mg/dl	101.9 ± 32.3	102.0 ± 26.5	98.1 ± 15.6	102.7 ± 39.7	102.4 ± 38.8	108.7 ± 44.5
Mean blood pressure, mmHg						
Systolic	129.8 ± 14.8	128.5 ± 15.7	133.8 ± 16.8	128.3 ± 14.0	126.9 ± 15.3	126.4 ± 14.5
Diastolic	81.4 ± 11.6	79.6 ± 11.2	80.6 ± 13.9	79.5 ± 10.0	79.1 ± 9.8	77.8 ± 10.5
Type 2 diabetes, n (%)	1 (1.6)	0	0	21 (6.8)	26 (8.4)	15 (9.7)

Note: Data presented as mean ± SD unless otherwise specified.

Abbreviations: BMI, body mass index; BSA, body surface area; HDL, high density lipoprotein; LDL, low density lipoprotein; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PsA, psoriatic arthritis; SD, standard deviation; TIL, tildrakizumab.

TABLE 2 Summary of statistical analyses of week 12 coprimary and key secondary endpoints

Endpoint, n (%)	**Placebo (n = 32)**	**TIL 100 mg (n = 64)**	**% difference vs placebo (95% CI; *P* value)**	**TIL 200 mg (n = 62)**	**% difference vs placebo (95% CI; *P* value)**
Coprimary endpoints					
PGA (0/1) response	3 (9.4)	35 (54.7)	46.4 (27.7, 60.8; $P < 0.001$)	35 (56.5)	47.1 (28.1, 61.2; $P < 0.001$)
PASI 75 response	2 (6.3)	35 (54.7)	49.7 (31.8, 63.2; $P < 0.001$)	34 (54.8)	48.4 (30.4, 62.0; $P < 0.001$)
Key secondary endpoints					
PASI 90 response	1 (3.1)	17 (26.6)	24.0 (9.0, 37.1; $P = 0.005$)	22 (35.5)	32.2 (16.2, 45.7; $P < 0.001$)
PASI 100 response	1 (3.1)	4 (6.3)	3.4 (−9.9, 13.5; $P = 0.476$)	6 (9.7)	6.6 (−7.1, 17.4; $P = 0.251$)

Note: Data are shown as n (%) unless otherwise noted.

Percentages are based on subjects with data, which includes both observed and imputed data.

Difference and CIs are calculated using Miettinen–Nurminen stratified by body weight (≤90 kg, >90 kg) and prior exposure to biologic therapy for psoriasis (yes/no) with sample size weights. *P* values are calculated using the Cochran–Mantel–Haenszel test stratified by body weight (≤90 kg, >90 kg) and prior exposure to biologic therapy for psoriasis (yes/no). *P* values are not adjusted for multiplicity.

Abbreviations: CI, confidence interval; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; TIL, tildrakizumab.

at week 28 and continued receiving tildrakizumab 100 mg in part 3, the PASI score at week 64 was <2 in 53.3%, <3 in 60.0%, and <5 in 70.0% of patients (Figure 4c); in responders or partial responders to tildrakizumab 200 mg at week 28 who continued receiving the same dose, 32.4% had PASI <2, 35.1% had PASI <3, and 64.9% had PASI <5 at week 64 (Figure 4d). Since Japanese patients had higher

TABLE 3 Proportions of patients achieving PASI 75/90/100 and PGA 0/1 at week 28

Endpoint, n (%)	TIL 100 mg (n = 60)	TIL 200 mg (n = 60)	Placebo to TIL 100 mg (n = 15)	Placebo to TIL 200 mg (n = 13)
PGA 0/1	37 (61.7)	39 (65.0)	14 (93.3)	11 (84.6)
PASI 75	39 (65.0)	44 (73.3)	12 (80.0)	12 (92.3)
PASI 90	31 (51.7)	28 (46.7)	11 (73.3)	8 (61.5)
PASI 100	7 (11.7)	15 (25.0)	6 (40.0)	4 (30.8)

Note: Data are shown as n (%).

Missing data were not imputed.

Abbreviations: PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; TIL, tildrakizumab.

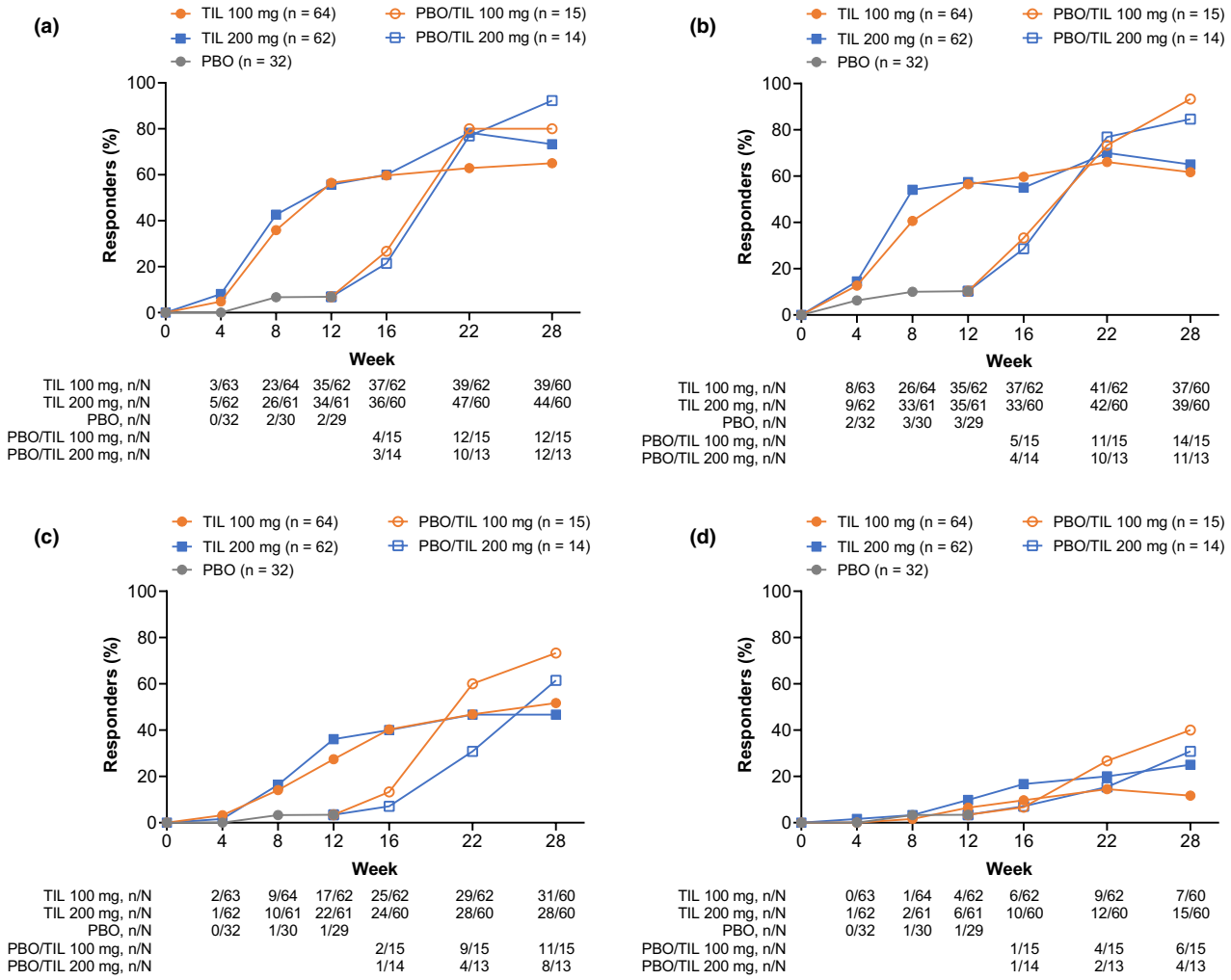

FIGURE 2 Proportions of patients achieving (a) PASI 75, (b) PGA 1 or 0 with ≥2 grade decrease from baseline, (c) PASI 90, and (d) PASI 100 through week 28. PASI, Psoriasis Area and Severity Index; PBO, placebo; PGA, Physician Global Assessment; TIL, tildrakizumab

mean PASI scores at baseline relative to the overall reSURFACE 1 population, the mean percentage change in PASI from baseline to week 28 was stratified by baseline PASI <40 versus ≥40. Among patients receiving tildrakizumab 100 mg, PASI score decreased from baseline by 20 (83.9%) in those with baseline PASI <40 (n = 54) and by 34 (72.2%) in those with baseline PASI ≥40 (n = 6) at week 28. In those treated with tildrakizumab 200 mg, the decrease in PASI score from baseline to week 28 was 19 (85.0%) in patients with baseline PASI <40 (n = 55) versus 47 (82.6%) in those with baseline PASI ≥40 (n = 5).

3.3 | Safety

In part 1 (i.e. baseline to week 12), AEs occurred in 31/64 (48.4%) patients receiving tildrakizumab 100 mg and 23/62 (37.1%) patients

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TABLE 4 Proportions of patients with DLQI of 0 or 1 at weeks 12 and 28

Endpoint, n (%)	Placebo	TIL 100 mg	% difference vs placebo (95% CI; *P* value)	TIL 200 mg	% difference vs placebo (95% CI; *P* value)	Placebo to TIL 100 mg	Placebo to TIL 200 mg
Week 12							
N	32	63		62		NA	NA
DLQI = 0 or 1	3 (9.4)	14 (22.2)	13.7 (−3.3, 27.7; *P* = 0.110)	26 (41.9)	33.1 (14.7, 47.8; *P* = 0.001)	NA	NA
Week 28							
N	NA	62	NA	60	NA	15	14
DLQI = 0 or 1	NA	24 (38.7)	NA	31 (51.7)	NA	8 (53.3)	10 (71.4)

Note: Data are shown as n (%) unless otherwise noted.

Percentages are based on subjects with data.

Difference and CIs are calculated using Miettinen–Nurminen stratified by body weight (≤90 kg, >90 kg) and prior exposure to biologic therapy for psoriasis (yes/no) with sample size weights. *P* values are calculated using the Cochran–Mantel–Haenszel test stratified by body weight (≤90 kg, >90 kg) and prior exposure to biologic therapy for psoriasis (yes/no). *P* values are not adjusted for multiplicity.

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; NA, not applicable; TIL, tildrakizumab.

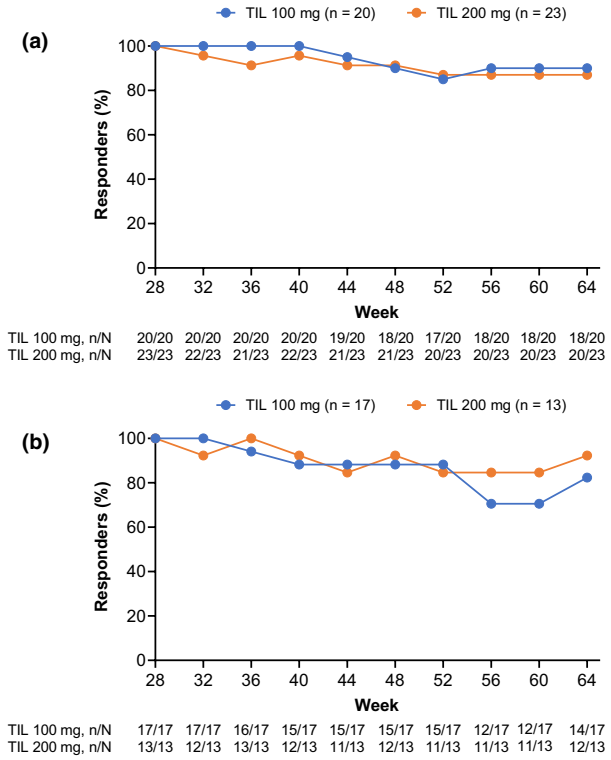

FIGURE 3 Proportions of patients who maintained (a) PASI 75 and (b) PASI 90 responses from week 28 through week 64. PASI, Psoriasis Area and Severity Index; TIL, tildrakizumab

receiving tildrakizumab 200 mg compared with 17/32 (53.1%) of placebo-treated patients (Table 5). After week 12 through week 28, 60/151 (39.7%) patients receiving tildrakizumab 100 or 200 mg experienced an AE; after week 28 to week 64, 101/145 (69.7%) patients receiving tildrakizumab 100 or 200 mg experienced an AE. Rates of SAEs were low during all three parts of the study, with SAEs reported in three (1.9%) patients through week 12, one (0.7%) after week 12 to week 28, and two (1.4%) after week 28 to week 46. No deaths were reported during the study. One patient receiving tildrakizumab 200 mg discontinued the study due to an AE before week 12, and two patients receiving tildrakizumab 100 mg discontinued treatment due to AEs after week 28; of these, an association with treatment could not be ruled out for one AE of psoriasis in a patient receiving tildrakizumab 100 mg that led to discontinuation after week 28. The most common AE was nasopharyngitis.

Three tildrakizumab-treated patients experienced Tier 1 TEAEs. One patient treated with tildrakizumab 200 mg experienced a serious infection (epiglottitis) before week 12. The event was treated with corticosteroids, antibiotics, and tranexamic acid. The AE resolved and did not influence study medication administration. Two patients experienced hypersensitivity reactions, one patient receiving tildrakizumab 200 mg before week 12 and one patient receiving tildrakizumab 100 mg after week 28. Both events were urticaria of mild intensity and were treated with antihistamines. Both events resolved and did not influence study medication administration. There were no solid or hematological malignancies, nonmelanoma skin cancer, melanoma, or MACE reported.

4 | DISCUSSION

Among Japanese patients in reSURFACE 1, treatment with tildrakizumab 100 or 200 mg was associated with a significant increase in the proportions of patients achieving PASI 75, PGA 0/1, and PASI 90 responses and improved skin-related QoL relative to placebo treatment. The proportion of patients achieving PASI 75 at week 12, one of the coprimary endpoints, was numerically lower in patients treated with tildrakizumab 100 and 200 mg (54.7% and 54.8%, respectively) compared with that observed in the overall reSURFACE 1 population (64.2% and 62.3%, respectively). Proportions of patients achieving PGA 0/1, PASI 90, and PASI 100 responses at week 12 were also slightly lower among Japanese patients relative to the overall study population, except PASI 90 in patients receiving tildrakizumab 200 mg. The reasons for this are unclear but may be

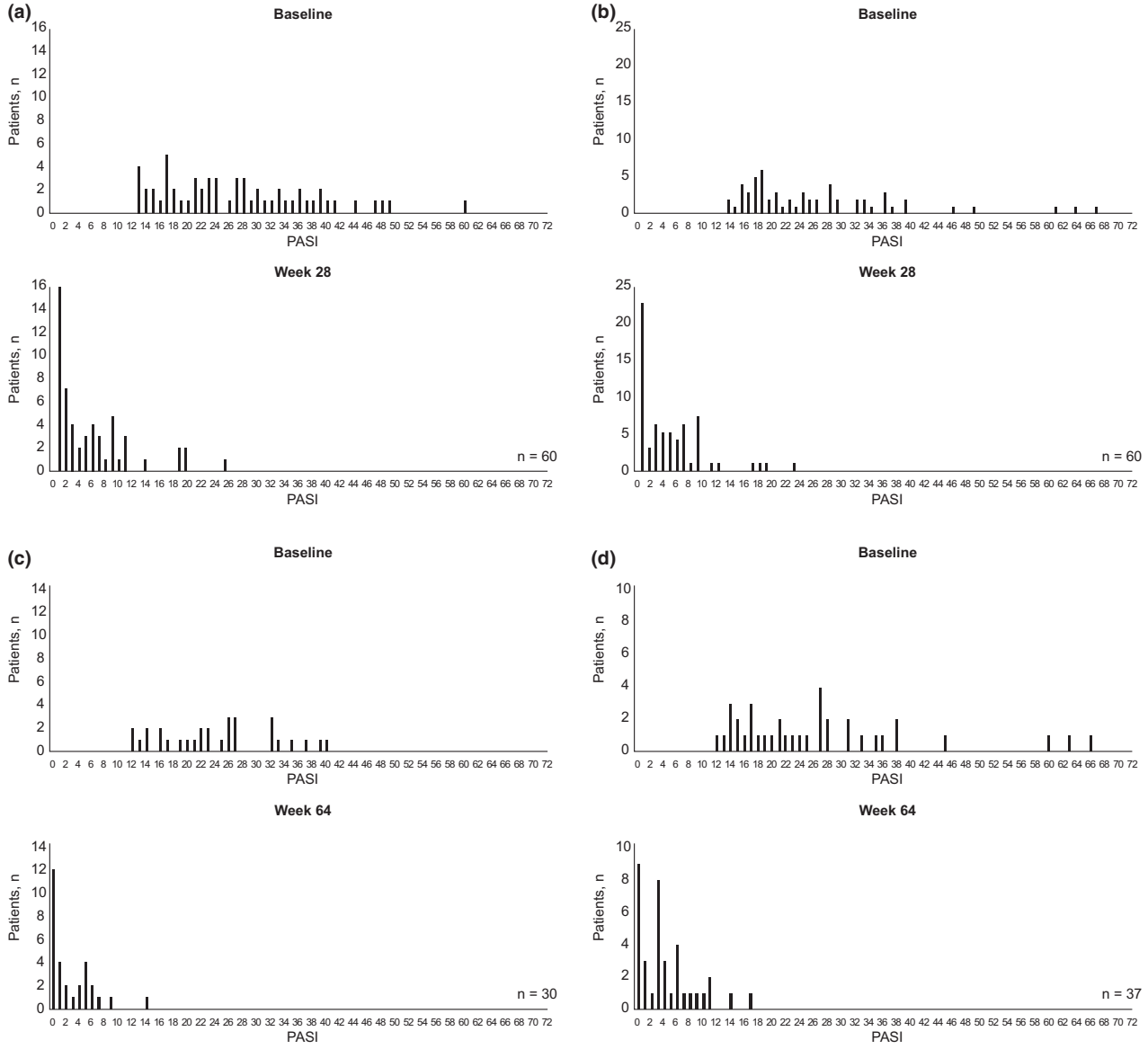

FIGURE 4 Distribution of PASI scores at baseline and week 28 among patients treated with (a) tildrakizumab 100 mg and (b) tildrakizumab 200 mg, and distributions of PASI scores at baseline and week 64 among patients who were responders or partial responders at week 28 receiving (c) tildrakizumab 100 mg or (d) tildrakizumab 200 mg at week 64. PASI, Psoriasis Area and Severity Index

related to the higher PASI scores at baseline for Japanese patients and their greater BSA involvement relative to the overall reSURFACE 1 population. Furthermore, baseline PASI scores were not normally distributed (Figure 4), and outliers could have influenced mean PASI score improvement. In patients with especially high baseline PASI scores, percentage PASI changes from baseline were lower despite a greater improvement of PASI scores, suggesting the change in absolute PASI score is also influenced by the distribution of baseline PASI score.

Tildrakizumab treatment also demonstrated efficacy in patients who were initially randomized to placebo but were rerandomized to tildrakizumab at week 12. These patients tended to achieve responses at numerically higher rates relative to patients treated with tildrakizumab from baseline. This difference may be due to assessment bias; although the blind was maintained, investigators could have suspected the change from placebo to tildrakizumab treatment due to the abrupt change in signs and symptoms after week 12. Alternatively, because the response rates in placebo-treated patients who switched to tildrakizumab treatment at week 12 remained higher relative to patients continuously treated with tildrakizumab from baseline through week 28, it may be more likely that the difference was an artifact of the small number of patients in the subgroups.

The efficacy of tildrakizumab continued to improve over the first 28 weeks of treatment, with maximal improvements achieved between weeks 22 and 28. The responses were durable, with the majority of patients with PASI 75 or PASI 90 responses at week 28 maintaining that response through week 64. These findings were consistent with response patterns in the global reSURFACE 1 population.[6,12] Notably, more than half of patients receiving

TABLE 5 Summary of adverse events and adverse events of special interest through week 64

	Part 1				Part 2			Part 3		
	Placebo	TIL 100 mg	TIL 200 mg	Total	TIL 100 mg	TIL 200 mg	Total	TIL 100 mg	TIL 200 mg	Total
n	32	64	62	158	77	74	151	65	80	145
>1 AE	17 (53.1)	31 (48.4)	23 (37.1)	71 (44.9)	32 (41.6)	28 (37.8)	60 (39.7)	47 (72.3)	54 (67.5)	101 (69.7)
Serious AEs	0	1 (1.6)	2 (3.2)	3 (1.9)	0	1 (1.4)	1 (0.7)	1 (1.5)	1 (1.3)	2 (1.4)
Deaths	0	0	0	0	0	0	0	0	0	0
Discontinued due to an AE	0	0	1 (1.6)	1 (0.6)	0	0	0	2 (3.1)	0	2 (1.4)
Most common AEs										
Nasopharyngitis	1 (3.1)	13 (20.3)	6 (9.7)	20 (12.7)	7 (9.1)	6 (8.1)	13 (8.6)	19 (29.2)	19 (23.8)	38 (26.2)
Pruritus	4 (12.5)	4 (6.3)	0	8 (5.1)	1 (1.3)	0	1 (0.7)	0	5 (6.3)	5 (3.4)
Psoriasis	7 (21.9)	1 (1.6)	0	8 (5.1)	1 (1.3)	2 (2.7)	3 (2.0)	5 (7.7)	6 (7.5)	11 (7.6)
AEs of special interest										
Severe infections	0	0	1 (1.6)	1 (0.6)	0	0	0	0	0	0
Malignancies[a]	0	0	0	0	0	0	0	0	0	0
NMSC	0	0	0	0	0	0	0	0	0	0
Melanoma	0	0	0	0	0	0	0	0	0	0
Confirmed MACE[b]	0	0	0	0	0	0	0	0	0	0
Hypersensitivity reactions	0	0	1 (1.6)	1 (0.6)	0	0	0	1 (1.5)	0	1 (0.7)

Note: Data shown as n (%).

Abbreviations: AE, adverse event; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; TIL, tildrakizumab.

[a]Excluding cervical carcinoma in situ.

[b]Includes nonfatal myocardial infarction, nonfatal stroke, unstable angina, coronary revascularization, and deaths confirmed as "cardiovascular."

tildrakizumab achieved absolute PASI ≤3 and 42%–47% achieved PASI ≤2 at week 28 after three injections, indicating minimal or no disease activity.

Psoriasis has an adverse effect on QoL similar to that of other chronic diseases (e.g. ischemic heart disease, diabetes).[3,13] Both tildrakizumab 100 and 200 mg significantly improved DLQI from baseline relative to placebo, indicating significant improvements in QoL. A greater proportion of these patients achieved a DLQI score of 0 or 1, which is within or approaches the range observed in the general population.[14]

Tildrakizumab treatment was generally well tolerated, with overall rates of AEs similar to or lower than for placebo-treated patients. Only three patients receiving tildrakizumab discontinued treatment before week 64 due to AEs. There were also few SAEs (≤2%) or AEs of special interest (i.e. severe infection, malignancies, skin cancer, MACE, and hypersensitivity) with a single instance of severe infection and two cases of hypersensitivity reactions. The Japanese Dermatological Association notes that treatment with IL-17 inhibitors can cause candidiasis and may be associated with inflammatory bowel disease, but no such risks were observed following tildrakizumab treatment in this study.[3]

Several biologic therapies have been approved for the treatment of psoriasis in Japan. This includes inhibitors of tumor necrosis factor (TNF)-α (adalimumab, infliximab), IL-17 (secukinumab, ixekizumab, and brodalumab), IL-12/23 (ustekinumab), and IL-23 (risankizumab, guselkumab, and now tildrakizumab).[3] As per guidance from the Japanese Dermatological Association, patients ≥16 years of age with plaque psoriasis (with or without psoriatic arthritis) are eligible for treatment with biologics if they are candidates for systemic therapy and they have not adequately responded to standard systemic therapies with rash covering ≥10% of the body surface, or who have refractory skin or joint symptoms that are intractable to standard systemic therapies and associated with significantly impaired QoL.[3]

Anti-TNF-α (adalimumab), anti-IL-17 (secukinumab, ixekizumab), anti-IL-12/23 (ustekinumab), and anti-IL-23p19 (guselkumab, risankizumab) have demonstrated substantial short-term efficacy in the treatment of moderate to severe plaque psoriasis among Japanese patients in phase 2/3 and phase 3 trials.[15-21] Although data specific to Japanese patients are not yet available, several clinical studies demonstrated superior efficacy of IL-23p19 inhibitors compared with placebo or TNF inhibitors.[6,22,23] The IL-17 inhibitor ixekizumab was superior to guselkumab for the proportion of patients with psoriasis who achieved PASI 100 after 12 weeks of treatment.[24] However, in an update of the same study, ixekizumab was noninferior but not superior to guselkumab by week 24 of treatment.[25] In long-term comparisons of IL-23p19 and IL-17 inhibitors, higher proportions of patients with psoriasis treated with guselkumab achieved PASI 90 at week 48 compared with secukinumab-treated patients, and risankizumab was superior to secukinumab for the proportion of patients achieving PASI 90 at week 52.[26,27] These findings

support the long-term benefit of anti-IL-23p19 treatment in patients with psoriasis.

The primary limitation of this study is that it is a post hoc subgroup analysis with a relatively small number of patients. Furthermore, the patient characteristics of the Japanese population differed from that of the overall study population with higher baseline PASI scores and greater BSA involvement among Japanese patients.

5 | CONCLUSION

Despite greater baseline disease severity in Japanese patients relative to the overall reSURFACE 1 population, tildrakizumab treatment resulted in durable efficacy through week 64 and was well tolerated in Japanese patients. Rates of AEs following tildrakizumab treatment were comparable with placebo treatment and similar to the results in the overall population.

ACKNOWLEDGMENTS

The studies were funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Analyses were funded by Sun Pharmaceutical Industries, Inc., Princeton, NJ, USA. Medical writing and editorial support were provided by Judy Phillips, DVM, PhD, of AlphaBioCom, LLC, and funded by Sun Pharmaceutical Industries, Inc.

CONFLICTS OF INTEREST

Dr. Igarashi has received honoraria as a member of an advisory board for AbbVie Inc., Celgene K.K., Eli Lilly Japan K.K., Janssen Pharmaceutical K.K., Maruho Co Ltd., Novartis Pharma K.K., and Sun Pharma Japan Ltd. Dr. Nakagawa received consulting fees and/or speaker honoraria from AbbVie, Janssen Pharmaceutical, Japan Tobacco, Kyowa Kirin, LEO Pharma, Maruho, Torii Pharmaceutical, and UCB Japan. Dr. Morita has received research grants, consulting fees, and/or speaker's fees from AbbVie, Boehringer Ingelheim, Celgene, Eisai, Eli Lilly, Janssen, Kyowa Hakko Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe, Nichi-Iko, Nippon Kayaku, Novartis Pharmaceuticals, Sun Pharmaceutical Industries, Inc., Taiho Pharmaceutical, and Torii Pharmaceutical, Ushio. Dr. Okubo has received research grants from Eisai, Torii, Maruho, and Shiseido, and has current consulting/advisory board agreements, and/or is on a speaker's bureau and/or is an investigator on clinical trials with AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eisai, Eli Lilly, Janssen Pharma, Jimro, Kyowa Kirin, LEO Pharma, Maruho, Novartis Pharma, Pfizer, Sanofi, Sun Pharma, Taiho, Tanabe Mitsubishi, Torii, and UCB Pharma. Dr. Sano has received research grants from AbbVie, Kaken, Kyowa Hakko Kirin, Maruho, Nihon Kayaku, Pola Pharma, Sanofi Aventis, Taiho, and Torii, and speaker's fees from AbbVie, Celgene, Eisai, Eli Lilly, Janssen, Kyowa Hakko Kirin, Maruho, Mitsubishi Tanabe, Novartis Pharma, Sanofi Aventis, Taiho, Torii, and UCB Japan. Dr. Imafuku has received consulting fees and/or honoraria from AbbVie, Eisai, Eli Lilly, Kyowa Kirin, Celgene, Taiho Yakuhin, Tanabe Mitsubishi, Torii Yakuhin, Maruho, LEO pharma, Janssen, and UCB Japan. Dr. Tada has received honoraria for research from Maruho, LEO Pharma, Eisai, AbbVie, Kyowa Hakko Kirin, Celgene, Meiji-Seika-pharma, Taiho, Torii, and Eli Lilly & Co., and for lecturing from Maruho, AbbVie, Taiho, Celgene, Mitsubishi Tanabe Pharma Co., Novartis Pharma K.K., UCB, Kyowa Hakko Kirin, LEO Pharma, Eli Lilly & Co., and Janssen Pharmaceutical. Dr. Honma has no conflict of interest to disclose in compliance with the guidance released by the Japanese Dermatology Association. Dr. Mendelsohn is an employee of Sun Pharmaceutical Industries, Inc.; and has individual shares in Johnson and Johnson, and as part of retirement account/mutual funds. Dr. Kawamura is an employee of Sun Pharmaceutical Japan, Ltd. Dr. Ohtsuki has received honoraria as a member of an advisory board for AbbVie Inc., Boehringer Ingelheim Co Ltd., Bristol-Myers Squibb Company, Celgene K.K., Eisai Co Ltd., Eli Lilly Japan K.K., Janssen Pharmaceutical K.K., Kyowa Hakko Kirin Co Ltd., LEO Pharma K.K., Maruho Co Ltd., Mitsubishi Tanabe Pharma Co., Novartis Pharma K.K., Pfizer Japan Inc., and Sun Pharma Japan Ltd.

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How to cite this article: Igarashi A, Nakagawa H, Morita A, et al. Efficacy and safety of tildrakizumab in Japanese patients with moderate to severe plaque psoriasis: Results from a 64-week phase 3 study (reSURFACE 1). *J Dermatol*. 2021;48:853–863. https://doi.org/10.1111/1346-8138.15789