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Population pharmacokinetic and exposure–response analysis of apremilast in Japanese subjects with moderate to severe psoriasis

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Abstract

Apremilast is an orally available phosphodiesterase 4 inhibitor used for the treatment of moderate to severe psoriasis. The aims of this analysis were to develop a population pharmacokinetic (PPK) model of apremilast based on observed data from phase 1 studies combined with clinical trial data from subjects with moderate to severe psoriasis, and to develop exposure–response (E-R) models to determine whether Japanese subjects with moderate to severe psoriasis achieve response to apremilast treatment similar to that observed in non-Japanese, predominantly Caucasian subjects with moderate to severe psoriasis. The PPK model demonstrated that apremilast plasma concentrations and overall apparent clearance rate were comparable between the Japanese and Caucasian subgroups. The E-R analyses of ≥75% or ≥50% improvement from baseline in Psoriasis Area and Severity Index score and achievement of static Physician Global Assessment score of 0 (clear) or 1 (almost clear) at week 16 indicated that apremilast treatment in Japanese subjects approached the maximal effect with response rates comparable to those in predominantly Caucasian subjects. Overall, the analyses confirm that the approved apremilast 30 mg b.i.d. dose is appropriate for Japanese subjects with moderate to severe psoriasis, with an efficacy profile similar to that previously observed in Caucasian subjects.

KEYWORDS
apremilast, Caucasian, Japan, pharmacokinetics, psoriasis

1 | INTRODUCTION

Psoriasis is a complex inflammatory disease that is mediated by several pro-inflammatory cytokines (e.g., tumor necrosis factor-α [TNF-α], interleukin [IL]-17, and IL-22).[1,2] Plaque psoriasis is reported in approximately 0.34% of the Japanese population, similar to its prevalence in other Asian countries.[3,4] For subjects with moderate to severe disease, long-term treatment may optimize symptom control, but the clinical benefits of drugs widely used in the management of psoriasis are often compromised by safety and tolerability issues, route of administration, and/or inconvenience.[5,6] There is an unmet need for oral therapies that provide long-term efficacy and

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a manageable safety profile for subjects with chronic, moderate to severe psoriasis.

Apremilast, an oral phosphodiesterase 4 inhibitor, regulates the expression of a broad array of pro- and anti-inflammatory genes involved in the pathogenesis of psoriasis, including TNF-α, IL-10, IL-23, IL-17A, and IL-22.[1,2,7–9] In Japan, apremilast is indicated for the treatment of adults with psoriasis vulgaris with an inadequate response to topical therapies, adults with psoriatic arthritis, and adults with oral ulcers associated with Behçet's disease with inadequate response to topical therapies.[10] In a phase 2b randomized, placebo-controlled study in Japanese subjects with moderate to severe plaque psoriasis (PSOR-011), treatment with apremilast resulted in statistically significant and clinically meaningful improvements compared with placebo for the primary end-point, achievement of a 75% or greater reduction from baseline in Psoriasis Area and Severity Index (PASI) score (PASI-75) at week 16.[11] The overall safety and tolerability profile of apremilast was consistent with that observed in the North American/European/Australian clinical trial programs,[12–14] and the dosing recommendation (30 mg b.i.d.) is the same for Japanese and non-Japanese populations.[10,15,16] Although the efficacy and safety of apremilast have been demonstrated in Japanese subjects with moderate to severe plaque psoriasis,[11] the relationship between apremilast exposure and response has not been described in Japanese subjects.

Variability in the activity of the hepatic cytochrome P450 (CYP) enzymes, a major pathway for the metabolism of many medications, can result in drug-exposure differences between race or ethnic populations.[17] Prevalence rates for genotypes or phenotypes associated with reduced CYP activity have been reported to vary between racial or ethnic groups, and differences between Japanese and Caucasian populations specifically have been documented.[17–21] Population differences in rates of drug metabolism, or plasma drug kinetics, can result in lower or higher than expected plasma drug levels and, consequently, may affect drug efficacy and safety such that dosing differences might be warranted.[18,19,22,23] Apremilast is extensively metabolized by both CYP- and non-CYP-mediated pathways; CYP-mediated metabolism is primarily via CYP3A4, with minor contributions from CYP1A2 and CYP2A6.[24,25] Because differences between Japanese and non-Japanese populations in the incidence of reduced- or enhanced-activity genotypes or phenotypes associated with each of these enzymes have been reported,[18] differences between Japanese and non-Japanese subjects in drug exposure and efficacy or safety during treatment with apremilast might occur. To date, there are no head-to-head pharmacokinetic (PK) or efficacy comparisons between Japanese and non-Japanese populations available to directly address this issue.

Population PK (PPK) modeling is an effective tool for determining indirectly whether potential differences between populations, such as age, disease state, or race, are expected to affect plasma drug levels.[26] Although non-compartmental methods can be used to estimate PK parameters, such as peak plasma drug concentration (C_{max}) and drug exposure over time (estimated as the area under the plasma concentration vs time curve [AUC]) for a study population, a PPK model incorporates observed data from multiple studies to provide estimates of PK parameters and describe the expected effect of demographic or clinical factors on PK, based on those data.[26] Similarly, an exposure–response (E-R) model can be used to explore the relationship between plasma drug levels and the probability of achieving efficacy outcomes or experiencing adverse effects, and predict whether those probabilities differ based on subjects' demographic or clinical characteristics.[27] PPK and E-R analyses are powerful tools to compare drug exposure and responses between ethnic populations.

The aims of this analysis were to develop PPK and E-R models to determine whether Japanese subjects with moderate to severe psoriasis display similar plasma drug concentration profiles and a comparable response to apremilast treatment versus non-Japanese, predominantly Caucasian subjects with moderate to severe psoriasis. Plasma apremilast concentrations obtained in PSOR-011 were first analyzed using non-compartmental methods to describe the PK of apremilast in Japanese subjects and then combined with data from Caucasian studies (used previously in developing an apremilast PPK model in Caucasians) to explore any differences in apremilast PK between Japanese and Caucasian populations. Finally, an E-R model was developed to determine whether Japanese subjects with moderate to severe psoriasis treated with apremilast would be expected to achieve efficacy outcomes that were similar to outcomes in non-Japanese subjects over the same drug concentration range.

2 | METHODS

2.1 | Source data

2.1.1 | Japanese subjects

Pharmacokinetic, efficacy, and tolerability data for Japanese subjects with moderate to severe psoriasis were obtained from the phase 2b multicenter, randomized, double-blind, placebo-controlled study PSOR-011 (ClinicalTrials.gov: NCT01988103), conducted at academic and community hospitals in Japan. Enrollment criteria, study design, and procedures have been described in detail.[11] Briefly, enrolled subjects were adults aged 20 years or older diagnosed with chronic, moderate to severe plaque psoriasis (PASI score ≥12, psoriasis-involved body surface area [BSA] ≥10%) for at least 6 months that was considered inappropriate (based on severity or extent of affected area) for topical therapy, or not adequately controlled by topical therapy despite at least 4 weeks of prior treatment (or per label) with one or more topical therapies for psoriasis. The study design included a 16-week, placebo-controlled period followed by a 52-week, randomized, double-blind apremilast treatment period (Figure 1). Eligible subjects were initially randomized (1:1:1) to placebo, apremilast 20 mg b.i.d., or apremilast 30 mg b.i.d. for 16 weeks. At week 16, subjects entered the double-blind apremilast treatment phase, in which subjects in the apremilast 20 and 30 mg b.i.d. groups continued treatment and subjects previously assigned to placebo were re-randomized (1:1) to apremilast 20 or 30 mg b.i.d., with titration; double-blind dosing was maintained to week 68.
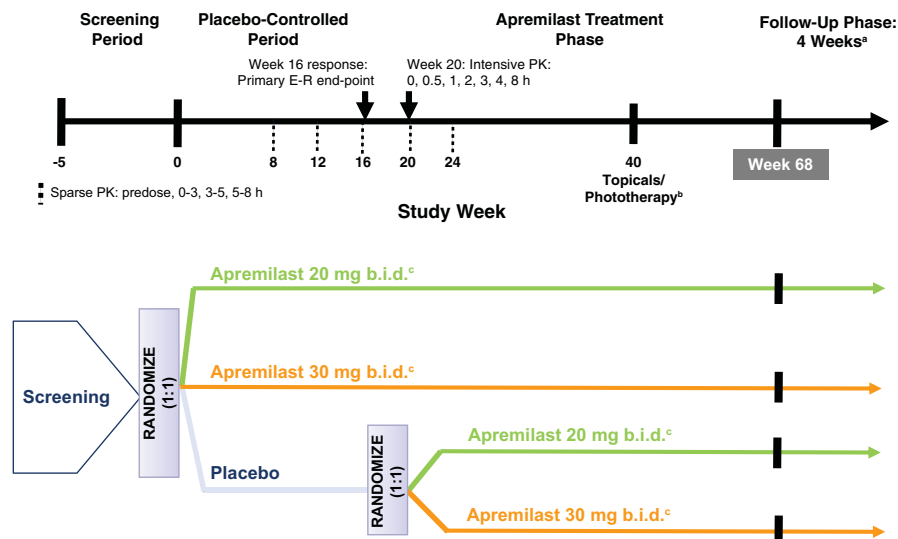
FIGURE 1 Study design for the phase 2b study enrolling Japanese subjects with moderate to severe psoriasis (PSOR-011). [a]Every subject was to enter a 4-week post-treatment observational follow-up phase at the time the subject completed or discontinued the study. [b]Starting at week 40, all non-responders (<PASI-50) had the option of adding topical therapies and/or phototherapy, at the discretion of the investigator. [c]Doses of apremilast were titrated during the first week of administration and at week 16 when placebo subjects were switched to apremilast. b.i.d., twice daily; E-R, exposure-response; PASI, Psoriasis Area and Severity Index; PASI-50, ≥50% reduction from baseline in PASI score; PK, pharmacokinetic

2.1.2 | Non-Japanese subjects

Plasma apremilast concentrations from non-Japanese individuals included in the PPK analysis were obtained from six phase 1 studies enrolling healthy adult subjects (five studies) or subjects with psoriasis, psoriatic arthritis, or rheumatoid arthritis (one study) and from a phase 2b multicenter, randomized, double-blind, placebo-controlled, dose-ranging, efficacy and safety study (PSOR-005; ClinicalTrials.gov: NCT00773734) and a phase 3 multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study (PSOR-008 [ESTEEM 1]; ClinicalTrials.gov: NCT01194219), each enrolling subjects with moderate to severe psoriasis. All studies enrolling non-Japanese individuals were conducted in Europe, Australia, and/or North America. Non-Japanese subjects in the six phase 1 apremilast studies received multiple apremilast 30 or 50 mg b.i.d. doses, or single p.o. doses of apremilast 20, 30, 40, or 50 mg. Details of each study are presented in Table 1.[11,12,14,28–32] Response (efficacy and safety) data from non-Japanese subjects for the E-R analysis were obtained from subjects with moderate to severe psoriasis treated with apremilast (10, 20, or 30 mg b.i.d.) or placebo in the PSOR-005 and PSOR-008/ESTEEM 1 studies.

2.2 | Sampling and bioanalytical methods

In the PSOR-011 Japanese study, blood samples for PK analysis were obtained from subjects in the placebo and apremilast groups. Subjects in the intensive PK sampling group provided blood samples at week 20 at predose and 0.5, 1.0, 2.0, 3.0, 4.0, and 8.0 h after the morning dose. Subjects in the sparse sampling group provided one or more samples from each of four time windows (predose or 0–3 h, 3–5 h, or 5–8 h after the morning dose) during scheduled clinic visits at weeks 8, 12, 16, 20, and 24. In non-Japanese subjects, sparse (PSOR-005 and PSOR-008/ESTEEM 1) and intensive (PSOR-005 only) samples were collected according to the sampling schemes listed in Table 1. Sampling schemes for the six phase 1 PK studies in non-Japanese subjects are also shown in Table 1.

Apremilast PK samples were analyzed using validated liquid chromatography/mass spectrometry methods with a lower limit of quantitation (LOQ) of 1.00 ng/mL (see Appendix S1 for further details).[29]

2.3 | Non-compartmental PK analysis

Pharmacokinetic parameters of apremilast in Japanese subjects following p.o. administration of apremilast 20 and 30 mg b.i.d. were calculated using non-compartmental analysis with WinNonlin 5.2 NCA model 200 software (Pharsight). AUC from time 0 (predose) to 8 h (AUC_{0-8}) and from time 0 to tau (AUC_τ), where tau = 12 h, were calculated using the trapezoid rule; C_{max}, time to C_{max} (T_{max}), and trough (minimum) plasma concentration (at the predose time point [C_{min}]) were observed directly from the data. The terminal (or disposition) rate constant was calculated from the slope of the terminal log-linear portion of the plasma concentration versus time curve and terminal (or disposition) half-life was calculated as $\ln 2/\lambda_z$. Apparent systemic clearance at steady state (CL_{ss}/F) was calculated as dose/AUC_τ and apparent central volume of distribution at steady state (V_{ss}/F) was

TABLE 1 Clinical studies included in the PPK and E-R models

Population and analyses	Study and country/region	Study description	Number of subjects	Apremilast dosing	PK sampling	Number of PPK samples included
Japanese subjects	PSOR-011[11] Japan	Phase 2b, in Japanese subjects with moderate to severe psoriasis	PPK: n = 104 E-R: n = 254	20 and 30 mg b.i.d.	Sparse: weeks 8, 12, 16, 20, and 24; at predose, 0–3 h, 3–5 h, or 5–8 h. Intensive: week 20: at predose, 0.5, 1, 2, 3, 4, and 8 h	651
Non-Japanese subjects, PPK and E-R analyses	PSOR-005[14] North America	Phase 2b, in subjects with moderate to severe psoriasis	PPK: n = 67 E-R: n = 335	10, 20, and 30 mg b.i.d.	Sparse: weeks 4, 6, 8, 10, 12, 16, 18, 20, and 22. Intensive: weeks 14 and 24; predose and 0.5, 1, 2, 3, 4, and 8 h	619
	PSOR-008/ESTEEM 1[12] North America, Europe, and Australia	Phase 3, in subjects with moderate to severe psoriasis	PPK: n = 166 E-R: n = 844	30 mg b.i.d.	Sparse: weeks 24, 32, 36, 40, 44, and 48; predose or after AM dose	513
Non-Japanese subjects, PPK analysis only	PK-008[28] USA	Phase 1, healthy adult males	PPK: n = 56	Days 1–4: 30 or 50 mg b.i.d. Day 5: single p.o. dose 30 or 50 mg	Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 12, and 23 h post-dose	1080
	PK-010[29] USA	Phase 1, subjects with psoriasis, psoriatic arthritis, or rheumatoid arthritis, receiving stable p.o. doses of methotrexate for ≥3 months	PPK: n = 14	Days 3–9: 30 mg b.i.d.	Trough: Day 6 before PM dose. Day 7: pre-AM dose, 0.5, 1, 1.5, 2, 3, 4, 6, 9, and 12 h post-AM dose. Day 8: pre-AM dose, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, and 48 h post-AM dose	289
	CP-022[30] USA	Phase 1, healthy adult females and males	PPK: n = 46	Single p.o. dose 30 mg (fasted/fed)	Predose, 0.5, 1, 1.5, 2, 2.5, 3, 5, 8, 12, 24, 36, and 48 h	1061
	CP-024 USA	Phase 1, healthy adult females and males 65–85 years of age	PPK: n = 36	Single p.o. dose 30 mg (fasted)	Predose, 0.5, 1, 1.5, 2, 2.5, 3, 5, 8, 12, 24, 36, and 48 h	430
	BA-001[31] UK	Phase 1, healthy adult males	PPK: n = 12	Single p.o. dose: 20 mg	Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 h post-dose	298
	BA-002[32] Canada	Phase 1, healthy adult males	PPK: n = 16	Single p.o. dose: 40 mg tablet or 2 × 20 mg capsules	Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 h post-dose	763

Abbreviations: AM, before noon; b.i.d., twice daily; E-R, exposure-response; PK, pharmacokinetic; PPK, population pharmacokinetic; p.o., orally.

calculated from CL$_{ss}$/F. Concentration values below the LOQ were set to 0 for the non-compartmental PK analyses. Plasma apremilast concentrations and PK parameters at week 20 were summarized using descriptive statistics for each apremilast dose group.

2.4 | Population PK analysis

Population PK analysis was undertaken to identify clinically relevant covariates, such as bodyweight, sex, age, or smoking history, that can impact dose–concentration relationships. The PPK model included the following elements: a base structural PK model to describe the relationship between plasma concentration and time (excluding effects of factors such as demographic or clinical characteristics on PK); a variance component describing between-subject variability in model parameters; and residual unexplained variability representing the sum of all variability that is not explained by the model, including bioanalytical variability, experimental noise, and variability that cannot be explained by the structural PK model. Model development was carried out in the following steps: (i) a base structural model was selected; (ii) a covariate analysis was performed to identify statistically significant sources of variability in plasma apremilast concentrations; (iii) the performance of the model, including covariates, was evaluated; and (iv) individual estimates of PK parameters and exposure for apremilast were calculated from the model for use in the subsequent E-R analysis. PPK model development and evaluation methods are summarized here and reported in detail in Appendix S2.

The PPK structural model (data on file; Celgene, CC-10004-PSOR-008-PK) used in the current analysis was based on a previously developed one-compartment PPK model for apremilast that used data from non-Japanese subjects enrolled in the six phase 1 studies and non-Japanese subjects with moderate to severe psoriasis enrolled in PSOR-005 (phase 2b) and PSOR-008/ESTEEM 1 (phase 3; see Appendix S3 for further details). This previously developed (non-Japanese) PPK model was selected as the base structural PK model for the current analysis and reevaluated to include plasma apremilast concentration data collected from subjects in the phase 2b Japanese study (PSOR-011) (Table 1). Apremilast concentration values below the LOQ (≤1.00 ng/mL) were excluded from the PPK analysis. No imputations for excluded values were performed. The base model was evaluated and validated based on standard statistical criteria of goodness-of-fit criteria and data visualization using diagnostic plots.

Covariates examined in this analysis included age (years), sex, race, bodyweight (kg), body mass index (kg/m^2), serum creatinine (mg/dL), potential drug–drug interaction, smoking status, disease status, apremilast dose (mg), total daily apremilast dose (mg), baseline calculated creatinine clearance (mL/min), ideal bodyweight (kg), and lean bodyweight (kg). Race was recorded as Caucasian, Japanese, black or African American, or other and tested in the model as Japanese versus non-Japanese. Disease status was coded as psoriasis, healthy, or other; other included

subjects with psoriatic arthritis or rheumatoid arthritis in one phase 1 study.[29] Potential drug–drug interactions included were previous methotrexate therapy and co-medication with CYP1A2 or CYP3A inducers or inhibitors. Covariates that statistically significantly improved the fit of the model to the data were retained in the final model using a stepwise forward inclusion and backward elimination approach.

The final PPK model was evaluated with non-parametric bootstrap resampling and visual predictive check (VPC), which allowed for a visual comparison between apremilast PK profiles from the simulations versus the observed profiles derived from the original datasets. Estimates of individual PK parameters and exposure after repeated administration of apremilast (steady-state, week 20; AUC$_{\tau,ss}$, C$_{max,ss}$, and C$_{min,ss}$) were obtained from the final PPK model.

2.5 | Exposure–response analysis

The E-R analysis included response data from non-Japanese subjects with moderate to severe psoriasis in PSOR-005 and PSOR-008/ESTEEM 1 and Japanese subjects with moderate to severe psoriasis in PSOR-011 who received either placebo or apremilast (10, 20, or 30 mg b.i.d.) and had data available for at least one response outcome (i.e., proportion of subjects who achieved PASI-75, PASI-50, or static Physician Global Assessment [sPGA] response [i.e., score of 0, clear; or 1, minimal]) during the designated analysis period (from weeks 2 to 24 in PSOR-005, from weeks 2 to 16 in PSOR-008/ESTEEM 1, and from weeks 2 to 40 in PSOR-011). The PASI and sPGA are key assessment tools for evaluating efficacy in clinical trials for psoriasis therapies,[33] and PASI-75 was the primary efficacy end-point in PSOR-005, PSOR-008/ESTEEM 1, and PSOR-011; PASI-50 and sPGA response were also included as efficacy end-points in each study.

Apremilast exposure measures included in the E-R analysis were AUC$_{\tau,ss}$, C$_{max,ss}$, and C$_{min,ss}$ values predicted from the apremilast PPK analysis. The primary end-point for the E-R analysis was proportion of subjects achieving PASI-75 at week 16 (at the apparent plateau for response). Proportions of subjects achieving PASI-50 and sPGA response at week 16 were secondary end-points. Initially, a safety response outcome based on adverse events (AE) was planned for the E-R analysis; however, due to the low frequencies of treatment-emergent AE, an analysis of exposure AE was not performed.

The relationships between individual apremilast exposure and probabilities of PASI-75, PASI-50, and sPGA response over time were first explored graphically. Individual apremilast exposure measures generated based on the final apremilast PPK model were linked to response variables using logistic regression. Differentiation and selection of E-R models were performed in a manner similar to the PPK analysis using visual and statistical methods.[26] The performance of the models was evaluated with VPC. Further details on the development of the E-R models are described in Appendix S4.

3 | RESULTS

3.1 | Non-compartmental PK analysis (Japanese subjects)

Serial blood samples were collected in a subset of 41 subjects in the Japanese study (PSOR-011) at week 20 (14 subjects in the 20 mg b.i.d. group; 15 subjects in the 30 mg b.i.d. group; and 12 subjects in the placebo b.i.d. group who had been rerandomized to 20 mg b.i.d. [$n = 7$] or 30 mg b.i.d. [$n = 5$] at week 16). For 17 subjects, the slope of the terminal phase (λ_z) was not assessable and therefore CL_{ss}/F, V_{ss}/F, and $t_{1/2}$ were not calculated (≤2 PK assessments after C_{max} [15 subjects]; $R^2 < 0.8$ for the log-linear regression in the terminal elimination phase of the concentration-time profile, whereas $R^2 ≥ 0.8$ was a prespecified condition to derive λ_z [two subjects]).

Mean (standard deviation [SD]) plasma concentration-time profiles of apremilast at week 20 in Japanese subjects, assessed following the morning dose of 20 or 30 mg b.i.d., are presented in Figure 2; non-compartmental plasma apremilast PK parameters are summarized in Table 2. Geometric mean AUC_τ (where $_\tau$ is 12 h) was 1957 ng·h/mL for the 20 mg b.i.d. group and 2397 ng·h/mL for the 30 mg b.i.d. group. Peak plasma concentrations were 304 and 374 ng/mL for the 20 and 30 mg b.i.d. groups, respectively; and week 20 trough values were 91 and 104 ng/mL, respectively. Median T_{max} was approximately 2 h post-dose for both apremilast dose groups.

3.2 | Population PK analysis (six phase 1 studies, three phase 2b/3 studies)

Baseline demographics and clinical characteristics for the phase 1 (non-Japanese healthy subjects) and phase 2b/3 (Japanese and non-Japanese subjects with moderate to severe psoriasis) studies included in the PPK analysis are summarized in Table 3. The combined data from the nine studies yielded a total of 5752 samples collected from 517 subjects; 48 samples that had values below the LOQ were excluded from the analysis, leaving a total of 5704 samples. Among those, 651 samples were from 104 Japanese subjects with psoriasis and 5053 samples were from non-Japanese subjects (233 subjects with psoriasis and 180 healthy subjects).

The base PK model was defined in terms of apparent clearance (CL/F), first-order absorption rate constant (Ka), lag time of absorption, and apparent central volume of distribution (Vc/F), with a mixed residual error model, and a block estimated variance on CL/F and Vc/F and a separate estimated variance on Ka. The apremilast PPK parameters predicted from the final model and effects of the covariates included in the model are summarized in Table 4. Diagnostic plots that compared observed plasma apremilast concentrations with concentrations predicted by the final apremilast PPK model with covariates demonstrated that the individual predicted concentrations were adequately fitted with the model (Figure S1). The 5th, 50th, and 95th percentiles of the observed concentration data for Japanese subjects were generally contained within the respective 95% confidence interval (CI) of the simulated data by the final PPK model (Figure S2).

Covariates that statistically significantly improved the model performance and were included in the final model were the effect of bodyweight on Vc/F, and effects of disease status, sex, age, and race on CL/F. The effect of bodyweight on Vc/F was described as (weight/82)$^{0.591}$, indicating that Vc/F would be 29% lower (yielding a greater proportion of drug in plasma) in a 45.5-kg individual and approximately 14% greater (yielding a smaller proportion of drug in plasma) in a 102-kg individual compared with a typical 82-kg individual. Psoriasis is expected to reduce CL/F by 0.834 or approximately 17% in subjects with psoriasis compared with healthy subjects. The effect of sex predicts that CL/F is 1.25-times faster in males versus females, and the effect of age indicates that apremilast clearance decreases with increasing age as described by the relationship (age/45)$^{-0.148}$. According to this equation, clearance is expected to be 14% faster in a 19-year-old than in a typical 45-year-old individual, and 8% slower in an 80-year-old compared with a 45-year-old. The effect of race on CL/F indicates that rate
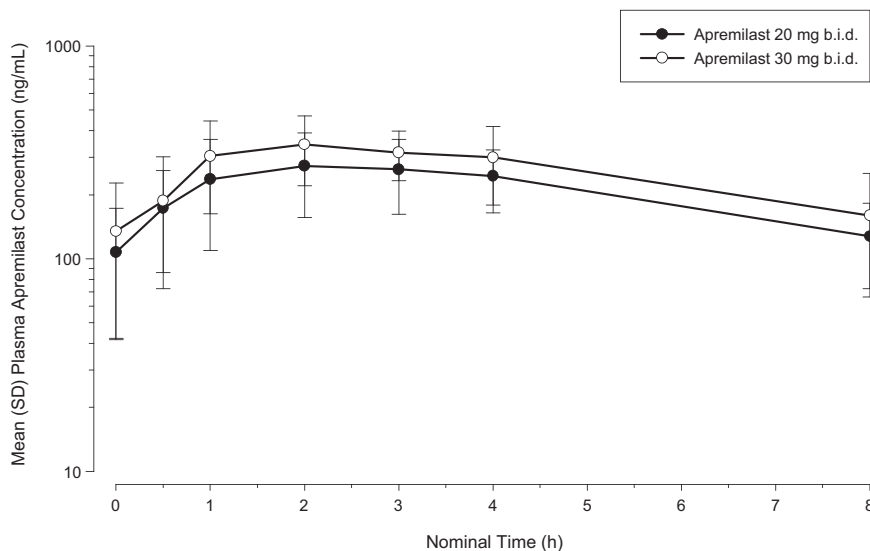

FIGURE 2 Mean (standard deviation) plasma concentration-time profiles of apremilast in Japanese subjects (PSOR-011) following morning dose after multiple p.o. dosing (week 20). b.i.d., twice daily

TABLE 2 Summary statistics of non-compartmental plasma PK parameters of apremilast at week 20 by non-compartmental analysis, Japanese subjects (*n* = 41)

	Geometric mean (CV% geometric mean)	
	20 mg b.i.d., *n* = 21	30 mg b.i.d., *n* = 20
AUC_{0-8} (ng·h/mL)	1599 (36.9)	1967 (36.3)
AUC_τ (ng·h/mL)	1957 (38.7)	2397 (39.5)
C_{max} (ng/mL)	304 (30.8)	374 (32.0)
C_{min} (ng/mL)	90.8 (50.1)	104 (66.6)
T_{max}^a (h)	2.03 (1.00, 4.00)	2.00 (0.98, 4.00)
$t_{1/2}$ (h)	4.31 (43.6)[b]	4.06 (23.6)[c]
CL_{ss}/F (L/h)	10.0 (39.9)[b]	12.9 (34.1)[c]
V_{ss}/F (L)	68.0 (42.6)[b]	83.1 (32.2)[c]

Abbreviations: AUC_{0-8}, area under the plasma concentration time-curve from 0 to 8 h after a dose; AUC_τ, area under the concentration time-curve from time 0 to tau over a dosing interval at steady state, where tau = 12 h and the concentration at 12 h is calculated as C_{last} · $e^{-\lambda}(12\text{-}t_{last})$, where C_{last} and t_{last} are the last observed concentration and time; b.i.d., twice daily; CL_{ss}/F, apparent systemic clearance at steady state; C_{max}, peak plasma concentration at steady state; C_{min}, predose (minimum) plasma concentration at steady state; CV, coefficient of variation; *n*, number of subjects; $t_{1/2}$, terminal (or disposition) half-life; T_{max}, time of C_{max} at steady state; V_{ss}/F, apparent central volume of distribution at steady state.

[a]Median (minimum, maximum).

[b]*n* = 11.

[c]*n* = 13.

of clearance for apremilast in a Japanese individual is predicted to be 1.17 -times the clearance rate in a non-Japanese individual. The magnitude of the covariate effects, however, are small and within the between-subject variability for CL/F or for Vc/F. Therefore, the predicted CL/F in Japanese subjects with moderate to severe psoriasis was considered comparable with CL/F in non-Japanese subjects (Figure 3).

The effect of race on apremilast concentration-time profiles was further examined by performing simulations for apremilast 20 and 30 mg b.i.d. at steady-state in Japanese and non-Japanese subjects with moderate to severe psoriasis. Predicted PK parameter values based on the final model for Japanese versus non-Japanese subjects with moderate to severe psoriasis are summarized in Table 5. Model-based apremilast plasma concentration-time profiles for Japanese and non-Japanese subjects were largely overlapping (Figure 4).

3.3 | Exposure–response analysis (three phase 2b/3 studies)

A total of 9087 observations of PASI-75 and PASI-50 response from 1433 subjects, and 9094 observations of sPGA response

from 1442 subjects, were included in the E-R analysis. For PASI-75, PASI-50, and sPGA response, exposure was described in terms of AUC_{ss} from the PPK model. The sPGA response model was the only model that was improved by including an effect of race (Japanese vs Caucasian; described below), which had a significant effect on both placebo and drug response. Diagnostic plots comparing observed and predicted rates of PASI response over time demonstrated that observed data were well predicted by the models (Figure S3; see Appendix S5 for additional information on the E-R models for PASI-75 and PASI-50).

The E-R models were used to predict the probability of response based on PASI-75, PASI-50, and sPGA (0 or 1) at median PPK model generated $AUC_{\tau,ss}$ values for apremilast doses of 10, 20, and 30 mg b.i.d. Median week 16 apremilast exposure levels derived from the PPK model were 1065.4 ng·h/mL for subjects receiving apremilast 10 mg b.i.d., 2030.6 ng·h/mL for subjects receiving 20 mg b.i.d., and 3169.2 ng·h/mL for subjects receiving 30 mg b.i.d. At those median exposure levels, the E-R models predicted 19.0%, 28.6%, and 36.5% probabilities of achieving PASI-75 response at week 16 (vs 6.1% with placebo) for apremilast doses of 10, 20, and 30 mg b.i.d., respectively. The same exposure levels for apremilast 10, 20, and 30 mg b.i.d. were predicted to result in 43.8%, 55.3%, and 62.8% probabilities of achieving PASI-50 response (vs 20.0% with placebo) and 16.2%, 22.7%, and 27.3% probabilities of achieving sPGA response at week 16 (vs 5.0% for placebo).

For the PASI-75 and PASI-50 response measures, apremilast treatment in Japanese subjects approached the maximal effect, and the probability of achieving response at typical exposure levels for apremilast 20 and 30 mg b.i.d. was similar in Japanese and non-Japanese subjects, as shown in Figure 5. For sPGA, the typical, model-derived exposure levels produced by apremilast 20 and 30 mg b.i.d. would result in a 33.8% probability of response at 20 mg b.i.d. and a 37.5% probability at 30 mg b.i.d. in Japanese subjects compared with 22.7% and 27.3% probabilities at 20 and 30 mg b.i.d. in non-Japanese subjects (14.1% and 5.0% probabilities, respectively, with placebo). Probability of response based on separate Japanese and non-Japanese model-derived exposure values for median $AUC_{\tau,ss}$ yielded similar results for apremilast 10, 20, and 30 mg b.i.d. (Table S1). In the final E-R models for PASI-75, PASI-50, and sPGA response, there were no observed differences between Japanese and non-Japanese subjects in expected effects of 0 exposure (time 0 in placebo subjects [intercept]), placebo response, change in placebo response over time ($K_{placebo}$), or maximal effect of apremilast (at infinite exposure; E_{max}) (Table S2). Exposures needed to achieve half of the maximal drug effect (E_{50}, measured as $AUC_{\tau,ss}$) estimated from the final models were 1733, 1656, and 1110 ng·h/mL for PASI-75, PASI-50, and sPGA response, respectively (Table S2). In Japanese subjects, the recommended therapeutic apremilast dose of 30 mg b.i.d. is expected to achieve $AUC_{\tau,ss}$ of 2727.2 ng·h/mL, which meets and exceeds the E_{50} values for PASI-75, PASI-50, and sPGA response by approximately 57%, 65%, and 146%, respectively.

TABLE 3 Baseline demographic and clinical characteristics for the PPK analysis population

Study number Population	BA-001, n = 12 Healthy subjects	BA-002, n = 16 Healthy subjects	PK-008, n = 56 Healthy subjects	PK-010, n = 14[a] Other subjects[b]	CP-022, n = 46 Healthy subjects	CP-024, n = 36 Healthy subjects	PSOR-005, n = 67 Psoriasis patients	PSOR-008/ESTEEM 1, n = 166 Psoriasis patients	PSOR-011, n = 104 Japanese psoriasis patients
Age, y, mean (CV%)	28.0 (15.2)	34.0 (30.1)	29.4 (27.5)	51.6 (19.5)	38.5 (35.0)	52.4 (36.7)	46.5 (28.6)	49.1 (27.6)	51.4 (24.1)
Weight, kg, mean (CV%)	77.0 (11.0)	77.3 (13.2)	82.8 (12.1)	81.1 (10.5)	75.3 (16.6)	77.7 (13.6)	96.3 (22.3)	94.9 (21.2)	70.2 (18.2)
Height, cm, mean (CV%)	177 (2.4)	176 (3.8)	179 (3.7)	168 (5.0)	169 (5.6)	170 (5.6)	172 (5.4)	172 (5.5)	167 (5.2)
BMI, kg/m², mean (CV%)	24.5 (10.6)	25.0 (11.2)	25.8 (11.1)	28.6 (9.7)	26.3 (12.6)	26.9 (9.0)	32.6 (21.3)	32.1 (20.1)	25.3 (16.3)
CRCL, mL/min, mean (CV%)	123 (13.7)	121 (19.0)	140 (20.1)	105 (21.3)	122 (21.0)	102 (27.6)	148 (38.5)	138 (34.6)	111 (25.9)
Male, n (%)	12 (100.0)	16 (100.0)	56 (100.0)	4 (28.6)	21 (45.7)	16 (44.4)	42 (62.7)	114 (68.7)	78 (75.0)
Race, n (%)									
Caucasian	7 (58.3)	15 (93.8)	35 (62.5)	12 (85.7)	31 (67.4)	24 (66.7)	66 (98.5)	155 (93.4)	0 (0.0)
Black/African American	3 (25.0)	1 (6.2)	20 (35.7)	2 (14.3)	13 (28.3)	11 (30.6)	0 (0.0)	4 (2.4)	0 (0.0)
Japanese	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	104 (100.0)
Smokers[c], n (%)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	20 (29.9)	49 (29.5)	35 (33.7)

Abbreviations: BMI, body mass index; CRCL, creatinine clearance; CV, coefficient of variation; E-R, exposure–response; PPK, population pharmacokinetic.

The E-R population included only subjects with moderate to severe psoriasis treated with apremilast (PSOR-005, PSOR-008/ESTEEM 1, and PSOR-011; shaded).

[a]One subject from PK-010 had all continuous covariates missing except age.

[b]Other = rheumatoid arthritis and psoriatic arthritis.

[c]Smoking is generally prohibited in phase 1 studies.

TABLE 4 PK parameters of apremilast derived from the final PPK model based on six phase 1 studies and three phase 2b and 3 studies ($n = 533$)

PPK parameter	Typical values (RSE %) for model parameters and covariate effects	Between-subject variability (RSE %)
CL/F, L/h	9.25 (3.4)	38.0 (4.3)
Disease status: psoriasis[a]	0.834 (4.0)	n/a
Sex: male[b]	1.25 (2.9)	n/a
Race: Japanese[c]	1.17 (4.3)	n/a
Age[d]	$(age/45)^{-0.148\ (26.9)}$	n/a
Vc/F, L	115 (2.2)	27.1 (6.1)
Bodyweight, kg[e]	$(weight/82)^{0.591\ (13.7)}$	n/a
Ka, h^{-1}	1.83 (11.7)	83.4 (8.7)
Lag, h	0.290 (11.7)	0 fix (n/a)
Error model		
Proportional error, %	36.5 (2.6)	n/a
Additive error, ng/mL	0.658 (30.0)	n/a

Abbreviations: CL/F, apparent clearance; Ka, first-order rate of absorption; Lag, lag time of absorption; n/a, not applicable; PK, pharmacokinetic; PPK, population pharmacokinetic; RSE, relative standard error; Vc/F, apparent central volume of distribution.

[a]For patients with psoriasis, CL/F = 0.834 · 9.25 L/h (typical value).

[b]For males, CL/F = 1.25 · 9.25 L/h.

[c]For Japanese individuals, CL/F = 1.17 · 9.25 L/h.

[d]CL/F decreases with increasing age, varying from 9.25 L/h for a typical 45-year-old according to the equation given.

[e]Vc/F increases with increasing bodyweight, varying from 9.25 L/h for a typical individual of 82 kg according to the equation given.
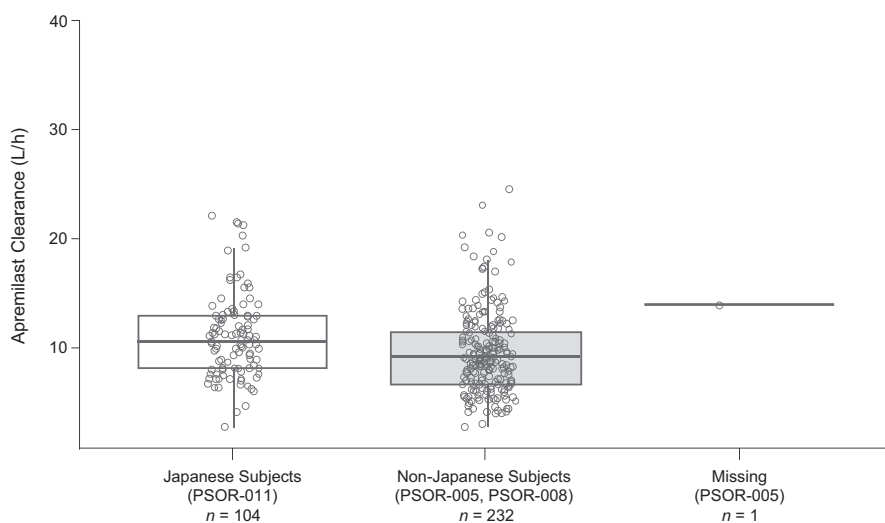

FIGURE 3 Apremilast clearance (L/h) in Japanese versus non-Japanese subjects with moderate to severe psoriasis. Open circles, individual derived CL/F values; horizontal line, median predicted CL/F; box, interquartile range; whiskers extend to highest and lowest CL/F values. CL/F, apparent clearance

4 | DISCUSSION

Population PK modeling and E-R analysis are valuable tools for understanding differences between populations in drug kinetics and exposure, and the potential clinical impact of variability in drug response, particularly when limited data are available for directly comparing populations within a single study.[26,27,34] In the current analysis, the methods were used together to determine whether the PK profile of apremilast is similar in Japanese and non-Japanese subjects and whether dosing recommendations

for apremilast in non-Japanese subjects are also appropriate for Japanese subjects.

The PK profile of apremilast determined for Japanese subjects in PSOR-011 using non-compartmental methods was similar to PK reported for Caucasian study populations. Apremilast was rapidly absorbed, with T_{max} occurring at approximately 2 h post-dose. Mean AUC_{τ} and C_{max} of apremilast increased with dose but not in a dose-proportional manner (~1.2-times increase with an increase in dose from 20 to 30 mg b.i.d.). Peak plasma concentration after administration of apremilast 30 mg b.i.d. was 374 ng/mL, and time to peak

TABLE 5 PK parameters with apremilast 20 mg b.i.d. or 30 mg b.i.d. in Japanese (PSOR-011) and non-Japanese (PSOR-005, PSOR-008/ESTEEM 1) subjects with moderate to severe psoriasis, predicted by the final PPK model as input for the E-R analysis

| | Geometric mean (geometric CV%) | | |
Study	$AUC_{\tau,ss}$, ng·h/mL	$C_{max,ss}$, ng/mL	$C_{min,ss}$, ng/mL
Japanese (PSOR-011)			
20 mg b.i.d. ($n = 121$)	1939.2 (27.4)	240.3 (25.1)	87.2 (34.9)
30 mg b.i.d. ($n = 120$)	2727.2 (20.7)	341.8 (18.0)	120.3 (28.0)
Non-Japanese (PSOR-005)			
10 mg b.i.d. ($n = 89$)	1098.9 (20.6)	124.0 (19.3)	58.7 (25.7)
20 mg b.i.d. ($n = 121$)	2185.2 (26.3)	247.7 (21.6)	115.6 (36.1)
30 mg b.i.d. ($n = 124$)	3337.2 (19.2)	376.7 (17.4)	178.3 (24.2)
Non-Japanese (PSOR-008/ESTEEM 1)			
30 mg b.i.d. ($n = 613$)	3352.4 (21.9)	377.0 (18.9)	179.9 (28.6)

Abbreviations: $AUC_{\tau,ss}$, area under the concentration-time curve from time 0 (predose) to tau, where tau equals 12 h, at steady state; b.i.d., twice daily; $C_{max,ss}$, maximal observed plasma concentration, at steady state; $C_{min,ss}$, minimum plasma concentration at the predose time point, at steady state; CV, coefficient of variation; E-R, exposure response; PK, pharmacokinetic; PPK, population pharmacokinetic.
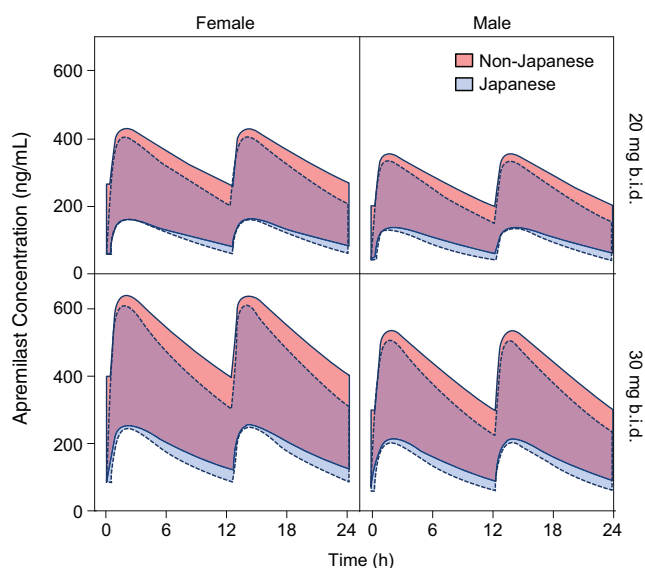

FIGURE 4 Simulated apremilast concentration-time profiles in Japanese and non-Japanese subjects, using the final population pharmacokinetic model. b.i.d., twice daily

concentration was 2.00 h post-dose. Exposure, based on AUC_{0-12}, was 2397 ng·h/mL, with a terminal half-life of 4.06 h. Similar values were reported in a prior analysis in predominantly Caucasian (white, $n = 27$; black, $n = 9$; Asian or Pacific Islander, $n = 3$), healthy subjects (mean [SD]: $C_{max} = 298$ [81.4] ng/mL, $AUC_{0-\infty} = 3270$ [1081] ng·h/mL, $t_{1/2} = 8.20$ [1.166] h; median [range]: $T_{max} = 2.0$ [0.5–5.0] h).[25] However, the PK of apremilast in Japanese versus primarily Caucasian populations were not directly compared in the prior analysis.

Results of the PPK analysis demonstrate that the PK profile of apremilast is generally similar in Japanese and predominantly Caucasian individuals. The PPK model was developed to describe phase 2b and 3 study data from Japanese and Caucasian subjects with moderate to severe psoriasis combined with phase 1 study data from non-Japanese subjects and provided an appropriate representation of apremilast PK characteristics based on the previous non-compartmental analyses of apremilast.[29] The model that best fit the observed PK data included an effect of race on clearance, which was approximately 17% faster in Japanese versus non-Japanese individuals. The effect of race on clearance was small and unlikely to be clinically meaningful because it was within the between-subject variability for CL/F. As shown in Figure 4, the simulation based on the final PPK model predicted that plasma apremilast profiles for Japanese individuals mostly overlapped and were contained within the exposure range of the Caucasian population. Therefore, based on this analysis, no clinically meaningful differences in apremilast exposure are expected between Japanese and Caucasian individuals.

The final PPK model included effects of age, sex, and psoriasis on apremilast clearance, in addition to race. As with the race effect, the magnitude of each of the statistically significant covariates was within the range of between-subject variability. Differences in the CL/F of apremilast between individuals with versus without psoriasis are likely due to the unbalanced demographic distribution between the patient population and healthy subject population. Neither smoking status, which increases CYP1A2 abundance,[35] nor co-medication with CYP1A2 or CYP3A inducers or inhibitors was found to have statistically significant effects on CL/F in the model. The contribution of CYP1A2 to apremilast metabolism is minor, but CYP3A4 is a major metabolic pathway and therefore modulators of the enzyme would be expected to alter the drug's clearance.[25] In PK studies examining the effect of co-administration of a potent CYP3A4 inhibitor (ketoconazole) on apremilast PK, the small increase in exposure (36%, 90% CI, 126.2–147.5) observed when the drugs were co-administrated was within the a priori defined 90% CI safety margin (50–200) and thus does not warrant dose adjustment.[25] However,
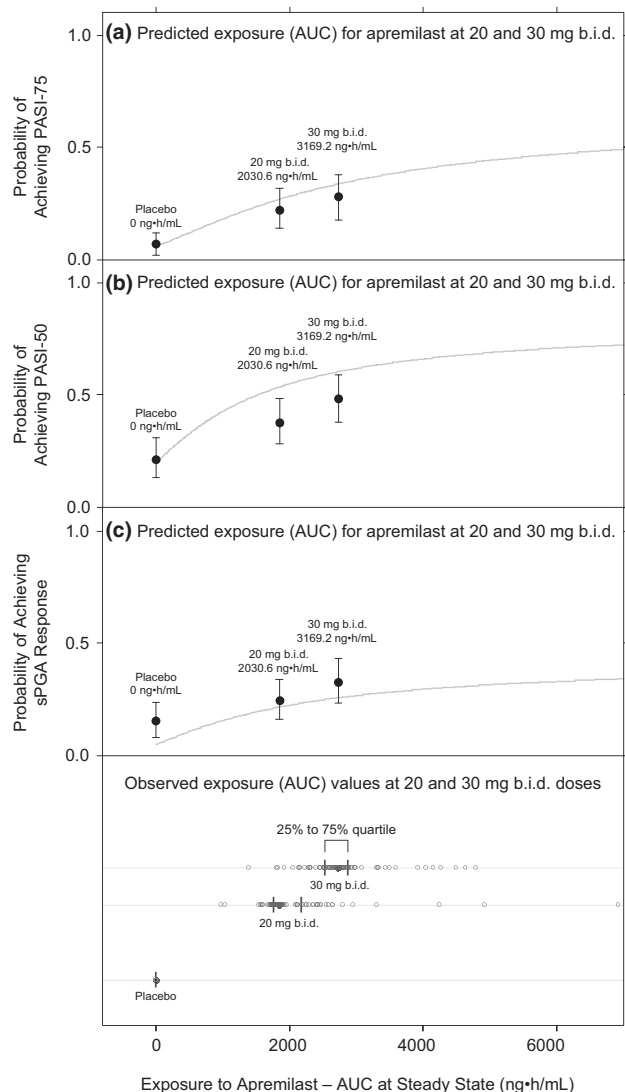
FIGURE 5 Observed and predicted probability of PASI-75 response (a), PASI-50 response (b), and sPGA response (c) at week 16 in Japanese versus Caucasian subjects with moderate to severe psoriasis. Upper panels (a–c) show mean (standard error) observed probability of response in Japanese subjects treated with placebo, apremilast 20 mg b.i.d., and apremilast 30 mg b.i.d.; the gray curves give the predicted probability of response modeled in Japanese and non-Japanese subjects. In the bottom panel, observed AUC_τ values from studies PSOR-005, PSOR-008/ESTEEM 1, and PSOR-011 are represented on separate horizontal lines for apremilast 20 and 30 mg b.i.d. treatment groups; dots show individual AUC_τ values with vertical lines indicating the 25% to 75% quartile range. AUC, area under the plasma concentration vs time curve; b.i.d., twice daily; PASI, Psoriasis Area and Severity Index; PASI-50, ≥50% reduction from baseline in PASI score; PASI-75, ≥75% reduction from baseline in PASI score; sPGA, static Physician Global Assessment

strong induction of CYP3A4 with multiple p.o. doses of rifampicin resulted in a 3.6-times increase in apremilast clearance and approximately a 72% decrease in exposure.[25] The current PPK analysis did not include data from subjects prospectively administrated CYP3A inducers, and lack of statistically significant effect in the PPK model is likely due to the very small sample size (inducers,

$n = 7$ vs no inducers, $n = 440$; see Table S3 for additional information on number of subjects and strength of CYP3A and CYP1A2 inhibitors and inducers). It is important to note that caution is advised when co-administrating apremilast with CYP3A4 inducers, as the plasma concentration and efficacy of apremilast may be reduced due to increased CYP3A4 metabolism.[10] Co-administration of apremilast with strong CYP3A4 inducers, such as rifampin, is not recommended.[25]

Using $AUC_{\tau,ss}$ values from the PPK analysis as input, together with observed measures of clinical response in subjects treated for moderate to severe psoriasis, the E-R analyses modeled the probability of PASI-75, PASI-50, and sPGA response (Table S1). The effect of race was statistically significant in the model for sPGA response but not in the models for PASI-75 and PASI-50 response. For the PASI-75 and PASI-50 response measures, the probability of achieving response at typical exposure levels for apremilast 20 and 30 mg b.i.d. was similar for Japanese subjects and non-Japanese subjects. The probability of achieving sPGA response predicted by the E-R model was somewhat higher in Japanese subjects compared with predominantly Caucasian subjects receiving apremilast 20 and 30 mg b.i.d. (32.9% and 36.3% vs 23.2% and 27.5%, respectively). Although race contributed to the variability in sPGA response (and was therefore included as a factor in the E-R model), the magnitude of the effect (~9% higher for the apremilast 30 mg dose in Japanese subjects) was not clinically meaningful.

Rates of PASI-75, PASI-50, and sPGA response to apremilast 20 and 30 mg b.i.d. treatment predicted by the E-R models for Japanese subjects were therefore generally in agreement with those predicted for predominantly Caucasian subjects, in line with results from the phase 2b and 3 studies. In PSOR-011, which enrolled only Japanese subjects with moderate to severe psoriasis, rates of PASI-75 and sPGA response (0 or 1) at week 16 achieved with apremilast 30 mg b.i.d. (28.2% and 29.6%, respectively)[11] were largely similar to response rates in PSOR-005 (40.9% and 33.0%, respectively) and PSOR-008/ESTEEM 1 (33.1% and 21.7%, respectively) and significantly greater than placebo in all studies.[12,14] The treatment effect (difference in proportions between apremilast 30 mg b.i.d. and placebo) for PASI-75 and sPGA response was similar across studies (PSOR-011: 21.1% and 20.8%; PSOR-005: 35.2% and 21.1%; PSOR-008/ESTEEM 1: 27.8% and 17.8%, respectively). E_{50} values for PASI-75, PASI-50, and sPGA response were estimated to be 1733, 1656, and 1110 ng·h/mL, well below the predicted steady-state apremilast exposure ($AUC_{\tau,ss}$) with the 30 mg b.i.d. dosage in Japanese subjects (2727.2 ng·h/mL). Together, these results indicate that the clinical efficacy of apremilast for the treatment of moderate to severe psoriasis is similar in Japanese and Caucasian subjects, and that the 30 mg b.i.d. dose provides appropriate exposure for apremilast efficacy in Japanese individuals.

In support of the current findings of similar efficacy for the treatment of psoriasis in Japanese and Caucasian subjects, results of a recent analysis of pro-inflammatory cytokine levels during apremilast treatment indicate that the pharmacodynamics (PD) of apremilast are also similar between Japanese and Caucasian

subjects. Among subjects enrolled in the PD subsets of PSOR-009 (ESTEEM 2; conducted in North America and Europe) and PSOR-011 (conducted in Japan only), apremilast 30 mg b.i.d. significantly reduced plasma IL-17A, IL-17F, and IL-22, with a similar magnitude of decrease observed in the two studies.[36] Thus, although there are no direct comparisons between apremilast efficacy and plasma exposure in Japanese versus Caucasian subjects, results from the current PPK and E-R models, as well as a prior PD analysis, demonstrate that the PK and efficacy profile is comparable between Japanese and non-Japanese populations in response to the approved dosage of apremilast.

In conclusion, the PPK modeling demonstrates that the PK profile of apremilast in Japanese subjects with moderate to severe psoriasis is comparable to the PK profile in Caucasian subjects with moderate to severe psoriasis. Exposure for apremilast in Japanese subjects with moderate to severe plaque psoriasis is expected to be similar to that in Caucasian individuals at the 20 and 30 mg b.i.d. doses. The probability of achieving clinical efficacy for the treatment of moderate to severe psoriasis was comparable between Japanese and non-Japanese subjects at typical apremilast exposure levels in the E-R analysis. The 30 mg b.i.d. dose approved for apremilast treatment based on studies in predominantly Caucasian study populations is also an appropriate dose for Japanese subjects with moderate to severe plaque psoriasis.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.