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ARTICLE

Pharmacokinetics, pharmacodynamics, and exposure–efficacy of dupilumab in adults with atopic dermatitis

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Abstract

The pharmacokinetics (PKs) and exposure–efficacy of dupilumab have not been fully described for adults with atopic dermatitis (AD). Our objectives were to analyze the PKs and exposure–efficacy of dupilumab in adults with AD and compare the results of Japanese and overall populations. Adults with moderate-to-severe AD were randomly assigned to dupilumab (300 mg weekly [qw] or every 2 weeks [q2w], 200 mg q2w, 300 mg every 4 weeks [q4w], or 100 mg q4w) or placebo for 16 weeks in a randomized, double-blind, placebo-controlled, dose-ranging phase IIb trial (NCT01859988). This analysis included 379 patients (58 Japanese). Functional dupilumab concentrations increased in a dose-dependent manner; at lower concentrations, increases were greater than dose-proportional because of nonlinear, target-mediated clearance. Dupilumab pharmacokinetics were comparable in Japanese and non-Japanese patients with similar body weights. Week 16 efficacy parameters, including Investigator's Global Assessment score 0/1, greater than or equal to 75% reduction from baseline in the Eczema Area and Severity Index (EASI), and percentage change from baseline in EASI and pruritus Numerical Rating Scale, generally increased with week 16 trough concentration; the plateau of these exposure–efficacy relationships occurred for most patients at exposures associated with the 300 mg q2w and 300 mg qw regimens. Japanese ethnicity did not remain in the population PK model as covariate with or without accounting for body weight differences. In Japanese and non-Japanese patients, efficacy responses increased with week 16 dupilumab trough concentrations in a similar manner. Dupilumab 300 mg qw and q2w regimens were recommended for further evaluation in larger phase III studies.

Mohamed A. Kamal and John D. Davis contributed equally to this work.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Dupilumab, which blocks the shared receptor subunit for IL-4 and IL-13, has shown efficacy with acceptable safety in type 2 immune diseases, such as atopic dermatitis (AD). However, the pharmacokinetics (PKs) and exposure–efficacy of dupilumab have not been fully described in adults with AD.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study aims to analyze dupilumab PKs and exposure–efficacy in adults with AD and to compare the results in the Japanese population with the overall population.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study is the first to characterize dupilumab exposure–response relationships on efficacy end points in adult patients with AD. No statistically significant or clinically relevant differences were observed in the central volume and elimination rate of dupilumab between Japanese and non-Japanese populations with and without adjustments for weight. At week 16, efficacy responses increased asymptotically with increasing trough concentrations in Japanese and non-Japanese patients.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study provides a more complete picture of the PK and exposure–efficacy profile of dupilumab in adults with AD and confirms comparability between Japanese and non-Japanese populations.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory systemic disease characterized by intense pruritus (itch) and eczematous lesions.[1] AD is one of the most prevalent chronic skin diseases, affecting up to 20% of people in developed countries at some point during their lives,[1] with evidence of increasing prevalence.[2] The burden of AD is considerable for patients and society; severe AD can lead to substantial anxiety, depression, sleep loss, and impaired quality of life for patients,[2] ultimately translating into a high socioeconomic burden.[3]

Dupilumab, a fully human VelocImmune®-derived[4,5] monoclonal antibody, blocks the shared receptor subunit for IL-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13. Dupilumab has shown efficacy with acceptable safety in type 2 immune diseases, such as AD,[6–10] asthma,[11–13] chronic rhinosinusitis with nasal polyposis,[14] and eosinophilic esophagitis.[15] The exposure–response relationships of dupilumab have not been previously described in the literature for adults with AD, the first type 2 disease indication for dupilumab.

Presentation of AD can vary in people of different racial or ethnic origins. Filaggrin mutations, which are implicated in disease severity, have been reported as being more common in patients of Western origin compared with patients from Japan.[16,17] In addition, a more "psoriatic" phenotype of AD characterized by T-helper (Th) 17 and Th22 activation, and a strong Th2 component is reported more often in Asian patients with AD compared with patients of Western origin.[18] Although the estimated prevalence of AD in Japanese adults ranges from 2% to 10%, which is similar to that in most Western countries,[19–22] it remains unknown whether critical differences exist in the pathophysiology of AD in Japanese versus patients of Western origin. Nevertheless, Japanese adults with AD experience substantial disease burden similar to adults with AD in US and European countries compared with the general population.[23–25]

A subgroup analysis of clinical trial data in Japanese patients with moderate-to-severe AD showed that dupilumab improved signs and symptoms of AD with acceptable safety, similar to the overall patient population.[26] Because ethnic differences among populations may impact the safety, efficacy, dose, and dosage of a medicine, there is a need to assess potential pharmacokinetic (PK) and exposure–efficacy differences among specific ethnic populations.[27] For example, an assessment of PK differences of selected monoclonal antibodies in Japanese and non-Japanese healthy volunteers found that most, but not all, antibodies exhibited comparable behavior regardless of ethnicity.[28–30] Nevertheless, given the broad use of dupilumab in treatment of type 2 inflammatory diseases in Japanese and non-Japanese patients, the hypothesis of

lack of a difference in the PKs, and exposure–efficacy of dupilumab should be corroborated.

Here we analyze the PKs, pharmacodynamics (PDs), and exposure–efficacy relationships of dupilumab across multiple efficacy end points of AD from a multicenter, randomized, double-blinded, placebo-controlled, parallel-group, dose-ranging phase IIb study of adults with moderate-to-severe AD (NCT01859988).[31] This study was well suited for the primary objective of identifying exposure–efficacy relationships, regardless of ethnicity, as it used a wide range of dose levels resulting in a broad range of dupilumab exposure across adult patients with AD. As a secondary objective, we compared the PK and exposure–efficacy relationships of the Japanese population with the overall population.

METHODS

Study design

The design and patient population of the multicenter, randomized, placebo-controlled, double-blinded, parallel group, dose-ranging phase IIb study (NCT01859988) have been previously described in detail.[31] Briefly, the study included 380 patients aged greater than or equal to 18 years with moderate-to-severe AD that could not be adequately controlled by topical medications or for whom topical treatment was inadvisable. Among other inclusion criteria, all patients were required to have an Investigator's Global Assessment (IGA) score of 3 or 4 at screening and baseline visits.

Patients were randomly assigned (1:1:1:1:1:1) to receive subcutaneous dupilumab 300 mg weekly (qw), 300 mg every 2 weeks (q2w), 200 mg q2w, 300 mg every 4 weeks (q4w), 100 mg q4w, or placebo qw for 16 weeks, with a subsequent 16-week follow-up period. On day 1, patients assigned to receive the 100, 200, or 300 mg dose of dupilumab received a loading dose of 400, 400, or 600 mg, respectively. To maintain blinding, patients assigned to receive dupilumab q2w or q4w received volume-matched placebo in the weeks that dupilumab was not administered. Randomization was stratified by severity of AD (moderate or severe) and region (Japan or the rest of the world). Following the completion of the 16-week treatment period, some patients enrolled in a subsequent open-label extension study of dupilumab, starting at week 20.

The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization Good Clinical Practice guideline, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trial.

PK assessment

The PK study population consisted of all patients who received the study drug or placebo (safety population) and who had at least one (nonmissing) postbaseline measurement of functional dupilumab available for statistical analysis. Predose blood samples were taken at baseline and at study weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, 15, and 16 (end of the treatment period), then during the follow-up period at weeks 18, 20, 22, 24, 26, 28, 30, and 32 (end of study), or at the time of early termination if the patient discontinued the study, or at unscheduled visits.

Serum samples for evaluation of functional dupilumab were analyzed using a validated enzyme-linked immunosorbent assay, as previously described.[32] In this functional assay, dupilumab was used as the assay standard and recombinant human IL-4Rα protein served as the capture reagent. Dupilumab concentrations were measured of dupilumab with either one or two unoccupied binding sites (functional drug). The assay did not detect dupilumab when both binding sites were occupied by soluble IL-4Rα or when at least one site was presumably bound to the membrane-bound IL-4Rα not present in serum. The lower limit of quantitation of functional dupilumab is 0.078 mg/L in undiluted human serum.

Population PK analysis

A population PK analysis was performed using data from the phase IIb dose-ranging study. The model and methodology have been described previously.[33] In this analysis, Japanese ethnicity was tested as an additional covariate in the model. As the new covariate was explored, all covariates were reassessed. Covariate inclusion and exclusion criteria were the same as those described previously (i.e., a parameter remained in the model when the addition of the covariate resulted in $\alpha \leq 0.01$ and removal of the covariate resulted in $\alpha \geq 0.001$).[33] As a steep target-mediated phase caused an increased variability of the objective function value (OFV) whereas the model remained stable,[33,34] the Wald test was utilized to select covariates. The Wald test performed well based on comparison to log-likelihood[33] and on stability of Wald p values evaluated by changing initial values of parameters.

In the population PK analysis, 296 of 318 patients on active drug were included in the primary analysis dataset.

Nine patients were excluded due to nonphysiological profiles (i.e., profiles look physiologically impossible due to multiple outliers), eight patients were excluded because they had moderate or high anti-drug antibody (ADA) titers (6 of these 8 patients were non-Japanese), and five patients were excluded because they had less than two observations above the lower limit of quantification (LLOQ) level; patients with low ADA titers remained in the analysis. Overall, 5056 of 5657 dupilumab concentrations were used in the analysis. Outliers and samples collected before the first dose were excluded from the analysis. The same patients and samples from the phase IIb study were used in the analysis, as in the previously published model of integrated data.[33] Visual predictive checks and standard model diagnostics, including plots of observed versus predicted concentrations and residual plots, were provided to demonstrate the model's goodness-of-fit. The same data points and subjects were excluded from the phase IIb data of the integrated analysis used for regulatory submissions[33] and from the analysis of phase IIb data in this paper. A sensitivity analysis with all observations included in the dataset was performed for both the cited and current analyses to confirm that the exclusion of outliers and subjects who developed ADA did not impact the primary results. The central volume and elimination rate were response variables in the analysis of covariates.

Forward inclusion and backward elimination were applied to build both the base and covariate models. A parameter remained in the model when the addition of the covariate resulted in α less than or equal to 0.01 and removal of the covariate resulted in α less than or equal to 0.001.

Efficacy end points

The following efficacy end points were analyzed over time through end of treatment (week 16) and end of study (week 32) for the overall population to assess both dose response and dissipation of effect: percentage of patients achieving IGA score 0 or 1 (0, clear, and 1, almost clear) from baseline, percentage of patients achieving greater than or equal to 75% improvement from baseline in Eczema Area and Severity Index (EASI-75), mean percentage change from baseline in EASI, and mean percentage change from baseline in peak weekly average pruritus Numerical Rating Scale (NRS) score. These end points were analyzed only at week 16 in the Japanese population due to the small sample size.

Exposure–efficacy analysis

Relationships between functional dupilumab exposure and PD measures (treatment response) were assessed for each treatment group. Dupilumab blocks signaling by binding to target receptors, and its efficacy is related to steady-state trough concentrations (C_{trough}); therefore, observed dupilumab C_{trough} at week 16 was selected as the primary exposure metric. Exposure–efficacy relationships were investigated using scatter plots of dupilumab exposure versus drug effect for continuous efficacy end points (percentage change from baseline in EASI and percentage change from baseline in peak weekly average pruritus NRS score) or logistic regression (linear or nonlinear) for binary efficacy end points (probability of achieving IGA score of ≤1 and probability of achieving EASI-75). Logistic regression converts a categorical binary end point (e.g., IGA ≤1) into the probability—which is bound and continuous—of achieving the categorical end point, thereby enabling visualization of a continuous representation of a binary dependent variable versus a continuous independent variable (e.g., drug concentration). In addition, logistic regression analysis allows for determination of the statistical significance of hypotheses that no relationships exist between the binary response variable and independent continuous or categorical independent variables. Nonlinear logistic regression analysis of efficacy end points used a nonlinear maximum effect (E_{max}) function $(E0 + E_{max} \cdot \text{concentration})/(EC50 + \text{concentration})$ to characterize the exposure–efficacy curve as well as to allow for the placebo response above a probability of zero and plateau below a probability of 1.

Statistical analysis

Efficacy outcomes included all observed values with censoring after rescue medication use and missing values treated as nonresponders; by contrast, the published primary analysis used the method of last observation carried forward to account for data recorded after rescue-treatment use for continuous end points.[31] Analyses were performed using Statistical Analysis Software version 9.4 (SAS Institute, Cary, NC) and R version 3.5.1 (R Foundation, Vienna, Austria).

RESULTS

Patients

Baseline demographics, efficacy, and safety results from this study have been previously reported.[31] This PK and exposure–efficacy analysis included 379 patients assigned to receive 16 weeks of treatment with dupilumab and a Japanese subpopulation of 58 patients (Table 1). All Japanese patients were enrolled at sites in Japan.

Of note, mean weight and body mass index (BMI) were lower in the Japanese population (mean weight range: 56.4–72.88 kg; mean BMI range: 21.5–25.47 kg/m^2) compared with the overall population (mean weight range: 74.0–80.6 kg; mean BMI range: 25.42–27.34 kg/m^2; Table 1).

Dupilumab concentrations

Median concentrations of functional dupilumab in serum are presented for all treatment groups by time point in Figure 1a. In general, dupilumab exposure increased with dose. At lower concentrations, the increases were greater than dose proportional as a result of nonlinear, target-mediated clearance; as the concentration increased and became sufficient to saturate the target-mediated pathway, concentrations increased in a dose-proportional manner.

In patients receiving dupilumab q4w (100 or 300 mg), the influence of loading dose on median concentration rapidly declined and approached steady-state C_{trough} levels by week 8 (Figure 1a). In patients receiving dupilumab 200 or 300 mg q2w, based on median concentration, steady-state was achieved after the first dose (Figure 1a). Patients receiving dupilumab 300 mg qw after a 600 mg loading dose achieved steady-state by week 14.

During the active treatment period (up to week 16), the median exposure to functional dupilumab trended numerically higher in Japanese than in non-Japanese patients, and C_{trough} levels were similar between the two populations at the approved dose of 300 mg q2w (Figure 1a). Furthermore, Japanese and non-Japanese patients of a similar body weight had comparable median C_{trough} levels of functional dupilumab at a given dose (Figure 1b). Week 16 C_{trough} tended to be similar in Japanese and the overall population (Table 2).

Population PK analysis

Due to the smaller sample size of this single study compared with the sample size that was used to build the original adult covariate model,[33] race, EASI, and BMI did not withstand the statistical inclusion or exclusion criteria and did not appear in the list of the final covariates. Weight, albumin, and ADA remained in the model. Based on the inclusion/exclusion criteria,[33] Japanese ethnicity did not remain in the model. The percent differences in the population PK parameters (K_e, elimination rate; V_c, central volume) between populations are presented in Table S1. All percent differences were small and statistically insignificant with large relative standard error expressed in percentage of the estimate (%RSE). These findings were unchanged whether or not adjusted for the other covariates, including weight, albumin, and ADA.

Visual predictive checks are presented by ethnicity (Japanese and non-Japanese; Figure S1) and by treatment group (Figure S2). Observed versus predicted concentrations of dupilumab by population and by treatment group are presented in Figures S3 and S4, respectively. Individual weighted residuals by ethnicity and by treatment are presented in Figures S5 and S6, respectively. The diagnostic plots indicated that the population PK model adequately described the observed data. The sensitivity analysis performed with all observations in the data (including outliers) confirmed the primary results.

Pharmacodynamic and exposure–efficacy analysis

Efficacy responses at week 16 are shown in Table 2 (overall and Japanese populations) and over time up to week 32, including the 16-week follow-up period in Figure 2a–d (overall population only due to the small number of Japanese patients in each dose group).[31] In general, efficacy responses at week 16 tended to increase with dose (placebo < dupilumab 100 mg q4w < 300 mg q4w < 200 mg q2w < 300 mg q2w < 300 mg qw), as previously reported.[31]

At week 16, the PD effects appeared to reach steady-state in the dupilumab 200 mg q2w, 300 mg q2w, and 300 mg qw treatment groups, and signs of reaching the maximum PD effect were observed with the largest monthly dose of 300 mg qw (Figure 2a–d). This observation is consistent with the C_{trough} seen in the 300 mg q2w and 300 mg qw treatment groups, resulting from saturation of the target-mediated clearance.

The 100 mg q4w regimen resulted in similar PD–time profiles as the other treatment groups through approximately week 6, at which point responses began to diverge. This finding is consistent with (a) the decreasing dupilumab concentrations in the 100 mg q4w regimen after the initial concentrations achieved with the loading dose; and (b) the lag time observed between PK and PD responses. At week 16, the pruritus NRS score generally demonstrated a greater dose response than did the EASI score. The maximum effect on the pruritus NRS score occurred earlier and returned to baseline faster than did the maximum effect on the EASI score, suggesting that the pruritus NRS score was more temporally responsive to change in dupilumab concentration.

Following the end of dupilumab treatment at week 16, a reduction of efficacy improvements was seen as early as week 18 for most doses, and clinical benefits were lost over the course of the follow-up period as efficacy responses trended toward baseline values by week 32 (Figure 2a–d).

TABLE 1 Baseline demographics and clinical characteristics

Characteristic	Population	Placebo qw $N = 61/N1 = 8$	100 mg q4w $N = 65/N1 = 11$	300 mg q4w $N = 65/N1 = 11$	200 mg q2w $N = 61/N1 = 9$	300 mg q2w $N = 64/N1 = 10$	300 mg qw $N = 63/N1 = 9$
Age, years	Overall	37.2 (13.1)	36.6 (11.6)	36.8 (10.8)	35.8 (14.9)	39.4 (12.01)	36.2 (10.7)
	Japanese	37.0 (11.1)	34.5 (8.7)	36.9 (5.3)	31.1 (6.1)	38.0 (8.4)	35.3 (6.6)
Race, *n* (%)	White	40 (65.6)	50 (76.9)	39 (60.0)	44 (72.1)	40 (62.5)	44 (69.8)
	Black/African American	6 (9.8)	2 (3.1)	11 (16.9)	2 (3.3)	7 (10.9)	5 (7.9)
	Asian	15 (24.6)	12 (18.5)	15 (23.1)	12 (19.7)	15 (23.4)	13 (20.6)
	Other/Native American/Alaskan Native	0	1 (1.5)	0	3 (4.9)	2 (3.1)	1 (1.6)
Male sex, *n* (%)	Overall	40 (65.6)	34 (52.3)	40 (61.5)	36 (59.0)	41 (64.1)	43 (68.3)
	Japanese	6 (75.0)	4 (36.4)	7 (63.6)	8 (88.9)	8 (80.0)	7 (77.8)
Weight, kg	Overall	79.0 (23.8)	75.9 (21.9)	74.6 (17.1)	74.0 (17.9)	80.6 (19.1)	78.4 (18.0)
	Japanese	59.9 (11.0)	56.4 (11.5)	69.05 (19.6)	62.11 (8.0)	72.88 (16.2)	64.0 (11.1)
Body mass index, kg/m^2	Overall	27.30 (7.5)	25.73 (6.1)	25.42 (5.2)	25.82 (6.0)	27.34 (6.0)	25.72 (5.4)
	Japanese	21.50 (3.0)	21.67 (2.5)	25.47 (6.0)	22.17 (3.4)	25.38 (3.8)	22.75 (3.7)
Duration of AD, years	Overall	31.2 (14.2)	28.0 (14.7)	27.1 (11.6)	25.6 (13.2)	28.6 (16.5)	25.8 (12.2)
	Japanese	27.5 (7.9)	30.8 (9.3)	26.9 (11.1)	29.3 (6.0)	28.3 (11.7)	32.3 (6.9)
EASI score	Overall	32.9 (13.8)	32.2 (13.5)	29.4 (11.5)	32.9 (15.5)	33.8 (14.5)	30.1 (11.2)
	Japanese	38.6 (18.2)	36.4 (14.2)	33.5 (12.7)	49.4 (15.4)	37.6 (12.6)	32.9 (12.1)
Peak weekly average pruritus NRS score	Overall	6.3 (1.8)	6.7 (1.9)	6.8 (1.9)	7.0 (2.3)	6.7 (2.1)	6.5 (1.5)
	Japanese	5.9 (1.8)	6.1 (2.0)	6.0 (1.7)	7.8 (1.4)	6.6 (2.5)	5.8 (1.4)

Note: Values are given in mean (SD) unless stated otherwise.

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; *N*, total number of patients per group; *N*1, number of Japanese patients per group; NRS, Numerical Rating Scale; qw, every week; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation.

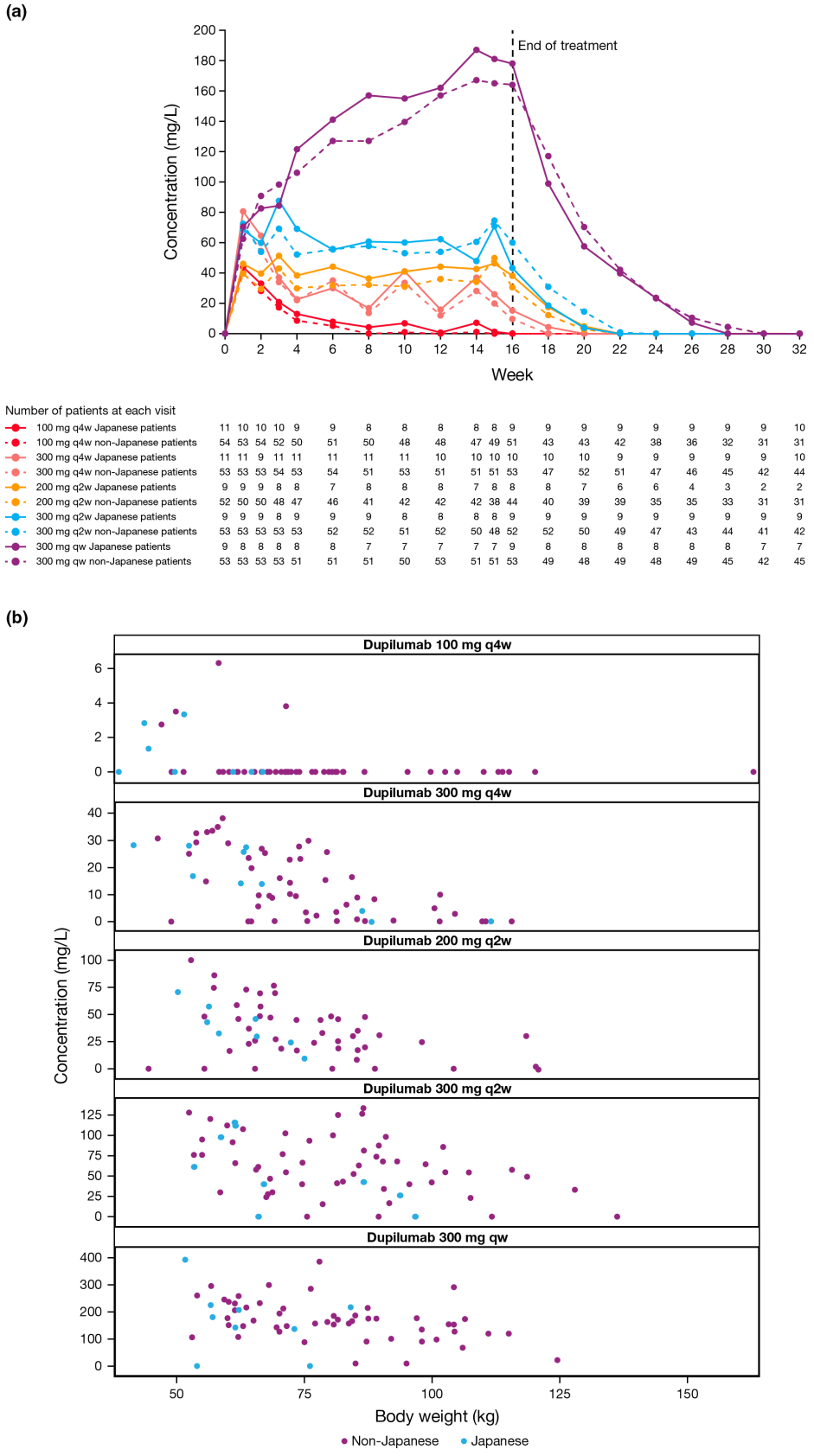

FIGURE 1 (a) Median concentrations of functional dupilumab in serum by dose regimen for each time point in the overall population in Japanese and non-Japanese patients; (b) the effect of body weight on trough concentrations of functional dupilumab at week 16 in Japanese and non-Japanese patients. Abbreviations: qw, every week; q2w, every 2 weeks; q4w, every 4 weeks.

TABLE 2 Concentration and efficacy at week 16 in Japanese and overall populations

Value at week 16	Population	Placebo qw *N* = 61/*N1* = 8	100 mg q4w *N* = 65/*N1* = 11	300 mg q4w *N* = 65/*N1* = 11	200 mg q2w *N* = 61/*N1* = 9	300 mg q2w *N* = 64/*N1* = 10	300 mg qw *N* = 63/*N1* = 9
C_{trough}, mean (SD), mg/L	Overall	0	0.4 (1.2)	13.8 (12.1)	35.9 (24.6)	61.5 (36.7)	168 (80.8)
	Japanese	0	0.8 (1.4)	15.7 (11.5)	39.1 (19.2)	55.2 (44.6)	165 (119)
Patients achieving IGA score 0/1, %	Overall (*p* value)	1.6	12.3 (0.0242)	21.5 (0.0004)	27.9 (<0.0001)	29.7 (<0.0001)	33.3 (<0.0001)
	Japanese	0	27.3	0	22.2	10.0	22.2
Patients achieving EASI-75, %	Overall (*p* value)	11.5	29.2 (0.0147)	49.2 (<0.0001)	55.7 (<0.0001)	53.1 (<0.0001)	60.3 (<0.0001)
	Japanese	0	36.4	27.3	55.6	60.0	44.4
Percentage change of EASI score from baseline, mean (SD)	Overall (*p* value)	−32.9 (40.3)	−53.9 (40.9) (0.0009)	−73.1 (27.7) (<0.0001)	−74.8 (26.6) (<0.0001)	−77.4 (21.4) (<0.0001)	−78.0 (22.0) (<0.0001)
	Japanese	−9.0 (54.9)	−78.9 (23.1)	−72.6 (13.3)	−82.0 (19.5)	−75.8 (23.5)	−68.4 (31.6)
Percentage change from baseline in peak weekly average pruritus NRS score, mean (SD)	Overall (*p* value)	−5.1 (40.2)	−27.1 (34.7) (0.0029)	−41.9 (33.7) (<0.0001)	−48.4 (30.8) (<0.0001)	−49.3 (32.0) (<0.0001)	−56.5 (29.0) (<0.0001)
	Japanese	22.8 (34.78)	−27.52 (44.13)	−13.03 (34.34)	−48.40 (24.17)	−35.43 (46.24)	−34.57 (20.31)

Note: The *p* values are versus placebo. The *p* values versus placebo are provided for efficacy measures on the overall population, but not for the Japanese population due to small sample sizes and because the analyses were not prespecified.

Abbreviations: C_{trough}, trough concentration; EASI, Eczema Area and Severity Index; EASI-75, greater than or equal to 75% improvement from baseline in EASI; IGA, Investigator's Global Assessment; *N*, total number of patients per group; *N*1, number of Japanese patients per group; NRS, Numerical Rating Scale; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation.

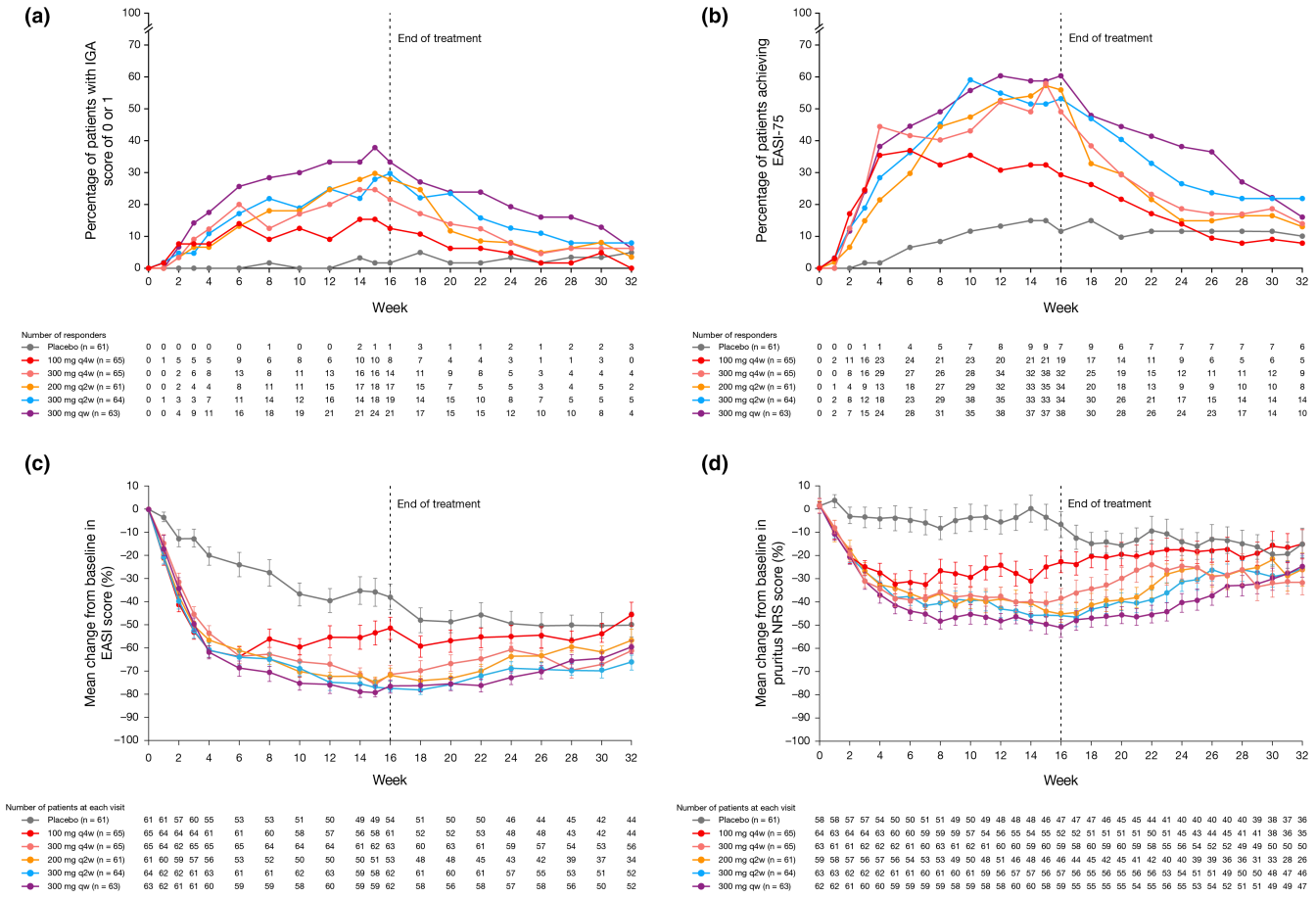

FIGURE 2 (a) Percentage of patients with IGA score of 0 or 1 from baseline through week 32; (b) percentage of patients achieving EASI-75 through week 32; (c) mean percentage change from baseline in EASI through week 32; (d) mean percentage change from baseline in peak weekly average pruritus NRS score through week 32. EASI, Eczema Area and Severity Index; EASI-75, greater than or equal to 75% improvement from baseline in EASI; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; qw, every week; q2w, every 2 weeks; q4w, every 4 weeks.

The probabilities of achieving an IGA score 0 or 1 or of achieving EASI-75 by concentration are shown in Figure 3a,b, respectively. The probability of achieving these end points increased asymptotically with C_{trough} and was highest prior to reaching the mean concentration achieved by patients receiving the 300 mg q2w regimen, regardless of Japanese versus non-Japanese ethnicity. The exposure–efficacy relationships between percentage change in EASI score and percentage change in pruritus NRS score and dupilumab concentrations are presented in Figure 3c,d, respectively, showing that, in general, improvement of efficacy parameters was seen with increasing exposure and that the plateau of response for most patients occurred at exposures associated with the 300 mg q2w and 300 mg qw regimens.

DISCUSSION

Dupilumab PK parameters were comparable in Japanese and non-Japanese patients in that exposure generally increased with dose, but lower concentrations were characterized by nonlinear target-mediated clearance. Exposure to functional dupilumab trended numerically higher in Japanese compared with non-Japanese patients during the treatment period. However, the 300 mg q2w regimen provided similar C_{trough} levels of dupilumab in both Japanese and non-Japanese patients. Japanese and non-Japanese patients of a similar body weight had comparable C_{trough} levels of functional dupilumab at a given dose. In general, week 16 efficacy responses to dupilumab in the overall population correlated dose-dependently with total monthly dose and mean concentrations of dupilumab, and efficacy diminished over the follow-up period. The probability of response was comparable between Japanese and non-Japanese adults, with small differences attributable to differences in body weight.

In the population PK analysis, Japanese ethnicity did not remain as a covariate in the final model. This finding is consistent with the current dupilumab dosing guidelines, showing the same posology in Japanese and non-Japanese

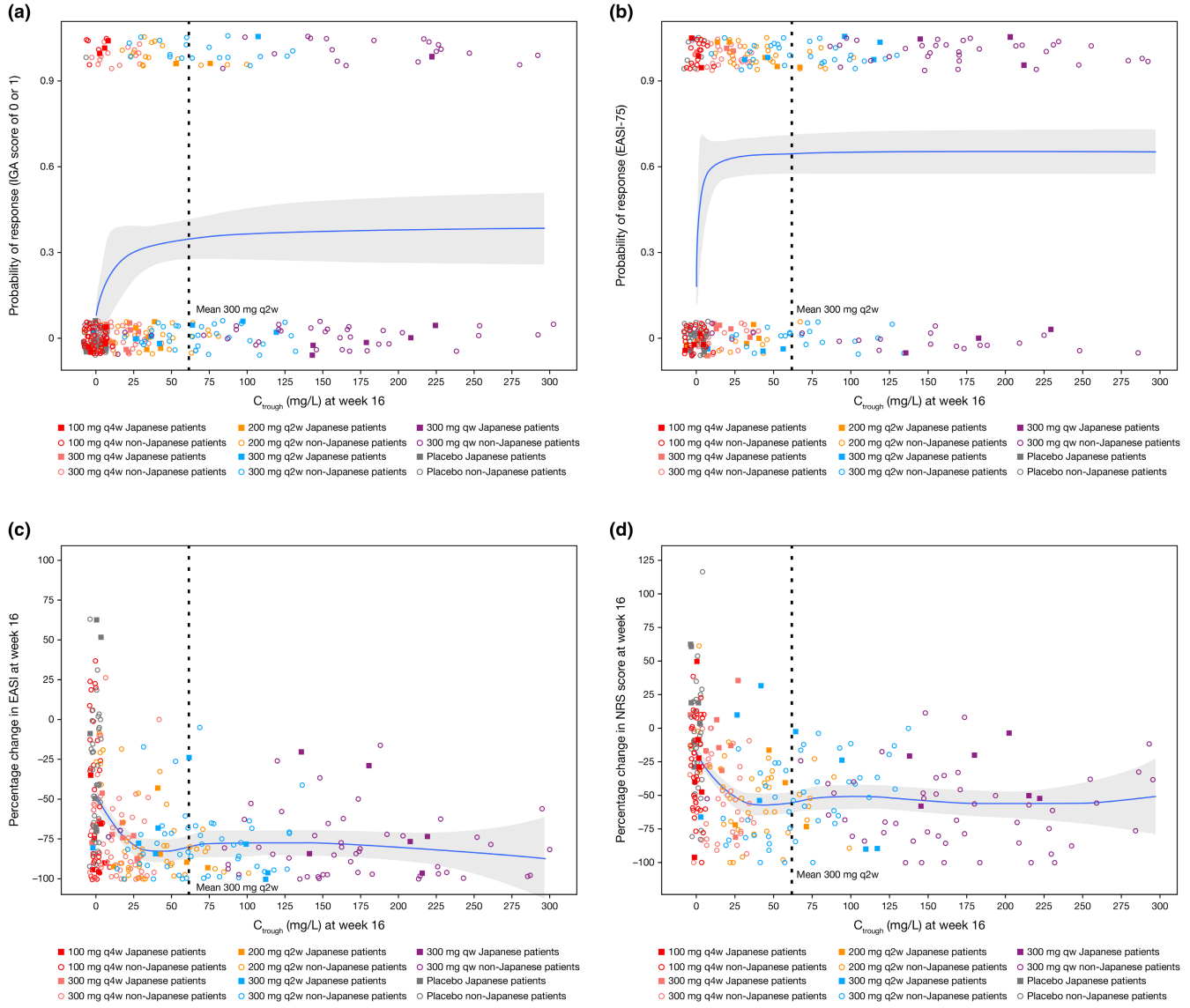

FIGURE 3 (a) Probability of response (IGA score 0 or 1) versus C_{trough} (mg/L) at week 16; (b) probability of response (EASI-75) versus C_{trough} (mg/L) at week 16; (c) exposure–efficacy relationship: scatter plot of percentage change from baseline in EASI score with functional dupilumab concentrations at week 16; (d) exposure–efficacy relationship: scatter plots of percentage change from baseline in pruritus NRS score with functional dupilumab concentrations at week 16. C_{trough}, trough concentration; EASI, Eczema Area and Severity Index; EASI-75, greater than or equal to 75% improvement from baseline in EASI; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; qw, every week; q2w, every 2 weeks; q4w, every 4 weeks.

patients with AD. The finding that Japanese ethnicity did not impact the PK profile of dupilumab is consistent with other studies reported in the literature assessing the impact of Japanese ethnicity on the PK profile of monoclonal antibodies.[28–30]

Based on these results and other safety and efficacy results from this phase IIb study, dupilumab 300 mg qw and q2w were selected to be investigated in phase III studies in moderate-to-severe AD. The findings of these phase III studies supported approval of the 300 mg q2w dosing regimen for adults with moderate-to-severe AD.[35–37]

The PK properties of dupilumab are known to be nonlinear and characterized by target-mediated drug disposition, with dupilumab clearance rapidly increasing at lower concentrations.[33] Conversely, as systemic concentrations of dupilumab increase with increasing dose and become sufficient to saturate the target-mediated pathway, the kinetics of dupilumab can be described as linear because concentration increases proportionally with dose at these high concentrations. The time course of dupilumab serum concentrations after subcutaneous administration has been described by a two-compartment model with parallel linear and Michaelis–Menten elimination from the central compartment and with transit-compartment model of absorption, based on a population PK model derived from early-phase studies in healthy volunteers

and patients with AD.[33] The PK analysis described here showed that the serum PK properties of dupilumab are consistent with those previously reported.[33] The current analysis expanded on these findings and explored the relationship between PK and PD parameters by using various dupilumab regimens, results of which informed dose selection for the phase III program.

Exposure–efficacy analysis of categorical efficacy endpoints (IGA score 0 or 1 and EASI-75) as well as continuous end points (percentage change from baseline in EASI and pruritis NRS scores) versus dupilumab C_{trough} at steady-state show that mean C_{trough} exposures associated with the 300 mg q2w regimen lie at or near the plateau of these exposure–efficacy relationships. Moreover, when analyzed by individual data, these analyses reveal that both Japanese and non-Japanese patients receiving dupilumab 300 mg q2w achieved maximal or near-maximal response. Consistent with expectation, the exposure–efficacy also shows that mean exposures associated with the 300 mg q2w regimen lie deeper in the plateau of the exposure–efficacy relationship of the less stringent efficacy end points (e.g., EASI-75) compared with the more stringent endpoint of IGA score 0 or 1 (Figure 3a,b). Of note, variability in exposure explains some, but not all, variability in response. Overall, these exposure–efficacy analyses reveal that Japanese and non-Japanese adults exhibit a similar exposure–efficacy to dupilumab.

The purpose of the loading dose was to increase early exposure of dupilumab in order to reduce the time to achieve dupilumab concentrations sufficient to saturate IL-4 receptors throughout the entirety of the dosing interval, thereby achieving more rapid onset of effect. Compared with the 200 mg q2w, 100 mg q4w, and 300 mg q4w regimens, the 300 mg qw and q2w regimens provided optimal efficacy. These findings are based not only on efficacy endpoints but also on exposure–efficacy analyses. The approved dupilumab dose coincides with the peak of the exposure–efficacy curve in Japanese and non-Japanese adults, showing that a certain amount of exposure to dupilumab (C_{trough}) is critical to effectively control AD in both Japanese and non-Japanese adults.

Unlike prior analyses of this phase IIb trial,[31] here, we analyzed the efficacy results from the 16-week follow-up period following the 16-week treatment period to assess dissipation of effect. Reduced efficacy from week 16 (end of treatment) to week 32 (end of study) occurred due to reduced mean concentration of dupilumab compared with the peak of exposure, with the pruritus NRS score more sensitive than the EASI score in reflecting reduced concentration based on data from the follow-up period. For all but the highest monthly dose, dupilumab disappeared from serum 6 weeks after discontinuation; therefore, regular dupilumab administration at the approved 300 mg q2w regimen without treatment interruption is ideal to achieve sustained efficacy.

This is the first report of the PK of dupilumab in Japanese patients with moderate-to-severe AD. Exposure was slightly higher in Japanese than in non-Japanese patients; however, this difference did not have clinical consequences. Overall, the PK findings agree with published results from healthy Japanese volunteers who received dupilumab,[32] whereas the safety and efficacy of dupilumab in Japanese patients (included in this phase IIb trial and phase III trials) were previously presented and showed comparable data to the overall populations of the trials.[26]

This analysis has some limitations. Although the data support selection of the 300 mg q2w regimen, it is unclear whether a subset of patients with higher body weight and more severe baseline disease may benefit from more frequent dosing. Furthermore, the sample size was relatively small, especially in the Japanese subgroup. Finally, some patients enrolled in a subsequent open-label extension study of dupilumab, starting at week 20, that may have confounded efficacy outcomes during the follow-up period.

In conclusion, this analysis showed that week 16 efficacy parameters generally increased with week 16 trough concentration; the plateau of these exposure–efficacy relationships occurred for most patients at exposures associated with the 300 mg q2w and 300 mg qw regimens, regardless of ethnicity. Dupilumab 300 mg qw and q2w regimens were recommended for further evaluation in larger phase III studies.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. P.K., E.L.S., and M.A. designed the research. E.L.S., T.N., M.S., and A.I. performed the research. M.A.K., J.D.D., P.K., and K.S. analyzed the data.

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CONFLICT OF INTEREST

M.A.K., J.D.D., P.K., K.S., and M.A. are employees and shareholders of Regeneron Pharmaceuticals, Inc. E.L.S. is a consultant to AbbVie, Anacor Pharmaceuticals, Bristol Myers Squibb, Dermira, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, LEO Pharma, MedImmune, Menlo, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi, Valeant and has received grants/research funding from Amgen, Anacor Pharmaceuticals, Bristol Myers Squibb, Chugai, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, MedImmune, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Roivant Sciences, Sanofi, Tioga Pharmaceuticals, Vanda Pharmaceuticals. T.N. has received speaker fees from Maruho and Sanofi. M.S. has received speaker fees from Mitsubishi Tanabe Pharma and Sanofi. A.I. is a consultant and/or received speaker honoraria from AbbVie, Eli Lilly Japan, Japan Tobacco, LEO Pharma, Maruho, Novartis, Sanofi, and Torii Pharmaceutical and received research grants from AbbVie, Amgen, Eli Lilly Japan, Pfizer, Novartis, Otsuka Pharmaceutical and Sanofi. C.X. and K.A. are employees of Sanofi and may hold stock and/or stock options in the company.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this paper. Individual anonymized participant data will be considered for sharing once the product and indication has been approved by major health authorities (e.g., the FDA, EMA, PMDA, etc.), if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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