Base and Covariate Population Pharmacokinetic Analyses of Dupilumab in Adolescents and Children ≥6 to <12 Years of Age Using Phase 3 Data

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Abstract

Population pharmacokinetic (PK) base and covariate analyses were conducted using data from adolescents with moderate-to-severe atopic dermatitis (AD) and children ≥6 to <12 years of age with severe AD. Two phase 3 studies were analyzed (165 adolescents and 241 children on active treatment). A 2-compartment model with linear and Michaelis-Menten elimination and 3 transit compartments describing lag time in absorption was utilized. Weight, albumin, body mass index, and Eczema Area and Severity Index score were statistically significant covariates in at least 1 of the age populations. Only body weight had a consequential effect on central volume. Although an absorption rate and target-mediated clearance somewhat decreased with age, no dose adjustment was needed in addition to the adjustment for weight already implemented in the phase 3 studies. Otherwise, population PK parameters and covariates were similar across the 2 pediatric subpopulations and in adults. No allometric changes in elimination rate and beta half-life were observed with weight. Parameterization of models in terms of rates was a useful alternative to parameterization in terms of clearances, allowing for an absence of repeated covariates and preventing overparameterization. The model adequately described dupilumab pharmacokinetics in the pediatric populations.

Atopic dermatitis (AD) is a chronic inflammatory skin condition that affects both pediatric and adult patients. AD is characterized by eczematous lesions and intense pruritus, and its pathophysiology is influenced by both genetic and environmental factors.[1,2] Abnormal skin-barrier function in patients with AD may allow for transcutaneous allergen penetration, immune response activation, inflammation, susceptibility to skin infections, and chronic pruritus, which can substantially impair quality of life among adolescents and children with AD.[2,3]

Dupilumab is a human VelocImmune®-derived[4,5] immune globulin (IgG)4 monoclonal antibody (mAb) that has been extensively studied in adults.[6–12] Dupilumab blocks the shared receptor component for interleukin (IL)-4 and IL-13, which are key and central drivers of type 2 inflammation.[13] The binding of dupilumab to human IL-4 receptor alpha blocks the functions of IL-4 and IL-13 signal transduction through this receptor pathway.[6–10,14]

Population pharmacokinetic (PK) models have been developed to characterize dupilumab's PK profile in adult patients with AD and normal volunteers.[15,16]

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These analyses found that a 2-compartment population PK model with parallel linear and nonlinear Michaelis-Menten (MM) elimination and transit compartments, which characterize the lag time of absorption, adequately described dupilumab's pharmacokinetics in adult trials.[16] Dupilumab demonstrated distribution, linear elimination, and target-mediated elimination phases after intravenous administration, and absorption, linear elimination, and target-mediated elimination phases following subcutaneous dosing,[15,16] which are consistent with a human IgG mAb directed against a membrane-bound target. Dupilumab also demonstrated a steep target-mediated phase, which is attributed to the presence of the target receptor on the surface of circulating mononuclear blood cells.[17] Statistically significant covariates in adults included weight, body mass index (BMI), race, albumin, antidrug antibodies (ADAs) at any time, and Eczema Area and Severity Index (EASI). No dose adjustment for covariates was needed in adults because of a clinically insignificant impact of the covariates on exposure and because of dupilumab's high therapeutic index.

The aims of this work are to present population PK analyses applied to unpublished PK data from phase 3 trials in adolescents with moderate-to-severe AD and in children ≥6 to <12 years of age with severe AD who received subcutaneous dupilumab and to compare the results with a previously published analysis of adult data.[16] This article explains the methodology and results of 2 separate population PK analyses, which were provided in 2 successful supplemental biologics license applications (sBLA) for adolescents and children ≥6 to <12 years of age. These pharmacometric analyses were essential for supporting posology in pediatric AD patients, including adolescents and children ≥6 to <12 years old.

Methods

Study Design and Population

A population PK analysis was performed using data from 2 trials described in Supplemental Table 1. The studies presented here were performed in accordance with Good Clinical Practice guidelines and adhered to the Declaration of Helsinki. The study protocols and procedures were approved by the appropriate institutional review boards and ethics committees at each study site. All participants provided written informed consent before any study procedure was undertaken.

Overall, population PK analyses in children ≥6 to <12 years of age and adolescents are provided in this article. In the primary analysis of adolescent data (study NCT03054428 [R668-AD-1526]), 162 of 165 participants on active treatment and 827 of 1006 samples were included; in the primary analyses of children ≥6 to <12 years of age (study NCT03345914 [R668-

AD-1652]), 239 of 241 participants on active treatment and 925 of 1173 samples were included. Reasons for sample or patient exclusion from the primary analyses were: (1) samples collected before the first dose, (2) outliers, (3) patients with fewer than 2 samples above the lower limit of quantification (LLOQ), and/or (4) ADA titers ≥ 1000. Most excluded samples were collected before the first dose. In both studies, PK samples were collected on days 1, 29, 57, and 113 and at the end of treatment.

Patients in the population PK analysis set were randomized as follows. Children ≥6 to <12 years of age on active drug were randomized to the following treatment groups: (1) dupilumab every 2 weeks, 100 mg for patients < 30 kg (n = 63) or 200 mg for patients ≥ 30 kg (n = 59); and (2) dupilumab every 4 weeks, 300 mg (n = 119). Adolescents on active drug were randomized to the following treatment groups: (1) dupilumab every 2 weeks, 200 mg (43 patients < 60 kg) or 300 mg (39 patients ≥ 60 kg); and (2) dupilumab every 4 weeks, 300 mg, irrespective of weight (n = 82).

Among children in active treatment groups, mean ± standard deviation (SD) age was 8.5 ± 1.7 years, mean ± SD weight was 31.6 ± 10.2 kg, and 49.8% were males. Among adolescents in active treatment groups, mean ± SD age was 14.4 ± 1.59 years, mean ± SD weight was 65.3 ± 22.0 kg, and 56.7% were males.

Assay Methodology

Quantitation of functional dupilumab was performed using a validated enzyme-linked immunosorbent assay,[15] with an LLOQ of 0.078 mg/L in undiluted human serum. ADAs were assessed in serum samples using a validated electrochemiluminescence bridging immunoassay. Accuracy and precision of the functional dupilumab pharmacokinetic assay were 96%-106% and 3%-9%, respectively. Assays are described in greater detail elsewhere.[16]

Population PK Analysis

A population PK model, originally developed for adults, was applied to the pediatric data without changes in the structure of the model (Figure 1).[16] The model is a 2-compartment population PK model with parallel linear and MM elimination and transit compartments[18] describing lag time in absorption.

The population PK of dupilumab was conducted using Monolix version 2019R2 (LIXOFT, Antony, France) and NONMEM version 7.4.1 (ICON Development Solutions, Dublin, Ireland). Monolix was used to conduct base and covariate population PK analyses. NONMEM was used to conduct bootstrapping and simulations.

Parameterization of the model in terms of rates was chosen to avoid repetitive covariates (a covariate affecting more than 1 parameter), thus minimizing potential
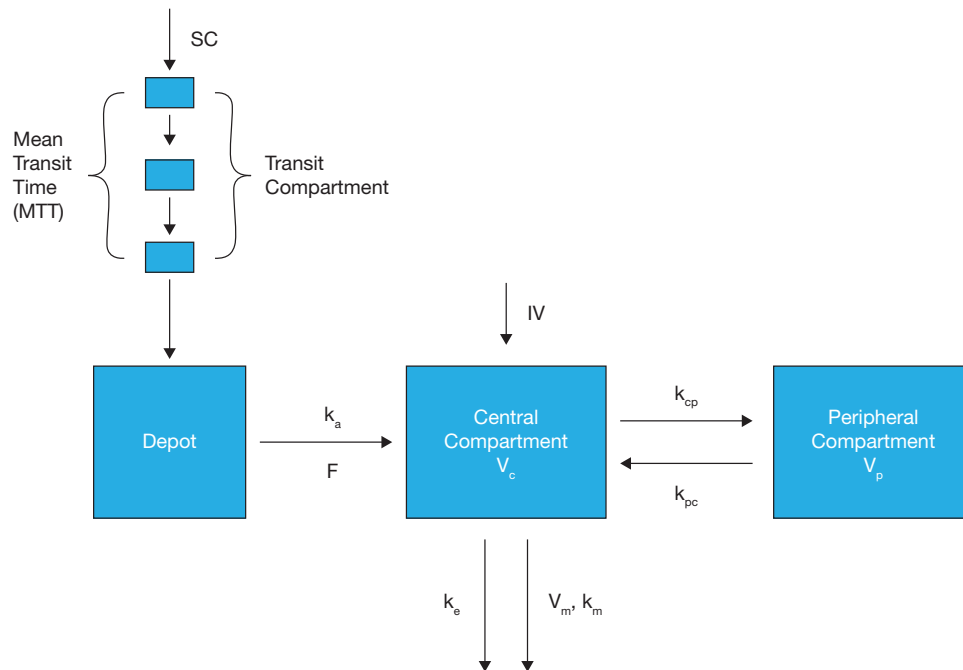
Figure 1. Structural representation of model with parallel Michaelis-Menten and linear elimination of dupilumab. F, bioavailability; IV, intravenous; k_a, absorption rate; k_{cp}, central-to-peripheral rate; k_e, elimination rate; K_m, Michaelis-Menten constant; k_{pc}, peripheral-to-central rate; MTT, mean transit time; V_c, central volume of distribution; V_m, maximum target-mediated rate of elimination; V_p, peripheral volume; SC, subcutaneous.

overparameterization.[15,16] A sensitivity analysis using linear clearance (CL) instead of rate as a parameter in the model was also conducted to demonstrate the consistency of the classic parameterization with this parameterization in terms of rates.

The phase 3 PK data were sparse and mostly trough level, and there were fewer subjects than in the adult studies, making it difficult to obtain precise parameter estimates. The substantially nonlinear PK of dupilumab and the dominance of concentrations in the beta phase further complicated the task. The beta phase, comprised of an underlying linear (predominate) and a nonlinear target-mediated (secondary) pathway, occurs after the distribution phase (alpha phase) and before the nonlinear target-mediated phase, which comprised underlying linear (secondary) and nonlinear (primary) target-mediated pathways. Beta half-life is defined as the half-life during the linear elimination phase, when the target-mediated clearance has a small impact on this half-life (beta phase).

Forward inclusion and backward elimination were applied to validate the use of the adult base model in adolescents and children and to build a covariate model. A covariate was retained in the model when the addition of that covariate resulted in $\alpha \leq .05$, and removal of the covariate resulted when $\alpha > .005$; these P values are associated with changes in objective function value (OFV) of 3.84 and 7.88, respectively.

While using both Monolix and NONMEM, the stochastic approximation expectation-maximization method was utilized to achieve convergence of population PK parameters in the presence of the steep target-mediated phase (singularity),[16] sparse data, predominant trough concentrations, and data below the limit of quantitation (BLQ) values; the importance sampling method followed the stochastic approximation expectation-maximization method to estimate OFV.

The BLQ values were used in the analysis to better characterize the nonlinear elimination phase.[15,16] The frequently used Beal M3 method[19] was implemented to incorporate BLQ observations in the objective function.

Two approaches to model comparison were used. When comparing nested models, P values were obtained using the OFV. The objective function is a mathematical equation describing the deviation of model prediction from observed data to be minimized. When comparing nonnested models, the Bayesian information criterion (BIC) was applied. The BIC is a model selection criterion; the model with the lowest BIC is preferred. An important advantage of the BIC is that it can be used to compare nonnested models.[20]

In the analysis of adolescent data, intercompartmental rates (k_{cp} and k_{pc}), absorption rate (k_a), mean transit time (MTT), and bioavailability (F) were fixed

to adult values to ensure stability of the model. Central volume (V_c), elimination rate (k_e), and target-mediated clearance (V_m) were estimated. The MM constant (K_m) was assessed based on log-likelihood profiling, the way it was done in adults because of the 1-sided stability of this parameter.[16] A similar approach was used in children ≥6 to <12 years of age, except that (1) V_m was estimated using the base model and fixed in the covariate model, and (2) k_a was estimated using semisparse data from the phase 2a R668-AD-1412 study.

The rationale of using study R668-AD-1412 was to account for potential changes in k_a with age and allow for predicting maximum serum concentration (C_{max}) with a higher precision. The data from study R668-AD-1412[21] were not used in the model building because of a higher prevalence of ADAs resulting from the interrupted dosing regimen and because of a small representation of patients ≥6 to <12 years of age with severe AD; a very low incidence of ADAs was found in 2 later phase 3 studies analyzed in this article. As ADAs form within weeks after dosing, C_{max} is observed within days, and absorption of IgG happens before C_{max}, ADAs did not have a meaningful impact on the estimated k_a and predicted C_{max}. This was confirmed by removing patients with high, moderate, and high or any ADA titers from the analysis and comparing k_a.

The rationale of fixing V_m in the covariate model of children ≥6 to <12 years of age was a reduction in the variability of OFV. Although parameters in a base model with estimated V_m were stable, estimates of the OFV had an inflated variability, making *P* values based on the OFV less precise. This was because of the sparsity of the data, predominant trough concentrations, and the pronounced nonlinearity of the target-mediated phase, with a slope approaching a large negative value toward singularity[16] as concentrations approached the LLOQ. Similar to the adult analyses,[16] this singularity resulted in small changes in PK parameters, causing substantial changes in ratios of observed to predicted values and, consequently, in the OFV. The value of V_m was re-estimated in a sensitivity analysis of the covariate model to confirm that it was not affected by added covariates.

Weight was included as a covariate in base models because it is well established that weight is an important covariate of V_c for mAbs.[15,16,22] Weight was also used as a covariate of CL when the model was parameterized using CL instead of rate.

A multiplicative model was used to test for continuous covariates:

$$Y(\lambda_i) = Y \cdot \left[\frac{\lambda_i}{\text{Central value} (\lambda_i)} \right]^{\theta}$$

where $Y(\lambda_i)$ is a population PK parameter adjusted for the covariate, λ_i is an individual value of the covariate, *i* is a subject number, Y is a population PK parameter at median or another selected level of covariate called the central value, and θ is a parameter describing an effect of the covariate on the population PK parameter. When weight was explored as a covariate, the central value was set to 75 kg in the primary analyses. This was done to allow for easy comparison across the age populations. The median value of weight was used in a sensitivity analysis. This is a log-linear relationship, as after log transformation, this widely used nonlinear equation represents a linear relationship between $\ln(Y[\lambda_i])$ and λ_i.

The following multiplicative model was used to test for dichotomous covariates:

$$Y(\lambda_i) = Y \cdot e^{\theta \cdot \lambda_i}$$

where Y is a population PK parameter when $\lambda_i = 0$, and λ_i is equal to 0 or 1.

The NONMEM rather than Monolix definition of shrinkage was used, which is $100\% \cdot (1 - \text{SD}(\eta)/\omega)$, where η is the between-individual variation term (also called ETA) and ω is the population model estimate of the standard deviation in η. Notable shrinkage appears when the data are sparse and/or insufficient to precisely estimate the individual parameters. In such cases, individual parameters shrink toward the population value, reducing $\text{SD}(\eta)$ while leaving ω mostly intact. Shrinkage is specific to individual parameter estimates and does not necessarily reflect the precision of population PK estimates of a covariate impact.

Covariates that were statistically significant in adults[16] were tested in adolescents and in children ≥6 to <12 years of age. These covariates include weight, BMI, race, ADAs at any time, and EASI.[23] As age is of particular interest in children, it was tested as a covariate in multiple sensitivity analyses of the covariate models.

Response variables for the primary covariate model included V_c and k_e. As phase 3 observations were primarily at concentrations at which linear clearance predominates, covariates were not tested on the maximum target-mediated rate of elimination (V_m). In a sensitivity analysis parameterized using CL instead of k_e, V_c and CL were response variables.

Correlated covariates were tested separately and together in sensitivity analyses to confirm results of forward inclusion and backward elimination and to reveal if a statistically significant impact of 1 covariate occurs only because of an association with another covariate. A similar approach was applied to a repetitive covariate to reveal if an impact of this covariate on one parameter occurs only to compensate an absence of this covariate in the model as a predictor of another parameter.

The stability of the base and covariate models was evaluated based on random changes in initial

parameters (empirical assessment of stability), condition numbers (theoretical index of stability), and comparison of the primary and sensitivity analysis results. Model validation was performed by bootstrapping (repeated resampling of subject data from the analysis data set with replacement); visual predictive checks (VPCs); comparison of modeling results across children, adolescents, and adults; sensitivity analyses; and comparison of estimated PK parameters with those published for mAbs.[20,24,25] Bootstrapping was conducted to obtain bootstrap confidence intervals of parameter estimates. VPCs show 10th, 50th (median), and 90th percentiles of observed dupilumab concentrations and model-predicted confidence intervals around predicted percentiles, allowing for visual comparison of observed and model-predicted data. Model-predicted 10th, 50th (median), and 90th percentiles were also added to the VPCs.

The developed models were extensively used to conduct the following simulations for sBLA: (1) exposure (area under the curve C_{max}, and C_{trough}) after the first dose and at steady state, (2) alternative dosing regimens, (3) different loading doses and loading regimens, (4) PK profile and exposure in different weight subgroups, (5) PK profile at different weight cutoffs used to change dosing regimens, and (6) simulations to reveal an impact of covariates on exposure. Variability in weight was simulated within NONMEM simulation codes; weight distribution was assessed using study data and was well approximated by lognormal probability density with 3 parameters. The simulations were used for regulatory submissions and responses, exposure-response analyses, and dose justification. During earlier stages of the dupilumab pediatric program, the phase 2a R668-AD-1412 study[21] was used to predict concentrations in phase 3 studies. Dose selection, dose adjustment, and selection of weight cutoffs in phase 3 studies were based on simulations conducted during phase 3 study design and were intended to ensure that C_{trough} was similar to that in the adult treatment of 300 mg every 2 weeks and C_{max} did not exceed that in the adults. When there were uncertainties in the distribution of weight, age was simulated using a uniform distribution, and parameters of the lognormal distribution of weight were approximated as a function of age using approximations of growth tables from the Centers for Disease Control and Prevention.

As children ≥ 6 to <12 years of age and adolescents were analyzed separately in the sBLAs, the analyses are provided separately in this article. The rationale for analyzing children, adolescent, and adult data separately in the sBLAs was to avoid contamination of the results for a specific pediatric group by the large data set from adults (2041 participants[16]) or by data from a different pediatric group. Contamination of the F, k_{cp}, k_{pc}, k_a, and MTT parameters (which require rich data for assessment) by sparse data in adults was discussed previously.[16] In short, these parameters are based on a small and a rich data set. When small rich and large sparse data sets are integrated, improvement in OFV because of finding their best values is similar to or smaller than the variability in OFV caused by the steep target-mediated phase (singularity).[16] Contamination can also occur, for example, if a parameter-covariate relationship is more complex than the log-linear (the first formula in the Methods section) or stepwise (the second formula in the Methods section) relationship. If a modeled parameter-covariate relationship is not valid, the covariate parameter may gravitate toward an age subgroup with the largest sample size and/or the largest variability in covariates. For example, if there is an association between a PK parameter and a covariate in pediatric patients and there is no such relationship in adults, then an estimate can be closer to the adult one.

Results

Estimates of population PK parameters for the base model are presented in Table 1 for children ≥ 6 to <12 years of age, adolescents, and adults. A full version of Table 1 with between-subject variability in the parameters, variability in residual error, and bootstrap confidence intervals is presented in Supplemental Table 2. The observed versus predicted concentrations are presented in Supplemental Figures 1 and 2 for children ≥ 6 to <12 years of age and adolescents, respectively.

Estimates of population PK parameters for the covariate model are presented in Table 2 for children ≥ 6 to <12 years of age, adolescents, and adults.[16] A full version of this table with between-subject variability in the parameters, variability in residual error, and bootstrap confidence intervals is presented in Supplemental Table 3. The observed versus predicted concentrations are presented in Supplemental Figures 3 and 4 for children ≥ 6 to <12 years of age and adolescents, respectively.

Overall, fewer covariates were identified in the pediatric models compared with the adult model. Population PK parameters were similar across the age groups in both base and covariate models, with a decreasing trend in V_m and k_a and an increasing trend in V_c with age, where V_c was adjusted to the central value of 75 kg. Confidence intervals around k_e overlapped across the age groups. No allometric trends in k_e and beta half-life were observed in the studied populations within or across the weight and age groups (ie, k_e and beta half-life were similar across children, adolescents, and adults, and weight and age were not statistically

Table 1. Base Models: Population PK Parameters in Children ≥6 to <12 Years of Age, Adolescents, and Adults

	Parameter Estimate (SE)		
Parameter Name	Children ≥6 to <12 Years of Age	Adolescents ≥12 to <18 Years of Age	Adults ≥18 Years of Age
PK parameter			
V_c (L)	2.22 (0.0945)	2.54 (0.0473)	2.76 (0.021)
k_e (1/d)	0.0444 (0.00155)	0.0508 (0.00172)	0.0448 (0.000490)
V_m (mg/L/d)	1.64 (fixed)	1.46 (0.0314)	1.07 (fixed)
K_m (mg/L)	0.01 (fixed)	0.01 (fixed)	0.01 (fixed)
k_{cp} (1/d)	0.211 (fixed)	0.211 (fixed)	0.211 (fixed)
k_{pc} (1/d)	0.310 (fixed)	0.310 (fixed)	0.310 (fixed)
k_a (1/d)	0.641 (fixed)	0.306 (fixed)	0.306 (fixed)
MTT (d)	0.105 (fixed)	0.105 (fixed)	0.105 (fixed)
F (unitless)	0.642 (fixed)	0.642 (fixed)	0.642 (fixed)
Covariate			
$V_c \sim$ weight	0.864 (0.0371)	0.853 (0.0438)	0.919 (0.027)

d, day; F, bioavailability; k_a, absorption rate; k_{cp}, central-to-peripheral rate; k_e, elimination rate; K_m, Michaelis-Menten constant; k_{pc}, peripheral-to-central rate; MTT, mean transit time; PK, pharmacokinetics; SE, standard error; V_c, central volume of distribution; V_m, maximum target-mediated rate of elimination.
SE of V_m in the pediatric base model, where it was estimated rather than fixed as 0.0511 mg/L/d.
Adult data are reproduced from Kovalenko et al, 2020,[16] with the permission of John Wiley & Sons, Inc.

Table 2. Covariate Models: Population PK Parameters (SE) in Children ≥6 to <12 Years of Age, Adolescents, and Adults

	Parameter Estimate (SE)		
Parameter Name	Children ≥6 to <12 Years of Age	Adolescents ≥12 to <18 Years of Age	Adults ≥18 Years of Age
PK parameter			
V_c (L)	2.18 (0.0872)	2.47 (0.0501)	2.74 (0.021)
k_e (1/d)	0.0446 (0.00152)	0.0520 (0.00188)	0.0477 (0.00078)
V_m (mg/L/d)	1.64 (fixed)	1.43 (0.0379)	1.07 (fixed)
K_m (mg/L)	0.01 (fixed)	0.01 (fixed)	0.01 (fixed)
k_{cp} (1/d)	0.211 (fixed)	0.211 (fixed)	0.211 (fixed)
k_{pc} (1/d)	0.310 (fixed)	0.310 (fixed)	0.310 (fixed)
k_a (1/d)	0.641 (fixed)	0.306 (fixed)	0.306 (fixed)
MTT (d)	0.105 (fixed)	0.105 (fixed)	0.105 (fixed)
F (unitless)	0.642 (fixed)	0.642 (fixed)	0.642 (fixed)
Covariates			
$V_c \sim$ weight	0.849 (0.0345)	0.755 (0.0517)	0.817 (0.031)
$V_c \sim$ albumin	−0.525 (0.149)	−	−0.653 (0.072)
$k_e \sim$ BMI	−	0.357 (0.116)	0.368 (0.053)
$k_e \sim$ EASI	0.169 (0.0471)	0.356 (0.0523)	0.143 (0.021)
$k_e \sim$ race (white)	−	−	0.123 (0.018)

—, covariate was not statistically significant; ADA, anti-drug antibody; BMI, body mass index; d, day; EASI, Eczema Area and Severity Index; F, bioavailability; k_a, absorption rate; k_{cp}, central-to-peripheral rate; k_e, elimination rate; K_m, Michaelis-Menten constant; k_{pc}, peripheral-to-central rate; MTT, mean transit time; PK, pharmacokinetics; SE, standard error; V_c, central volume of distribution; V_m, maximum target-mediated rate of elimination.
V_m and SE of V_m in the pediatric covariate model, where it was estimated rather than fixed, are 1.57 and 0.00830 mg/L/d, respectively.
Adult data are reproduced from Kovalenko et al, 2020,[16] with the permission of John Wiley & Sons, Inc.

significant covariates of k_e). The statistically significant but small numerical impact of race on k_e in adults[16] was not replicated in adolescents and children ≥6 to <12 years old. An impact of BMI on k_e, observed in adolescents and adults,[16] was not replicated in children ≥6 to <12 years old. An impact of albumin on V_c, which was observed in children ≥6 to <12 years of age and adults,[16] was not observed in adolescents.

Empirical assessment of stability revealed good stability of parameters in base and covariate models and
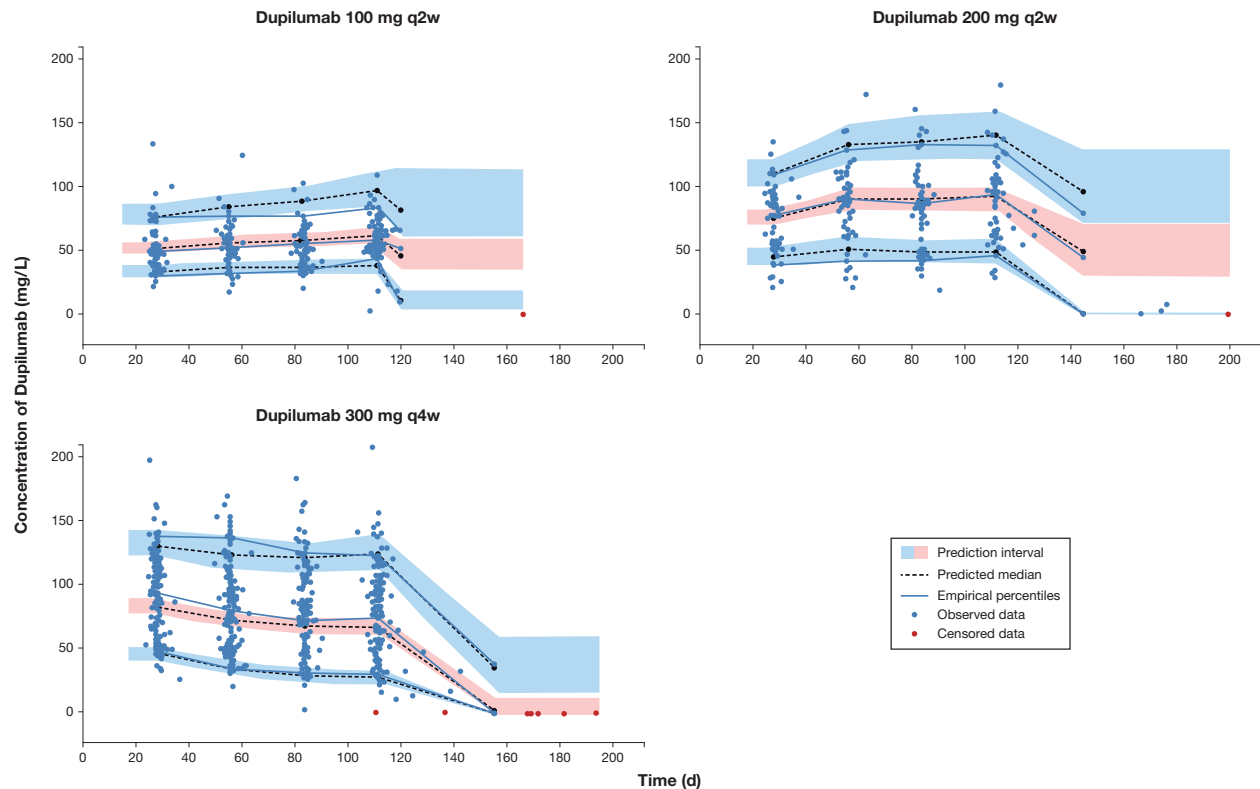
Figure 2. Visual predictive check of dupilumab concentrations by treatment regimen—primary covariate model for children ≥6 to <12 years of age. d, day; q2w, every 2 weeks; q4w, every 4 weeks.

with either estimated or fixed V_m in the covariate model developed for children.

Shrinkage of SDs of ETAs for k_e and V_c in the base model developed for patients ≥6 to <12 years of age was 28.3% and 33.5%, respectively; shrinkage in the base adolescent model was 11.6% and 30.3%, respectively. Shrinkage of SDs of ETAs for k_e and V_c in the covariate model developed for patients ≥6 to <12 years of age was 27.9% and 35.9%, respectively; shrinkage in the base adolescent model was 13.6% and 32.4%, respectively. The VPCs are presented in Figures 2 and 3 for children ≥6 to <12 years of age and adolescents, respectively.

Sensitivity analyses in which CL instead of k_e is a response variable are presented in Tables 3 and 4 for children ≥6 to <12 years of age and adolescents, respectively; a similar comparison of the parameterizations in adults was also published.[16] As fixed PK parameters are the same as in the base and covariate models (Tables 1 and 2), they are excluded from Tables 3 and 4. Full versions of these tables are provided in Supplemental Tables 4 and 5. In the model utilizing CL (Table 3, children ≥6 to <12 years of age), impact of albumin on V_c and CL was borderline significant at the backward elimination step; P values based on chi-square tests were somewhat lower or higher than .005 because of some vari-

ability in OFV, with significance depending on the initial parameters. A conservative approach was exercised in this case, and these covariates were included in the model. The parameters of the model specified using CL instead of k_e (Tables 3 and 4) were remarkably similar to those of the primary covariate model. In these analyses, significant covariates of V_c or k_e are also significant covariates of CL, with repetitive covariates occurring only in the model parameterized in terms of CL. The impact of weight on V_c when k_e was used (Table 2) was essentially the same as the impact of weight on CL in children (Table 3) and adolescents (Table 4). Likewise, values of covariate parameters that reflect an association between k_e and covariates were similar to those that reflect an association between CL and the same covariates.

As population PK parameters of the primary base and covariate models were estimated at a weight of 75 kg to allow for informed model comparisons across the age populations, a sensitivity analyses was conducted in which weight was set to median values, reducing V_c from 2.18 to 1.03 L in children ≥6 to <12 years of age and from 2.47 to 2.04 L in adolescents. The remaining parameter estimates were remarkably close to those obtained in the primary analyses.
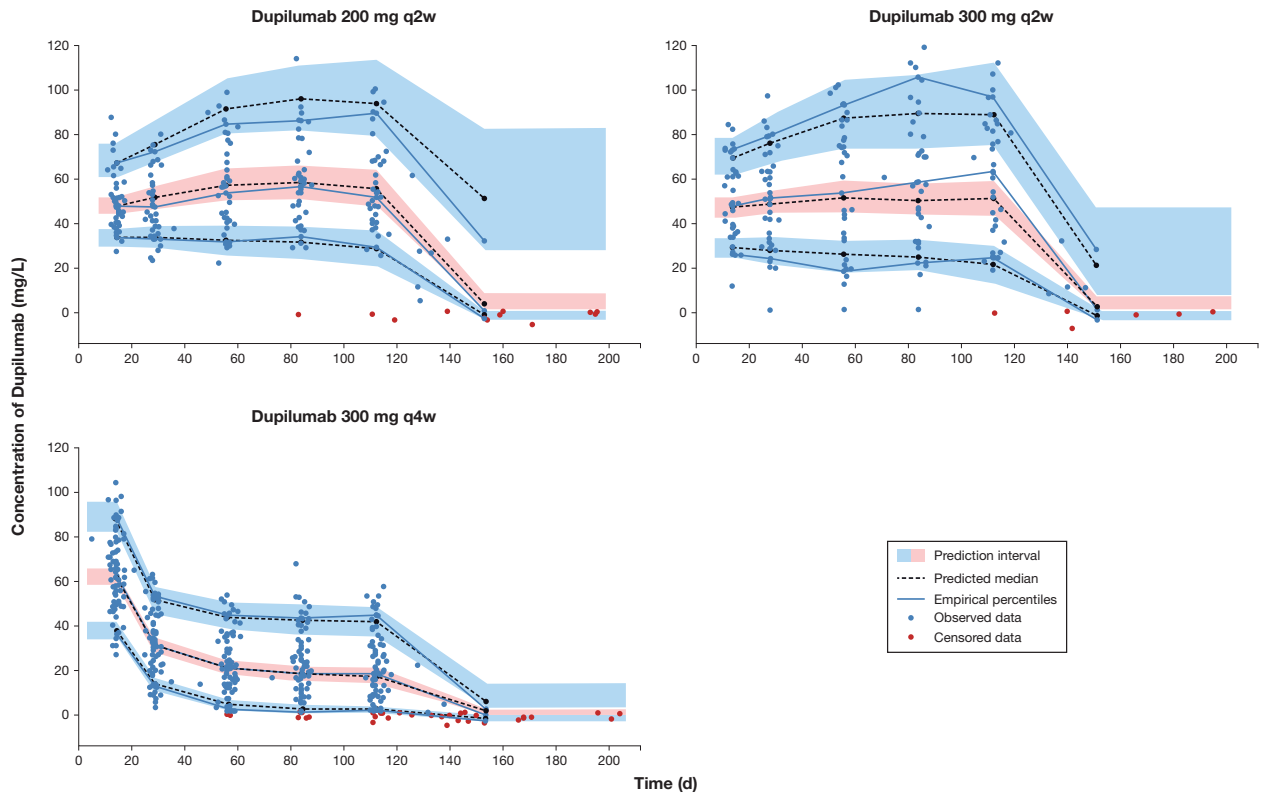
Figure 3. Visual predictive check of dupilumab concentrations by treatment regimen—primary covariate model for adolescents. d, day; q2w, every 2 weeks; q4w, every 4 weeks.

Table 3. Covariate Model Developed for Children ≥6 to <12 Years of Age: Parameterizations Using Clearance and Rate

Parameter Name	Parameterized Using CL		Parameterized Using k_e	
	Estimate (SE)	P	Estimate (SE)	P
PK parameter				
V_c (L)	2.09 (0.173)	–	2.18 (0.0872)	–
k_e (1/d)	0.0478[a]	–	0.0446 (0.00152)	–
CL (L/d)	0.100 (0.00492)	–	0.0972[a]	–
Covariates				
$V_c \sim$ weight	0.787 (0.0857)	$< 2.2 \times 10^{-16}$	0.849 (0.0345)	$< 2.2 \times 10^{-16}$
$V_c \sim$ albumin	−0.842 (0.355)	.0177	−0.525 (0.149)	.000428
$k_e \sim$ EASI	–	–	0.169 (0.0471)	.000347
CL $\sim$ weight	0.863 (0.051)	$< 2.2 \times 10^{-16}$	–	–
CL $\sim$ albumin	−0.451 (0.217)	.0374	–	–
CL $\sim$ EASI	0.163 (0.0483)	.000763	–	–
Log-likelihood estimation				
Bayesian information criterion	7484.68	–	7471.85	–

—, not calculated; BMI, body mass index; CL, clearance; EASI, Eczema Area and Severity Index; k_e, elimination rate; SE, standard error; V_c, central volume of distribution.
[a] Parameter was derived using estimated population PK parameters.

Fixing F to 1 instead of the adult value did not lead to meaningful changes in parameters other than V_c and did not impact model predictions.

Discussion

Overall, the population PK analyses presented here reveal similar modeling results for the adult and

Table 4. Adolescent Covariate Model: Parameterizations Using Clearance and Rate

Parameter Name	Parameterized Using CL		Parameterized Using k_e	
	Estimate (SE)	P	Estimate (SE)	P
PK parameter				
V_c (L)	2.45 (0.0583)	–	2.47 (0.0501)	–
k_e (1/d)	0.0539[a]	–	0.0520 (0.00188)	–
CL (L/d)	0.132 (0.00656)	–	0.128[a]	–
V_m (mg/L/d)	1.37 (0.0797)	–	1.43 (0.0379)	–
Covariates				
$V_c \sim$ weight	0.747 (0.0657)	$< 2.2 \times 10^{-16}$	0.755 (0.0517)	$< 2.2 \times 10^{-16}$
$k_e \sim$ BMI	–	–	0.357 (0.116)	.00212
$k_e \sim$ EASI	–	–	0.356 (0.0523)	9.89×10^{-12}
CL $\sim$ weight	0.712 (0.174)	4.28×10^{-05}	–	–
CL $\sim$ BMI	0.437 (0.212)	.0389	–	–
CL $\sim$ EASI	0.348 (0.0523)	2.92×10^{-11}	–	–
Log-likelihood estimation				
Bayesian information criterion	5348.79	–	5347.69	–

—, not calculated; BMI, body mass index; CL, clearance; EASI, Eczema Area and Severity Index; k_e, elimination rate; PK, pharmacokinetics; SE, standard error; V_c, central volume of distribution; V_m, maximum target-mediated rate of elimination.
[a] Parameter was derived using estimated population PK parameter.

pediatric populations, including an absence of substantial differences in PK parameters, a smaller but still similar set of covariates, an absence of allometric changes in k_e with changes in weight, and better performance and interpretability of the model parameterized in terms of rates (as opposed to CLs) in the presence of sparse data and steep target-mediated clearance.

Although k_a and V_m somewhat decreased with age, no further dose adjustment for covariates was needed in addition to that already implemented in the phase 3 studies.

As shrinkage mostly affects individual PK parameter estimates and as the population PK approach (rather than linear regression analysis of individual parameter vs covariates) was used for covariate search, it is unlikely that the observed moderate shrinkage had a meaningful impact on the covariate assessment.

The estimated k_a in children ≥6 to <12 years of age was somewhat higher than the adult value[16] and consistent with the reported higher k_a in children.[25,26] Sensitivity analyses demonstrated that a percent change in k_a leads to a considerably smaller percent change in C_{max}, implying that the potential impact of the change in k_a is negligible.

It is expected that when a target of mAb is in the blood, K_m will be comparable to a half-effective concentration because, at this concentration, mAbs clear 50% of the target in the central compartment. Therefore, with a K_m of 0.01 mg/L, a dupilumab concentration of 0.09 mg/L is expected to eliminate

90% of the target in circulation. The minimal model-predicted median steady-state trough concentration of dupilumab across pediatric biweekly treatment groups is ~57 mg/L; the monthly treatments were tested as potentially sub-efficacious in some patients. Concentrations of this or higher magnitude were selected to achieve the desired efficacy; the value of 57 mg/L far exceeds 0.09 mg/L, implying that some key target receptors may be located in tissue. An example of such tissue may be skin, which constitutively expresses IL-4r.[27]

The V_m estimates in children ≥6 to <12 years of age and adolescents were somewhat higher than in adults. In a sensitivity analysis, V_m was fixed to the adult value of 1.07 mg/L/d, leading to a statistically significant worsening in OFV in both pediatric populations. Thus, it is possible that there is a trivial inverse relationship between V_m and age.

Similar to the analyses of adult data,[16] the stepwise approach to covariate model building in children and adolescents (with some parameters fixed based on previous validated models) was essential to minimizing the effect of sparse data, predominant trough concentrations, and the steep target-mediated phase (singularity) on PK parameters, model convergence, and OFV variability.

The impact of BMI on k_e observed in adolescents and adults[16] was not replicated in children ≥6 to <12 years of age, presumably because of a smaller sample size and less variability in BMI in this age group (SD of 3.35, 6.91, and 5.47 kg/m² in children ≥6 to <12 years,

adolescents, and adults, respectively). Although variability in albumin was similar across age groups (SD of 3.19, 3.20, and 3.82 g/L in children ≥ 6 to <12 years, adolescents, and adults, respectively), albumin had an impact on V_c in children ≥ 6 to <12 years of age and adults,[16] but not in adolescents. This difference could be because of statistical variability and differences in the sample size.

The impact of rare ADAs on k_e or CL in adolescents was statistically significant, but exceedingly small. In the model developed for children ≥ 6 to <12 years of age, the impact of rare ADA was not statistically significant. As ADAs cannot be directly compared across various products because of different procedures, chemicals, equipment, and assays, the impact of ADAs is not presented.

Fixing bioavailability to the adult value[16] or any other value in the pediatric models had no impact on model prediction because the model adjusts V_c to account for changes in F. For example, if F is 1.1-fold higher in adolescents than in adults, the model will decrease V_c 1.1-fold in adolescents, making predictions the same as if bioavailability has been estimated. In a model parameterized in terms of rates, fixing F to another value will change V_c without impacting the remaining population PK parameters or model predictions; if CL is used instead of k_e, the model will decrease both V_c and CL proportionally without impacting the remaining population PK parameters or model predictions. Thus, potential changes in F with age were accounted by the model via changes in V_c and CL. These features make the assessment of F in pediatric patients mostly fruitless. An assessment of bioavailability in children requires intravenous studies with rich sampling, which are neither ethical nor necessary to collect.

An absence of meaningful or consistent allometric changes in k_e across or within the age groups (Supplemental Table 3) suggests that no allometric scaling of k_e of mAbs within species is necessary. As mAbs have longer half-lives during the early months of infancy than those after infancy,[28] this result cannot be extrapolated to infants. As beta half-life is a function of k_e, k_{cp}, and k_{pc}, this suggests no allometric changes in beta half-life occur. Similarity of k_e and derived beta half-life across the age populations based on sensitivity analyses, in which V_m in children ≥ 6 to <12 years of age and adolescents was fixed to the adult value of 1.07 mg/L/d, strengthened the conclusion that scaling across age groups may not be needed. The calculated beta half-life was 27.1, 23.4, and 25.4 days in children ≥ 6 to <12 years of age, adolescents, and adults, respectively; differences can be explained by variability in the parameter estimates. This result is different from the ~ 2-fold lower beta half-life in children than in adults

reported in the review by Bensalem et al[29] and also different from the allometric decline in k_e with increasing weight predicted by formulas used by Robbie et al.[25] During the early stages of the dupilumab pediatric program, the phase 2a R668-AD-1412 study[21] was used to develop a preliminary population PK model. The calculated beta half-lives in children ≥ 6 to <12 years of age and adolescents were similar to those estimated using phase 3 data, providing an external validation. Although the data suggest that no allometric scaling of k_e of mAbs within species is necessary, this notion considers 1 mAb only and must be validated by applying such analyses to other human mAbs.

Calculated beta half-life and CL in children and adolescents cannot be used to predict time to a concentration of interest because of markedly nonlinear kinetics. Predictions using population PK models should be used instead. Likewise, no useful terminal half-life can be calculated, as half-life continuously and substantially changes over time during the terminal target-mediated phase of elimination.[16] A plot of instantaneous half-life versus time in adults[16] demonstrated that it changes from ~ 25 days in the beta phase to a value approaching zero in the target-mediated phase. As adult and pediatric models and PK profiles are similar, this result is valid in pediatric patients.

The sensitivity analysis utilizing CL instead of k_e as a response variable confirmed the robustness of the models parameterized in terms of rates. Significant covariates of V_c or k_e were also significant covariates of CL, presumably because $CL = k_e \cdot V_c$. The presence of repetitive covariates only in the model parameterized in terms of CL is consistent with the results in adults.[16] Like the analysis of adult data,[16] parameterization of the covariate model in terms of rates required fewer covariates (Tables 3 and 4), demonstrated higher significance of covariates based on the Wald test and worsened BIC. The BIC worsened in children ≥ 6 to <12 years of age, and a slightly worsened BIC was observed in adolescents. Because of a smaller population and fewer covariates in pediatric than in adult analyses,[16] the impact of parametrization on the BIC was similar or lower, and the impact on stability was higher in pediatric patients. Although a statistically significant correlation between CL and V_c[16] was found in adult patients, this correlation coefficient was unstable in the pediatric models and was excluded from the analyses (Supplemental Tables 4 and 5). In addition, if the pediatric models are further reparameterized, with peripheral volume (V_p) and intercompartmental clearance (Q) replacing intercompartmental rates k_{cp} and k_{pc}, it is expected that covariates of V_c (weight and albumin) will also be associated with Q and V_p, because $Q = V_c \cdot k_{cp}$, and $V_p = V_c \cdot k_{cp}/k_{pc}$, respectively.[16] Not only does the sparsity of the data not allow for proper

estimation of covariate effects on V_p and Q, but it also does not allow for proper estimation of V_p and Q, and these parameters must be fixed. Although NONMEM and Monolix do not restrict us from applying covariates to fixed parameters, such an approach raises concerns and is difficult to justify. In such cases, increasing the sample size of sparse data does not resolve the issue of insufficient information in the data; intravenous administration and rich data are needed to estimate V_p and Q. An absence of covariates of V_p and Q in a model may skew some parameter estimates. For example, an absence of variability in modeled V_p and Q caused by a covariate may increase variability in V_c and CL, and an absence of impact of weight on V_p may increase the impact of weight on V_c. If rich intravenous data are available and V_p and Q can be estimated (which is rare in pediatric studies), the number of covariates repeatedly affecting different parameters may further increase. This can complicate interpretation and still overparameterize the model.

When a model is parameterized using rates, it is important to note that the impact of a covariate on V_c was propagated to CL, V_p, and Q because $CL = V_c \cdot k_e$, $Q = V_c \cdot k_{cp}$, and $V_p = V_c \cdot k_{cp}/k_{pc}$, respectively.[15,16,25] Furthermore, an impact of a covariate on k_e was propagated to CL because $CL = V_c \cdot k_e$.[16,25] Therefore, consistent with the adult data,[16] the parameterization of the covariate model in terms of rates can be a useful alternative to CL, Q, and V_p, because it implicitly accounts for the impact of weight on these parameters and can reduce the number of repetitive covariates, increase statistical significance of valid covariates, improve model convergence, stability, and BIC, and allow for a more mechanistic interpretation of the covariate impact.[16] The equations suggest that the model's parameterization in terms of rates is equal to parameterization in terms of clearances under the following conditions: (1) a covariate affecting V_c when rates are used is imposed on CL, Q, and V_p when CLs and V_p are used; (2) a covariate parameter is the same for V_c, CL, Q, and V_p; and (3) a covariate parameter affecting k_e when rates are used is imposed on CL when CL is used. Such parameterization becomes cumbersome and potentially difficult to follow. Allowing the same covariate (eg, weight) of V_c, CL, Q, and V_p to have different covariate parameters is likely to overparameterize the model. For example, it is well known that weight affects CL, Q, and V_p.[25] When weight was used as a covariate of CL, Q, and V_p in children, the model was overparameterized, whether Q and V_p were estimated or fixed. Thus, it was necessary to remove some repetitive covariates that are already known to affect V_c, CL, Q, and V_p. As a result, the covariates were not fully and properly accounted for. An alternative solution is to fix such covariates to historical values,[25] but such values can differ across drugs.

The advantages of model parameterization in terms of rates are likely to be less evident if the data set is rich and sufficiently large, but rich data are rarely collected in pediatric studies, particularly in phase 3 studies. However, as clinical pharmacologists are accustomed to the idea that CL is a primary PK parameter, it can be helpful to also present the alternate parameterization utilizing CL, depending on the questions being addressed.

Conclusions

The base and covariate population PK models described the PK of dupilumab in phase 3 clinical trials of children ≥ 6 to <12 years of age and adolescents well. The values below LLOQ supplied essential information for proper characterization of the target-mediated phase. Although there were several statistically significant covariates, only body weight had an important effect on V_c and was used for dose adjustment within pediatric age populations. Although k_a and V_m somewhat decreased with age, no dose adjustment was needed in addition to that already implemented in the phase 3 studies. A stepwise approach to pediatric model building, with some less influential parameters fixed to adult values,[16] was essential to account for the sparsity of the data, predominant trough samples, and the steep target-mediated phase. Parameterization of pediatric models in terms of rates can be a useful alternative to parameterization in terms of clearances, allowing for a reduced number or absence of repeated covariates and avoiding overparameterization while appropriately accounting for covariates. Finally, k_e and beta half-life were similar across and within the studied age groups, suggesting that no allometric scaling of k_e may be needed for dupilumab, keeping in mind that this result still has to be validated, applying similar analysis to additional human mAbs.

Conflicts of Interest

Funding

Author Contributions

P.K. wrote the first draft of the article. P.K., J.D.D., A.B., B.S., and A.T.D. designed the research; P.K. and M.A.K. performed the research; P.K., N.H., and C.X. analyzed the data. All authors reviewed and approved the final version of the article.

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Supplemental Information

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