ARTICLE

Population pharmacokinetic analysis of dupilumab in adult and adolescent patients with asthma

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Abstract

A population pharmacokinetic model was developed using data from healthy subjects and patients with moderate-to-severe asthma receiving intravenous or subcutaneous dupilumab doses. A total of nine phase I to phase III studies were pooled (202 healthy subjects and 1912 patients with asthma including 68 adolescents) in the model development. The best model was a two-compartment model with parallel linear and nonlinear Michaelis–Menten elimination with first order absorption. The PK parameter estimates were distribution volume of central compartment 2.76 L, linear elimination rate 0.0418 1/day, and subcutaneous bioavailability 60.9%. Pharmacokinetics (PK) properties of dupilumab in patients with asthma were determined to be comparable to those of healthy subjects and patients with atopic dermatitis. Only body weight exerts a notable effect explaining between-subject variability in dupilumab PK, but dose adjustment for weight is not warranted based on results from clinical studies. There is no PK difference between adolescent and adult patients with asthma after correction for body weight.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
No dupilumab population pharmacokinetic (PopPK) model for patients with asthma are available in literature. The knowledge gained on this topic will provide great value in the therapeutic area of asthma, and will benefit a broad community.

WHAT QUESTION DID THIS STUDY ADDRESS?
This PopPK model was developed to characterize the PK properties of dupilumab in patients with asthma and assess the covariate impact on dupilumab PK.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
The PK of dupilumab in adult and adolescent patients with asthma was adequately described by a two-compartment model with linear and nonlinear elimination plus first order absorption. PK properties of dupilumab in patients with asthma are comparable to those of patients with atopic dermatitis. Only body weight exerted a noticeable effect explaining between-subject variability in dupilumab PK. There is no PK difference between adolescent and adult patients after correction for body weight.

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HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/ OR THERAPEUTICS?
This PopPK model was used to optimize study design for dosing regimen according to the clinical need in future asthma studies.

INTRODUCTION

Asthma is a heterogenous disease usually characterized by variable airway limitation, airway hyper-responsiveness, and chronic airway inflammation, which lead to the occurrence of clinical symptoms (i.e., wheeze, shortness of breath, chest tightness, and cough).[1] Approximately 339 million people worldwide have asthma, which results in ~ 420,000 deaths each year.[2] Approximately 23–56% of patients with asthma worldwide have uncontrolled persistent disease despite therapy.[3–5] Patients with uncontrolled persistent asthma have an increased risk of severe exacerbations, hospitalization, morbidity, and death versus patients with well-controlled asthma.[6–11] Oral corticosteroids (OCS) are frequently prescribed to patients with uncontrolled persistent asthma, but are associated with substantial short- and long-term adverse effects and high costs of managing OCS-related morbidity.[5,12–14]

The poor response to current treatment options in some patients with asthma reflects the heterogeneity of asthma pathogenesis. Inflammation is an important component in the pathogenesis of asthma. Approximately 50–70% of patients with asthma have evidence of type 2 inflammation.[14–19] Type 2 inflammation is characterized by key cytokines, such as interleukin-4 (IL-4), interleukin-13 (IL-13), and interleukin-5 (IL-5) released by either innate or adaptive immune system.[19,20]

Dupilumab is a recombinant human immunoglobulin-G4 (IgG4) monoclonal antibody (mAb) that binds specifically to the shared receptor component for IL-4 and IL-13, thus inhibiting the dual signaling pathways. IL-4 and IL-13 are key and central drivers of type 2 inflammation in asthma and other type 2 inflammatory diseases, such as atopic dermatitis (AD) and chronic rhinosinusitis with nasal polyposis (CRSwNP).[1]

Dupilumab was approved in the United States for s.c. injection as an add-on maintenance treatment of patients with moderate-to-severe asthma aged greater than or equal to 12 years with an eosinophilic phenotype or with OCS-dependent asthma.[21] It was also approved in the European Union for the treatment of patients with severe asthma with type 2 inflammation characterized by raised blood eosinophils (EOS) and/or raised fractional exhaled nitric oxide (FeNO) who are inadequately controlled with high-dose inhaled corticosteroids (ICS) plus another asthma medicinal product for maintenance treatment,[22] and in Japan for the treatment of bronchial asthma (only in patients with severe or refractory asthma whose symptoms are inadequately controlled with existing therapy).[23] In addition to asthma, dupilumab is approved for adult and pediatric patients aged 6 years and older with AD and adult patients with CRSwNP.

The aim of this study was to develop a population pharmacokinetic (PopPK) model for dupilumab and assess the influence of intrinsic and extrinsic factors on dupilumab PK in patients with asthma. Data were integrated from nine phase I to phase III trials in adult healthy subjects and adult and adolescent patients with asthma. Prior PopPK assessments in healthy subjects and patients with AD provided the foundation for the analysis strategy of the asthma population. The final asthma PopPK model was used to characterize the PK of dupilumab in severe OCS-dependent patients with asthma (not included in model development) and the predictive performance of the final asthma PopPK model was evaluated.

METHODS

Study design and population

The PopPK analysis was performed with data pooled for healthy subjects after a single dupilumab dose by i.v. or s.c. routes (1–12 mg/kg i.v. or 75–600 mg s.c.) and for patients with moderate-to-severe asthma after repeated s.c. administration of 200 or 300 mg at every week (qw), every 2 weeks (q2w), or every 4 weeks (q4w). Dupilumab was either administered alone (phase I studies) or as an add-on treatment to medium-to-high-dose inhaled corticosteroids plus up to two long-acting β2 agonists (phase II and III studies). A summary of the nine studies included in the PopPK model development and one phase III study (NCT02528214) not included in the model development but used to assess the PopPK model predictive ability is provided in Table 1. These studies were conducted 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.

Assay methodology

Dupilumab concentrations in serum were measured using a validated enzyme-linked immunosorbent assay (ELISA).[24,25]

TABLE 1 Summary of clinical studies included in the PopPK analysis

Phase	Study	Dupilumab dose regimens[a]	Duration of treatment	Population	PK sampling	N[b]
1	NCT01015027	i.v.: 1, 3, 8 and 12 mg/kg; s.c.: 150 and 300 mg	Single dose	Healthy adults	Dense sampling	36
1	NCT01484600	s.c.: 300 mg	Single dose	Healthy adults	Dense sampling	36
1	NCT01537653	s.c.: 75, 150, 300, and 600 mg	Single dose	Healthy adults (Japanese)	Dense sampling	24
1	NCT01537640	s.c.: 300 mg	Single dose	Healthy adults	Dense sampling	30
1	PKM14161	s.c.: 300 mg	Single dose	Healthy adults	Dense sampling	38
1	PKM14271	s.c.: 200 mg	Single dose	Healthy adults	Dense sampling	38
2a	NCT01312961	s.c.: 300 mg qw	12 weeks	Adult patients with persistent moderate to severe eosinophilic asthma	Sparse sampling	52
2b	NCT01854047	s.c.: 300 mg q2w, q4w (with a 600 mg loading dose) and 200 mg q2w, q4w (with a 400 mg loading dose)	24 weeks	Adult patients with persistent moderate to severe asthma	Sparse sampling	611
3	NCT02414854	s.c.: 300 mg q2w (with a 600 mg loading dose) and 200 mg q2w (with a 400 mg loading dose)	52 weeks	Adult and adolescent patients with persistent moderate to severe asthma	Sparse sampling	1260
3	NCT02528214[c]	s.c.: 300 mg q2w (with a 600 mg loading dose)	24 weeks	Adult and adolescent patients with severe, OCS-dependent asthma	Sparse sampling	103

Abbreviations: OCS, oral corticosteroids; PK, pharmacokinetics; PopPK, population pharmacokinetic.

[a]In patients with asthma, dupilumab was an add-on maintenance treatment on top of asthma standard-of-care treatment.

[b]Number exposed to dupilumab in each study; First nine studies were used in the asthma PopPK model development, in which there were originally 2125 subjects, with 202 adult healthy subjects and 1923 patients with asthma (1855 adults and 68 adolescents). Eleven subjects were excluded in the final PopPK dataset after excluding less than the lower limit of quantification PK samples and greater than the lower limit of quantification predose PK samples.

[c]Data from study NCT02528214 were not included in the asthma PopPK model development but used to evaluate the established asthma PopPK model using maximum a posteriori probability Bayesian approach.

The assay determines the concentrations of dupilumab with either one or two available binding sites (referred to as functional dupilumab). Concentrations of functional dupilumab (i.e., dupilumab not bound to cell receptors and with at least one arm free for binding) were measured. In this functional assay, dupilumab was used as the assay standard, and human IL-4 receptor alpha (IL-4Rα) served as the capture reagent. The assay does not detect dupilumab when both binding sites are occupied by sIL-4Rα (soluble form), or when at least one site is bound to mIL-4Rα (membrane-bound form). The lower limit of quantitation (LLOQ) of dupilumab is 0.078 mg/L in undiluted human serum.

Anti-dupilumab antibodies (antidrug antibodies [ADAs]) were assessed in serum samples using a validated electrochemiluminescence bridging immunoassay.[24,25] The method involved ADA screening, confirmation, and titer determination in serum samples. The screening assay identified potentially positive samples, which were then analyzed in the confirmation (drug specificity) assay. Samples were considered negative for ADAs if either the screening or confirmation tests were negative. Samples that were positive in the confirmation assay were considered to be positive for ADAs and a titration assay was then used to determine the ADA titer.

PopPK analysis

The PopPK analysis was performed with NONMEM version 7.3 (ICON Development Solutions, Dublin, Ireland) running on a LINUX cluster of multiprocessor computers. Analysis dataset creation was conducted using SAS version 9.4 software (SAS Institute, Cary, NC). R statistical software version 3.3.2 was used for data tabulation, visualization, and simulations.[26]

Placebo data, predose and post-dose PK samples that were below the LLOQ, as well as predose PK samples above the LLOQ, were excluded from the analysis. A sensitivity analysis with the M3 likelihood-based method[27] for the handling of below the limit of quantitation (BLOQ) values was performed during model development and for final asthma PopPK model. Outliers were identified and excluded from the analysis based on visual inspection of the data, inspection of the output for absolute value of conditional weighted

residuals (CWRES) greater than or equal to five and diagnostic plots. The final PopPK model was evaluated using the dataset with and without outlier exclusion to assess the potential impact of the outliers on key PK parameters.[28]

Based upon PK similarity between asthma and AD populations, the base model structure of previously developed AD PopPK models[24,25] (2-compartment model with parallel linear and nonlinear elimination) served as the basis for asthma PopPK base model development with two options of absorption models (i.e., transit compartment and first order) evaluated. A step-wise modeling approach, which was utilized in the development of AD PopPK model, was explored in asthma PopPK model development. Briefly, PK parameters were first estimated using extensive PK data from phase I studies in healthy subjects. The asthma model was subsequently fitted to pooled data from healthy subjects and patients with asthma data with model parameters fixed at the prior values in the healthy subject model. An alternative one-step analysis approach of pooled data from healthy subjects and patients with asthma, with no parameter fixed at prior values, was also evaluated. The final asthma PopPK model structure and modeling approach were selected based on overall model performance, including the examination of parameter precision, objective function value (OFV), goodness-of-fit plots, and model prediction performance.

Given the previously well characterized body weight (WT) effect on dupilumab PK based on the AD PopPK model, WT was included as a covariate on central volume in the base model for patients with asthma.[24,25] After the base model selection, demographics (gender, age, and race), laboratory parameters (creatinine clearance calculated using the Cockcroft-Gault equation[29] and normalized to body surface area [CLCRN], albumin [ALB], alanine amino transferase [ALT], aspartate amino transferase [AST], alkaline phosphatase [ALP]), baseline biomarkers/disease markers (EOS, FeNO, forced expiratory volume in one second [FEV1] percentage of predicted normal), immunogenicity (stationary ADA [positive at any time or negative all the time], stationary ADA status at patient level [negative, pre-existing, treatment emergent, and treatment-boosted] or time varying ADA status at the sample level [positive or negative]), and population (healthy subjects vs. patients with asthma) were tested as potential covariates. The effect of concomitant medications (leukotriene antagonists, long-acting beta agonist, systemic corticosteroids, and methylxanthines) was tested by the comparison of post hoc predicted PK exposures.

A univariate analysis of each covariate with an observable trend was performed. The relationships between continuous or categorical covariates and the relevant PK parameters were evaluated mainly by (but not limited to) the following functions:

$$TVP = \theta_1 \times (COV/Median\ COV)^{\theta2}$$

$$TVP = \theta_3 \times (1 + \theta_4 \times CAT)$$

where TVP is the estimate of population PK parameter adjusted for covariate; COV or CAT is an individual value of continuous covariate or categorical covariate, which is equal to 0 or 1, respectively; θ_1 or θ_3 is the estimate of a population PK parameter at median or when CAT = 0; θ_2 or θ_4 is a parameter describing the effect of continuous or categorical covariate on population PK parameter, respectively.

Stepwise forward inclusion and backward elimination were applied to build covariate model. A covariate was retained in the model when the addition of the covariate provided a significant change in OFV (p value <0.01) during forward selection; only the covariates associated with a significant change in OFV (p value <0.001) were retained in the final model after backward elimination.

The validation of PopPK model was performed using visual predictive checks (VPCs) and bootstrap. VPCs were conducted to evaluate the predictive performance of the final PopPK model with multiple simulated datasets ($n = 500$ simulations) generated using the final model. Model stability was assessed by a bootstrap method ($n = 500$ simulations).

Simulations, taking interindividual variability (IIV) into account, were conducted using the final asthma PopPK model to evaluate the magnitude of covariate effect on dupilumab PK parameters and steady-state exposures. For each identified statistically significant covariate, simulations ($n = 500$ simulations in each scenario) were conducted for patients with median (i.e., typical patients), 5th and 95th percentile values of covariate distribution in the PK population. Tested covariates were considered to have no clinically meaningful effect if the fold change of dupilumab steady-state exposures in simulated patients relative to the typical patients was within 80% and 125%. The final asthma PopPK model was also used to generate post hoc estimates of individual PK parameters and steady-state exposures for each patient with asthma in phase II and III studies.

The final asthma PopPK model was also applied to the PK data from severe OCS-dependent patients with asthma in a phase III study (not included in model development), by using maximum a posteriori probability (MAP) Bayesian approach with all model parameters fixed to the values of final asthma PopPK model. Model-predicted dupilumab concentrations were compared with measured concentrations directly and by using relative root mean square error, which was calculated as the square root of the average of squared errors divided by the mean of observed values. The ability of final PopPK model to accurately predict dupilumab concentrations observed in severe OCS-dependent patients with asthma was assessed by standard diagnostic criteria.

RESULTS

PK data

Following exclusion of predose and postdose samples that were below the LLOQ ($N = 5702$ samples), predose samples above the LLOQ ($N = 13$ samples), and outlier concentrations ($N = 11$ samples), the final dataset contained 14,584 dupilumab concentrations from 202 healthy subjects and 1912 patients with asthma, including 68 adolescents (≥ 12 to <18 years old). Placebo data were excluded from the dataset. The pooled population was 40.4% male patients and ages ranged from 12 to 83 years. Healthy subjects had a modest range of weight (52–95 kg), and patients with asthma had a relatively broader range of weight (32–186 kg). The demographic and disease characteristics at baseline for model development and model evaluation are summarized in Table 2.

PopPK modeling

During base model selection, the candidate models with either first order or transit-compartment absorption submodel using stepwise or one-step analysis approach were explored and compared. The two best structural models were identified using the pooled data from three phase I and II studies (i.e., base model with transit compartment absorption and selected PK parameters fixed at healthy subject model estimate vs. base model with first order absorption and without fixed parameters). These two structural models were further evaluated using the final asthma PopPK dataset. Similar parameter precisions and comparable values of key PK parameters between these two models were found. The asthma PopPK model with first order absorption performed better than the model with transit compartment absorption with improvement in OFV, goodness-of-fit for the lower concentration data, and prediction of exposures in patients with asthma receiving 300 mg q2w treatment (the respective predicted mean steady-state trough concentrations 5% vs. 14.4% lower relative to the observed phase III study data).

The final structural model of dupilumab in healthy subjects and patients with asthma is presented in Figure 1. The PK of dupilumab in healthy subjects and patients with asthma were best described by a two-compartment with parallel linear and nonlinear Michaelis–Menten elimination model plus first order absorption using one-step modeling approach (without fixed parameters). IIV was estimated for first order elimination rate constant (K_e), distribution volume of central compartment (V_2), maximum target-mediated rate of elimination (V_{max}), absorption rate constant (K_a), and absorption bioavailability (F_{sc}). Residual error was described using a combined proportional and additive error model.

The PK parameters of the final asthma PopPK model and the covariates are summarized in Table 3. The population estimates of the key PK parameters in patients with asthma were total volume of distribution at steady-state 4.37 L, linear elimination rate 0.0418 1/day, and bioavailability 60.9%.

In general, the precision of the PK parameter estimates was high throughout (%RSE <30%). The magnitude of unexplained IIV was moderate for K_a (49.2% coefficient of variation [CV]), F_{sc} (36.3% CV), and V_{max} (24.3% CV), and relatively small for K_e (19.6% CV) and V_2 (9.13% CV). The IIV estimates for key PK parameters (i.e., K_e, V_2, and V_{max}) were decreased ~ 0.2%–1.6% after addition of other covariates compared to the base model. Estimates of shrinkage in variance of etas for K_e and V_2 were 47.3%, and 57.7%, respectively. No important systemic deviations or major bias in any of the goodness of fit plots were observed, as presented in Figure S1.

The results of VPC (Figure 2) showed that a large majority of the observed concentrations were within in the prediction range of 5th–95th percentiles, indicating the good predictive performance of the final PopPK model. The bootstrap success rate was 98.4%, with 492 of 500 runs obtained with a successful covariance step. All PK parameters were estimated with sufficient precision, as reflected by the bootstrap percentiles (Table 3). Hence, the final PopPK model was confirmed to be stable, robust, and accurate.

Among the tested covariates, WT, stationary ADA (positive or negative), ALB, and CLCRN were identified to be statistically significant covariates on dupilumab PK in patients with asthma. V_2 was related to WT and ALB; K_e was related to ADA, CLCRN, and WT; and V_{max} was related to body weight as shown below.

$$V_2 = 2.76 \cdot \left(\frac{\text{WT}}{78} \right)^{0.667} \cdot \left(\frac{\text{ALB}}{44} \right)^{-0.484} \cdot \exp\left(\eta_1 \right)$$

$$V_{max} = 1.39 \cdot \left(\frac{\text{WT}}{78} \right)^{0.224} \cdot \exp\left(\eta_2 \right)$$

$$K_e = 0.0418 \cdot (1 + 0.191 \cdot \text{ADA}) \cdot \left(\frac{\text{WT}}{78} \right)^{0.222} \cdot \left(\frac{\text{CLCRN}}{111} \right)^{0.217} \cdot \exp\left(\eta_3 \right)$$

where, the median values of WT, ALB, and CLCRN in the final dataset are 78 kg, 44 g/L, 111 ml/min/1.73 m^2, respectively. ADA is 0 for patients with negative ADA and 1 for patients with positive ADA.

All other covariates, including age, gender, race, laboratory parameters (ALT, AST, and ALP), biomarkers/disease markers (EOS, FeNO, and FEV1), population (patients vs. healthy subjects) had no statistically significant effect on dupilumab PK in patients with asthma. The effects of four classes of common concomitant asthma medications (leukotriene

TABLE 2 Descriptive statistics of demographic and disease characteristics at baseline for healthy subject and non-OCS patients with asthma used in model development population (N = 2114) and for OCS-dependent patients used for model evaluation (N = 103)

												For model evaluation		
	For model development											**Asthma patients[b]**		
	Healthy subjects			**Asthma patients[a]**			**Total**								
Continuous covariate	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)				N	Mean (SD)	Median (min – max)
Age (year)	202	34.6 (11.5)	32.0 (18–63)	1912	47.8 (14.8)	49.0 (12–83)	2114	46.5 (15.0)	48.0 (12–83)				103	51.9 (12.5)	53.0 (15.0–77.0)
Weight (kg)	202	76.0 (9.90)	77.3 (52–95)	1912	80.0 (19.8)	78.0 (32–186)	2114	79.6 (19.1)	78.0 (32–186)				103	78.7 (16.9)	78.0 (43.0–133)
Albumin (g/L)	202	43.9 (3.40)	44.0 (33–53)	1912	43.8 (3.50)	44.0 (30–55)	2114	43.8 (3.50)	44.0 (30–55)				103	44.3 (3.11)	44.0 (34.0–51.0)
CLCRN[c] (ml/min/1.73 m²)	202	115.9 (22.3)	114.2 (68.8–186)	1912	116.2 (37.1)	110.9 (30.1–377)	2114	116.2 (36.0)	111.3 (30.1–377)				103	116 (32.6)	112 (54.7–262)
Eosinophils (cells/μL)	202	154.4 (116.2)	110.0 (0–900)	1912	356.2 (390.8)	260.0 (0–8750)	2114	336.9 (378.1)	240.0 (0–8750)				103	370 (316)	280 (0.00–1830)
FeNO (ppb)	202	16.0 (0)	16.0 (16.0–16.0)	1912	35.4 (32.7)	25.0 (3–387)	2114	33.5 (31.6)	24.0 (3.0–387)				103	35.4 (28.1)	28.0 (6.00–199)
FEV₁ of predicted normal (%)	202	100.0 (0)	100.0 (100–100)	1912	64.7 (14.7)	65.0 (17–125)	2114	68.1 (17.4)	67.0 (17–125)				103	61.0 (18.5)	59.0 (21.0–120)

Categorical covariate	Subgroup	Healthy subjects Count (%)	Patients with asthma Count (%)	Total count (%)	OCS-dependent patients with asthma[a] Count (%)
Gender	Male	121 (59.9%)	734 (38.4%)	855 (40.4%)	41 (39.8%)
	Female	81 (40.1%)	1178 (61.6%)	1259 (59.6%)	62 (60.2%)
Age group	Adolescents	0 (NA)	68 (3.6%)	68 (3.2%)	1 (0.971%)
	Adults	202 (100%)	1844 (96.4%)	2046 (96.8%)	102 (99.0%)
ADA	Negative	135 (66.8%)	1635 (85.5%)	1770 (83.7%)	95 (92.2%)
	Non-negative	67 (33.2%)	277 (14.5%)	344 (16.3%)	8 (7.80%)

Abbreviations: ADA, antidrug antibody; CLCRN, creatinine clearance normalized by body surface area; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in one second; N, subject number; NA, not applicable; OCS, oral corticosteroids; SD, standard deviation.

[a]Non-OCS dependent asthma patients included in model development (see Table 1).

[b]OCS-dependent patients with asthma from study NCT02528214, which was not included in model development.

[c]The percentages of total subjects with CLCRN ≥90, 60–90, and 30–60 ml/min/1.73 m² are 77.3% (1635) and 21.1% (447), 1.51% (32), respectively.

FIGURE 1 Schematic structure of dupilumab asthma population pharmacokinetic (PopPK) model. K_a, absorption rate constant; V_2, central compartment volume; V_3, peripheral compartment volume; K_{23}, K_{32}, intercompartmental rate constants; k_e, elimination rate constant; V_{max}, maximum target-mediated rate of elimination; k_m, Michaelis constant
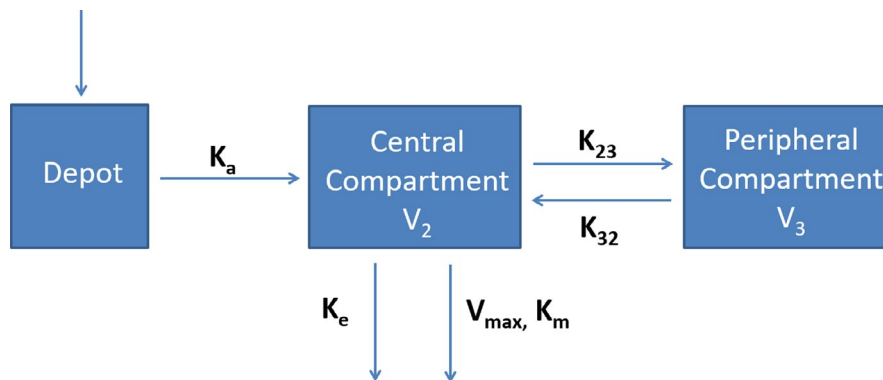

TABLE 3 Final PopPK model parameters estimated using the final dataset ($N = 2114$) and bootstrap resutls

Parameter	Estimate	% RSE	[95% CI]	Bootstrap median	Bootstrap [95% CI]
Typical value of K_e (θ_1, 1/day)	0.0418	2.77%	[0.0395; 0.0442]	0.0419	[0.0389; 0.0448]
Typical value of V_2 (θ_2, L)	2.76	2.43%	[2.63; 2.90]	2.76	[2.63; 2.91]
Typical value of K_{23} (θ_3, 1/day)	0.0952	6.97%	[0.0819; 0.108]	0.0955	[0.074; 0.119]
Typical value of K_{32} (θ_4, 1/day)	0.163	4.36%	[0.148; 0.177]	0.163	[0.142; 0.189]
Typical value of V_{max} (θ_5, mg/L/day)	1.39	3.80%	[1.28; 1.49]	1.39	[1.23; 1.56]
Typical value of K_m (θ_6, mg/L)	2.08	13.6%	[1.52; 2.65]	2.07	[1.49; 2.93]
Typical value of K_a (θ_7, 1/day)	0.263	3.80%	[0.243; 0.283]	0.263	[0.230; 0.287]
Typical value of F_{sc} (θ_8, 1/day)	0.609	3.27%	[0.569; 0.649]	0.609	[0.567; 0.650]
Power coefficient of weight on K_e	0.222	22.5%	[0.122; 0.321]	0.214	[0.149; 0.273]
Proportional coefficient of positive ADA on K_e	0.191	13.6%	[0.139; 0.243]	0.194	[0.112; 0.276]
Power coefficient of CLCRN on K_e	0.217	12.1%	[0.164; 0.269]	0.222	[0.118; 0.354]
Power coefficient of weight on V_2	0.667	3.89%	[0.615; 0.719]	0.665	[0.606; 0.725]
Power coefficient of albumin on V_2	−0.484	12.3%	[−0.604; −0.365]	−0.482	[−0.605; −0.352]
Power coefficient of weight on V_{max}	0.224	24.0%	[0.117; 0.332]	0.222	[0.075; 0.364]
Parameter	**Estimate**	**% RSE**	**[95% CI] (Shrinkage %)**	**Bootstrap Median**	**Bootstrap [95% CI]**
Interindividual variability (CV%)					
K_e	0.0385 (19.6%)	10.6%	[0.0303; 0.0466] (47.3%)	0.0388	[0.0301; 0.0494]
V_2	0.00834 (9.13%)	18.2%	[0.00530; 0.0114] (57.7%)	0.00861	[0.00330; 0.0230]
V_{max}	0.0589 (24.3%)	7.69%	[0.0499; 0.0680] (44.2%)	0.0584	[0.0381; 0.0737]
K_a	0.243 (49.2%)	7.68%	[0.205; 0.280] (57.6%)	0.247	[0.164; 0.392]
F_{sc}	0.132 (36.3%)	11.9%	[0.100; 0.163] (36.3%)	0.129	[0.0164; 0.189]
Residual variability					
Proportional term (CV%)	0.0388 (19.7%)	0.880%	[0.0381; 0.0395]	0.039	[0.035; 0.043]
Additive term (mg/L) (SD)	2.98 (1.73)	2.86%	[2.814; 3.155]	2.89	[1.68; 4.84]
Derived parameters					
CL (L/day)	0.115	NA	NA	0.116	NA
Q (L/day)	0.263	NA	NA	0.264	NA
V_3 (L)	1.61	NA	NA	1.62	NA

Abbreviations: ADA, antidrug antibody; CI, confidence interval; CL, linear clearance; CLCRN, Cockcroft-Gault equation[29] and normalized to body surface area; CV, coefficient of variation; F_{sc}, bioavailability; K_a, absorption rate constant; K_e, linear elimination rate constant; K_m, Michaelis constant; K_{23}, K_{32}, inter-compartment distribution rate constants; NA, not available; PopPK, population pharmacokinetic; Q, intercompartment distribution clearance; SD, standard deviation; V_{max}, maximum target-mediated rate of elimination; V_2, volume of central compartment; V_3, volume of peripheral compartment; %RSE, percentage of relative standard error (100% * SE/estimate); θ and ω are the PopPK parameters (θ) and the variance of their associated interindividual variability (ω).
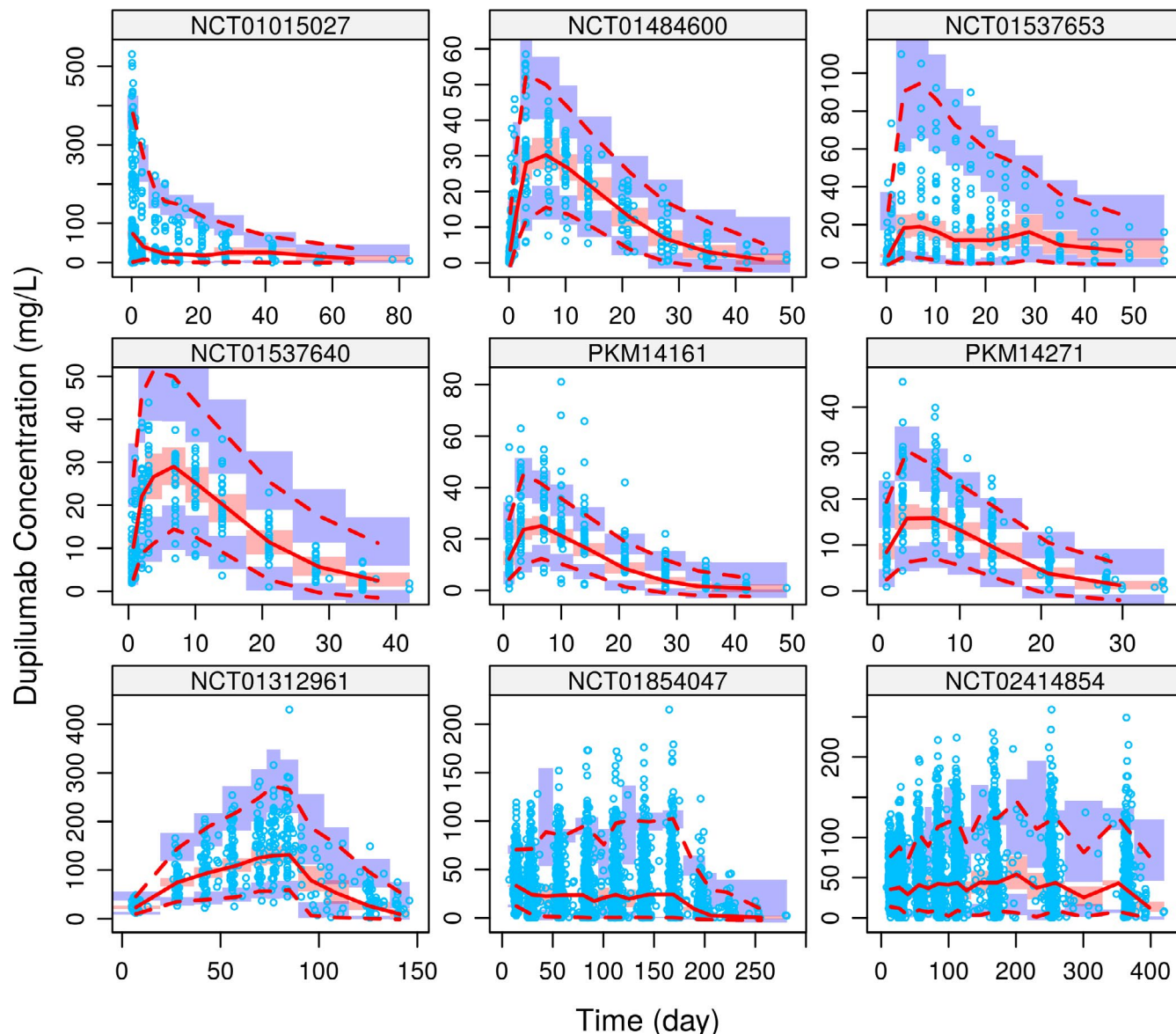
FIGURE 2 Visual predictive checks for the final population pharmacokinetic (PopPK) model by study. Blue dots: observations; red solid and dashed lines: the median and bounds (5th and 95th percentiles) of predicted concentrations at each time bin; pink and light blue areas: confidence intervals of median and centiles of predicted concentrations at each time bin

antagonists, long-acting beta agonists, systemic corticosteroids, and methylxanthines) on dupilumab PK were found to have little impact on dupilumab steady-state exposures in patients with asthma in a post hoc analysis using model-derived steady-state exposures.

The results of simulations to evaluate the impact of various statistically significant covariates on dupilumab PK revealed that only body weight exerted a notable effect explaining between-subject variability of dupilumab PK parameters as well as steady-state exposures in patients with asthma, with lower body weight associated with higher exposures, whereas ADA, ALB, and CLCRN have no clinically meaningful effect with less than 20% change in PK exposures relative to the typical patients, as shown in Figure 3.

Compared with a typical 78 kg (median) patient, steady-state area under the concentration time curve (AUC_{ss}) was 48.0% and 40.7% lower in a 116 kg (95th percentile) patient and 68.8% and 56.7% higher in a 52.9 kg (5th percentile) patient, at phase III study doses of dupilumab 200 and 300 mg q2w, respectively (Figure 3). Compared with a typical adult patient (78 kg), AUC_{ss} was 43.8% and 36.1% higher in a typical adolescent patient (60 kg), at doses of dupilumab 200 and 300 mg q2w, respectively. The impact of body weight on steady-state trough concentration was found to be similar as AUC_{ss}.

A similar PK profile was observed between adolescent and adult patients with asthma. The higher mean exposure of dupilumab in adolescent patients compared to adult patients
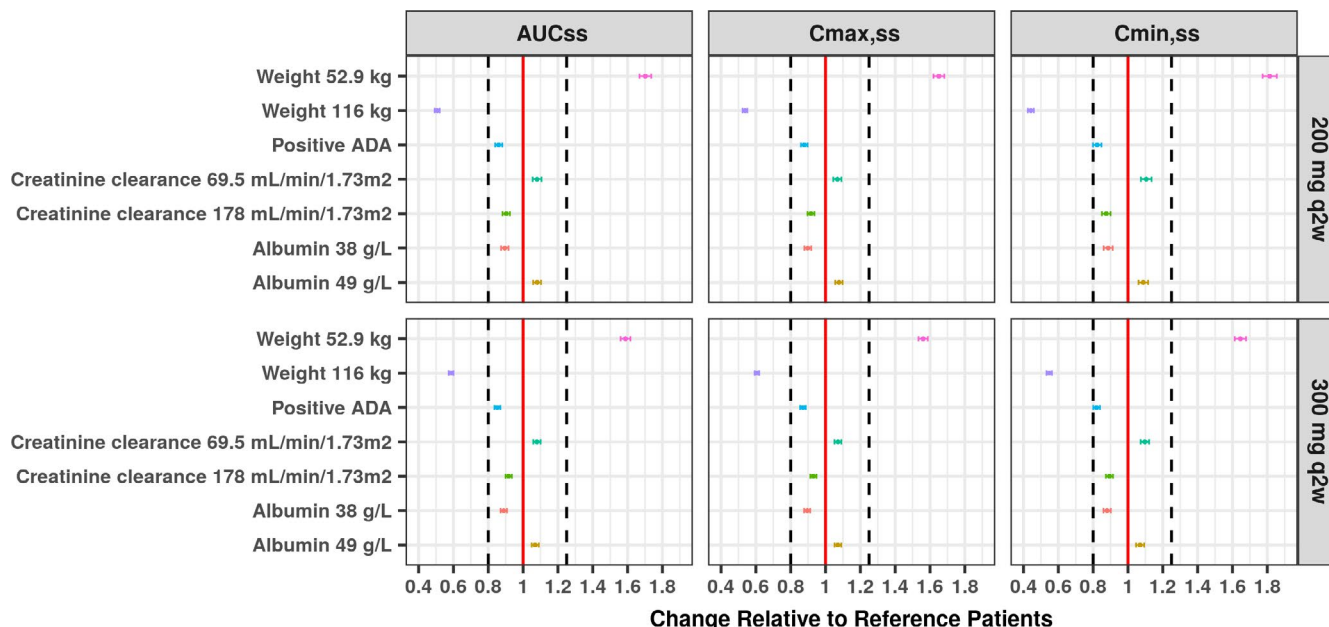
FIGURE 3 Forest plot of impact of covariates on steady-state exposures of dupilumab following 200 mg q2w or 300 mg q2w treatment in patients with asthma. AUC_{ss}, area under the concentration time curve from time 0 to 14 days at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; q2w, every 2 weeks. Typical patient: body weight of 78 kg, ADA negative, albumin of 44 g/L and creatinine clearance of 111 ml/min/1.73 m². The covariate values for simulation ($n = 500$) represented 5th and 95th percentile of the covariate distribution of the population pharmacokinetic (PopPK) population. Dupilumab mean steady state exposures (i.e., AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$) for the simulated typical patients are represented by the red solid vertical line. The black dashed vertical lines represent 80 and 125% of the typical mean steady state exposures for simulated patients. The solid square and error bars represent the mean and 95% confidence interval for the fold change of dupilumab steady state exposures in simulated patients relative to the typical patients

TABLE 4 Model-derived dupilumab steady-state exposure in asthma patients after 300 mg q2w

Study	Population	Phase	N	AUC_{ss}[a] (mg day/L)	$C_{max,ss}$[a] (mg/L)	$C_{min,ss}$[a] (mg/L)
NCT01854047	Non OCS-dependent	2b	154	983 (526) [53.4%]	78.6 (39.2) [49.9%]	58.9 (34.7) [58.9%]
NCT02414854[b]		3	630	1090 (593) [54.4%]	86.9 (44.8) [51.6%]	70.0 (40.9) [58.5%]
NCT02528214[c]	Severe, OCS-dependent	3	102	1064 (511) [48.0%]	85.4 (38.3) [44.8%]	64.5 (33.9) [52.6%]

Abbreviations: AUC_{ss}, area under the concentration time curve from time 0 to 14 days at steady-state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady-state; N, subject number; OCS, oral corticosteroid; q2w, every 2 weeks.

[a]Descriptive statistics for exposures are mean (SD) [% coefficient of variation].

[b]Two patients from study NCT02414854 with missing information for ADA were excluded from the summary.

[c]Using maximum a posteriori probability Bayesian approach. One patient from study NCT02528214 with missing information for antidrug antibodies was excluded from the summary.

(the respective mean C_{trough} at week 16 is 46.7 mg/L vs. 36.5 mg/L for 200 mg; or 107 mg/L vs. 67.8 mg/L for 300 mg q2w) is mainly explained by the difference in body weight between the age groups (median body weight of 57 kg in adolescent patients vs. 78 kg in adults) rather than age. After accounting for body weight, there is no apparent age effect on dupilumab.

The predictive performance of the final PopPK model was further assessed using Bayesian estimate of dupilumab exposures for 103 patients with severe OCS-dependent asthma in the phase III study NCT02528214. The mean (SD)

observed and predicted steady-state trough concentrations were 64.5 (33.9) and 60.0 (30.5) mg/L, respectively. Relative root mean square error was calculated to be 37.2%. As presented in Figure S2, goodness-of-fit plots for application of the final model to data from study NCT02528214 also demonstrated a reasonable model performance. These results indicated the reasonable predictive performance of the established PopPK model in severe OCS-dependent patients with asthma. Dupilumab PK in severe OCS-dependent patients with asthma (study NCT02528214) and in moderate-to-severe (or non-OCS dependent) patients with asthma (studies

NCT01854047 and NCT02414854) was highly comparable, as shown in Table 4. This inter-study comparison further confirmed the lack of notable effect of concomitant OCS use on dupilumab PK.

DISCUSSION

In this study, a PopPK model was developed to characterize the PK properties of dupilumab in patients with asthma and to assess the covariate impact on dupilumab PK using data pooled from 202 healthy subjects and 1912 patients with asthma. This is the first dupilumab PopPK model for adult patients with asthma and adolescent patients to be available in the literature. The model was a helpful tool to predict the impact of different dosing regimens or loading dose on the dupilumab PK profile, and to optimize the study design for dosing regimen in other asthma studies. It was also used to support exposure-response analysis and link to an indirect response model in the development of PopPK/pharmacodynamic (PD) model.

The results for the influence of outlier exclusion on model performance revealed that there were no appreciable changes in parameter estimates with or without the inclusion of 11 outliers (i.e., 11 unusual high trough concentrations with absolute values of CWRES ≥5). However, inclusion of these outliers resulted in significantly increase of minimum value of objective function (increase of +1453 unit), suggesting that the model fit was noticeably compromised with inclusion of outliers. Sensitivity analysis using the M3 method during model development resulted in similar parameter estimates with or without the BLOQ observations. The inclusion of BLOQs in the final PopPK model resulted in a termination of minimization procedure, indicating a compromised stability in model fitting.

The PopPK analysis results showed that population (healthy subjects vs. patients with asthma) had no statistically significant effect on dupilumab PK. Moreover, the disposition characteristics of dupilumab are comparable between asthma and AD population, as the population parameter estimates (in Table S1), the observed/predicted exposures, as well as the main sources of variability observed in patients, are consistent between the asthma and AD populations. The population mean estimate of total volume of distribution was 4.16 L in patients with AD and 4.37 L in patients with asthma, and clearance of dupilumab was 0.127 L/day in patients with AD and 0.115 L/day in patients with asthma.[25] Therefore, disease status did not influence dupilumab PK.

In the final PopPK model, the population estimate of Michaelis constant K_m is 2.08 mg/L. With respect to the mean steady-state minimum concentrations after 300 mg q2w (i.e., 59.8–70.0 mg/L in Table 4), the Michaelis constant K_m is small, indicating at steady-state after 300 mg q2w the elimination of dupilumab is predominantly through the linear, nonsaturable proteolytic pathway, due to the saturation of the target-mediated pathway.

Among the identified covariates, body weight was the primary factor that explained dupilumab PK variability, whereas the influence of ADA, ALB, and CLCRN on dupilumab PK was clinically unimportant (within 20% change). In the assessment of the ADA impact, most of the ADA positive responses were low titer for patients in phase IIb studies and phase III studies (NCT02528214) and there were few patients with high titers (~0.5%). In the assessment of CLCRN impact, the majority of subjects had normal renal function ($N = 1711$, 80.9%) or mild renal impairment ($N = 368$, 17.4%). A small number of subjects had moderate renal impairment ($N = 35$, 1.7%) and none had severe renal impairment. Based on this analysis, baseline blood eosinophil count (ranging from 0 to 8750 cells/μL), baseline FeNO (ranging from 3.0 to 387 ppb) as well as baseline pre-bronchodilator FEV_1 (% of predicted, ranging from 17 to 125%) did not significantly affect the PK of dupilumab, indicating that disease activity/severity at baseline does not influence dupilumab PK in the asthma population.

Even though body weight exerted a noticeable effect explaining between-subject variability in dupilumab PK in patients with asthma, given the magnitude of the effect on exposures and the limited difference in efficacy/safety across the weight categories, no dose adjustment is recommended with regard to body weight.

Except for body weight, there is no apparent age effect on dupilumab in adolescent and adult patients with asthma. This analysis with data from patients with asthma ranging in age from 12 to 83 years did not identify age as a significant covariate influencing dupilumab PK. It is to be noted that there were adequate number of adolescent ($N = 68$ patients 12 to <18 years of age, representing 3.22% of total) and elderly ($N = 199$ patients ≥65 years of age and $N = 33$ patients ≥75 years, respectively; representing 9.41% and 1.56% of total) patients in the PopPK dataset. The lack of age effect on dupilumab PK is also consistent with the previous finding in the adult AD patients.[24] This finding provided justification for the same dosing regimen between adolescent and adult patients with asthma.

Besides internal validation methods, the final PopPK model was further externally evaluated using data from study NCT02528214 consisting of 103 OCS-dependent patients with asthma. The final model was able to accurately predict the exposures of those OCS-dependent patients with asthma, which further confirmed the good predictive performance of this asthma PopPK model.

CONCLUSION

The PK of dupilumab in adult and adolescent patients with asthma was adequately described by a two-compartment

model with linear and nonlinear elimination plus first order absorption. PK properties of dupilumab in patients with asthma are comparable to those of patients with AD. Only body weight exerted a noticeable effect explaining between-subject variability in the PK of dupilumab, but dose adjustment for weight is not warranted based on limited difference in efficacy/safety across the weight categories. There is no PK difference between adolescent and adult patients after correction for body weight. Dupilumab PK was similar between OCS-dependent and non-OCS dependent patients with asthma. This PopPK model enabled robust prediction of the PK in OCS-dependent patients with asthma.

CONFLICT OF INTEREST
G.Y., X.C., K.V., and L.Q. are employees of Sanofi and may hold stock and/or stock options in the company. Z.L. and L.M. were employees of Sanofi at the time of the study, and may hold stock and/or stock options in the company. D.J.D. is an employee and shareholder at Regeneron Pharmaceuticals, Inc.

AUTHOR CONTRIBUTIONS
Z.L. and G.Y. wrote the manuscript. Z.L., L.M., D.J.D., K.V., and L.Q. designed research. Z.L., G.Y., X.C., K.V., and L.Q. performed the research. Z.L. and G.Y. analyzed the data.

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SUPPORTING INFORMATION

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