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# Model-based clinical pharmacology profiling and exposure-response relationships of the efficacy and biomarker of lebrikizumab in patients with moderate-to-severe asthma☆,☆☆

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ABSTRACT

Lebrikizumab is a humanized monoclonal antibody that binds to interleukin-13 and has been evaluated as a treatment for moderate-to-severe asthma. Objectives of this work were to characterize lebrikizumab pharmacokinetics (PK), identify influential covariates, and graphically explore exposure-response relationships in moderate-to-severe asthmatics.

Pooled PK data from 11 studies were used in the population PK model development. Full covariate modeling was used to evaluate the impact of pre-specified covariates. Response data (exacerbation rate, forced expiratory volume in 1 s [$FEV_1$], and fractional exhaled nitric oxide [FeNO]) were obtained from moderate-to-severe asthmatics (n = 2148) who received placebo, lebrikizumab 37.5 mg or 125 mg every 4 weeks (Q4W) in two replicate phase 3 studies. Graphical exposure-response analyses were stratified by numerous covariates, including biomarker subgroups defined by serum periostin level and blood eosinophil count at baseline.

Lebrikizumab PK was described by a two-compartment model with first-order absorption. Population typical values were estimated as 0.156 L/day for clearance (CL), 4.10 L for central volume (Vc), and 0.239 $day^{-1}$ for absorption rate (ka), 85.6% for bioavailability (inter-subject variability: CL, 33.3%; Vc, 36.3%; ka, 40.8%). The estimated mean terminal half-life was 25.7 days. Body weight was the most influential covariate. Generally, the exposure-response analyses of $FEV_1$ and FeNO showed increased response at higher exposure quartiles, while flat or unclear exposure-response relationships were observed in exacerbation rate.

Lebrikizumab PK is as expected for a typical immunoglobulin G4 monoclonal antibody. Results from the exposure-response analyses suggested that, compared to 125 mg Q4W, the 37.5 mg Q4W dose did not achieve the maximum responses for $FEV_1$ and FeNO, although it appeared to maximize the effect on exacerbation reduction. This suggests that the antibody levels needed to improve these outcomes may not be the same. In addition, the role of IL-13 in airflow obstruction/airway inflammation and asthma exacerbations might be different and targeting multiple pathways may be required to treat this heterogeneous disease and provide clinically meaningful benefits to asthma patients.



## 1. Introduction

Interleukin-13 (IL-13), a pleiotropic effector cytokine central to type 2 inflammation in severe asthma, contributes to many of the characteristic features of asthma, including mucus production, IgE synthesis, fibrosis, and airway hyper-responsiveness [1]. Lebrikizumab is a humanized monoclonal antibody (mAb) of the immunoglobulin (Ig) G4 subclass with a mutation in the hinge

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**Abbreviations**

| | |
|---|---|
| ADA | anti-drug antibody |
| AIC | inter-individual variability |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUCss | area under the concentration-time curve for a dosing interval at steady-state |
| BMI | body mass index |
| BSA | body surface area |
| BWT | body weight |
| CHO | Chinese hamster ovary |
| CI | confidence interval |
| CL | clearance |
| CrCL | creatinine clearance |
| $C_{ss,avg}$ | average concentration at steady state |
| $C_{ss,max}$ | peak concentration at steady state |
| $C_{ss,min}$ | trough concentration at steady state |
| CV | coefficient of variance |
| DPI | dry powder inhaler |
| ELISA | enzyme-linked immunosorbent assay |
| ETA | maximum a posteriori Bayes estimate of individual random effect |
| F | bioavailability |
| FeNO | fractional exhaled nitric oxide |
| $FEV_1$ | forced expiratory volume in 1 s |
| HRP | horseradish peroxidase |
| HV | healthy volunteers |
| ICS | inhaled corticosteroids |
| Ig | immunoglobulin |
| IIV | inter-individual variability |
| IL | Interleukin |
| IV | intravenous |
| Ka | absorption rate constant |
| mAb | monoclonal antibody |
| NS0 | nonsecreting murine myeloma cells |
| PD | pharmacodynamics |
| PI | prediction interval |
| PK | pharmacokinetics |
| Q | inter-compartmental clearance |
| Q1-4 | exposure quartile group 1 (lowest) to 4 (highest) |
| Q4W | every 4 weeks |
| $R_{ac(AUC)}$ | accumulation ratio of $AUC_{ss}$ to $AUC_{0-\tau}$ |
| SC | subcutaneous |
| SE | standard error |
| $t_{1/2}$ | half-life |
| TMB | tetramethylbenzidine |
| TVP | typical value of a parameter |
| Vc | central compartment volume of distribution |
| Vp | peripheral compartment volume of distribution |
| VPC | visual predictive check |
| $\tau$ | dosing interval |

region, which neutralizes IL-13 function by binding to soluble IL-13 with high affinity and thereby blocking signaling through the active IL-4 receptor (R)α/IL-13Rα1 heterodimer [2]. Consistent with its proposed mechanism of action, lebrikizumab has been shown to block IL-13 signaling as evidenced by the effect on downstream pharmacodynamics (PD) biomarkers in asthma patients [3,4]. In phase 2 trials, lebrikizumab showed trends of reduced asthma exacerbation rates and clinically meaningful improvements in lung function in patients with moderate-to-severe asthma who remained uncontrolled despite current standard-of-care treatment [3].

Two replicate phase 3 randomized controlled trials (LAVOLTA I and LAVOLTA II) were conducted in patients with uncontrolled asthma despite treatment with standard-of-care medication. In addition to efficacy and safety, these studies were designed to assess whether the biomarkers, serum periostin levels and blood eosinophil counts, could identify patients who were most likely to benefit from lebrikizumab treatment [4]. Lebrikizumab did not consistently show a significant reduction in asthma exacerbation in biomarker-high patients (biomarker-high defined as patients with serum periostin ≥50 ng/mL or blood eosinophil count ≥300 cells/μL at baseline) but was associated with improvement in forced expiratory volume in 1 s ($FEV_1$) in both studies [4]. In these trials, lebrikizumab demonstrated clinically relevant effects on PD biomarkers downstream of IL-13 and was generally well tolerated [4].

The objectives of this study were to develop a population PK model for lebrikizumab in healthy volunteers (HVs) and asthma patients using data from 11 phase 1–3 studies. The population PK model was used to characterize the PK properties of lebrikizumab and to assess the impact of the potential clinically relevant intrinsic and extrinsic covariates on lebrikizumab PK and exposure. The population PK model was also applied to predict the lebrikizumab exposures of individual subjects, which were used to characterize the exposure-response relationship of efficacy and biomarker endpoints in the LAVOLTA I and II studies. Efficacy and IL-13-related biomarker endpoints analyzed in this study were asthma exacerbation rate, $FEV_1$, and fractional exhaled nitric oxide (FeNO).

## 2. Methods

### 2.1. Data and study design

A total of 11 studies (3 phase 1, 5 phase 2, and 3 phase 3) were included in the population PK analysis. A listing of these studies and key study information, including population, dosing regimen, and number of subjects treated with lebrikizumab is provided in Table 1. All studies were approved by the institutional review board or independent ethics committee and were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Study 1 evaluated the safety, tolerability, PK, and PD of lebrikizumab with 0.3, 1, and 3 mg/kg every 4 weeks (Q4W) IV dose in mild asthma patients. Study 2 evaluated the absolute bioavailability of lebrikizumab with 1 mg/kg subcutaneous (SC) or intravenous (IV) single dose in HVs. Study 3 compared safety, tolerability, and PK of lebrikizumab in Japanese and Caucasian HVs with 125 mg, 250 mg, and 375 mg single SC dose.

Study 4 was an allergen challenge study to evaluate the efficacy and safety of lebrikizumab in the prevention of allergen-induced airway obstruction in adults with mild allergic asthma with 5 mg/kg SC dose Q4W [5]. Study 5 (MILLY) evaluated the safety, tolerability, and efficacy of lebrikizumab in adult patients with asthma who are inadequately controlled on inhaled corticosteroids (ICS) with 250 mg Q4W SC dose [6]. Study 6 (MOLLY) was a phase 2 dose ranging study to evaluate lebrikizumab in adult patients with asthma who were not taking ICS with 125 mg, 250 mg, and 500 mg Q4W SC dose plus one loading dose at week 1 [7]. Studies 7 and 8 (LUTE and VERSE) were replicate phase 2 studies to assess the

**Table 1**
Lebrikizumab studies included in population PK analysis.

| Study | Phase | Population | Subjects treated (N) | Dose regimen |
|---|---|---|---|---|
| 1 | 1 | Asthma (mild) | 37 | 0.3, 1, and 3 mg/kg IV, Q4W |
| 2 | 1 | Healthy volunteer | 22 | 1 mg/kg IV or SC, single dose |
| 3 | 1 | Healthy volunteer | 42 | 125, 250, 375 mg SC, single dose |
| 4 | 2 | Asthma (mild) | 13 | 5 mg/kg SC, Q4W |
| 5 | 2 | Asthma (moderate-to-severe) | 106 | 250 mg SC, Q4W |
| 6 | 2 | Asthma (mild-to-moderate) | 158 | 125, 250, 500 mg SC, Q4W +1 dose at week 1 |
| 7 | 2 | Asthma (moderate-to-severe) | 192 | 37.5, 125, 250 mg SC, Q4W |
| 8 | 2 | Asthma (moderate-to-severe) | 155 | 37.5, 125, 250 mg SC, Q4W |
| 9 | 3 | Asthma (moderate-to-severe) | 719 | 37.5, 125 mg SC, Q4W |
| 10 | 3 | Asthma (moderate-to-severe) | 712 | 37.5, 125 mg SC, Q4W |
| 11 | 3 | Asthma (mild-to-moderate) | 104 | 125 mg SC, Q4W |

efficacy and safety of lebrikizumab in patients with uncontrolled asthma who were on ICS and a second controller medication with 37.5 mg, 125 mg, and 250 mg Q4W SC dose [3].

Studies 9 and10 (LAVOLTA I and LAVOLTA II) were replicate phase 3 studies to assess the efficacy and safety of lebrikizumab in patients with uncontrolled asthma who were on ICS and a second controller medication with placebo, 37.5 mg, and 125 mg Q4W SC dose [4]. The 52-week placebo-controlled period of these studies are presented in this manuscript. Study 11 (STRETTO) evaluated the efficacy and safety of lebrikizumab in adult patients with mild-to-moderate asthma with 125 mg Q4W SC dose.

The analysis population consisted of 849 (38%) males and 1410 (62%) females with ages ranging from 18 to 75 years (median = 49 years) and baseline body weights ranging from 40 to 141 kg (median = 79 kg). Individuals in placebo treatment arms were not included in the population PK analysis.

### 2.2. Assays

Lebrikizumab serum concentrations were determined using a validated sandwich enzyme-linked immunosorbent assay (ELISA), with a minimum quantifiable concentration of 90 ng/mL. The assay was developed by Genentech, and assay validation and sample analysis were conducted at Covance Laboratories, Inc. (Chantilly, VA, USA). In the assay, biotin conjugated IL-13 was coated to streptavidin coated microtiter plates to capture lebrikizumab. Subsequently, horseradish peroxidase (HRP) conjugated mouse anti human IgG4 was applied for detection and HRP substrate 3,3′,5,5′-tetramethylbenzidine (TMB) was added for color development. The accuracy of the assay ranged from 1.3% to 4.7% difference, intra-sample precision ranged from 4.1% coefficient of variance (%CV) to 11.5%CV, and inter-sample precision ranged from 7.4%CV to 18.3% CV.

The presence of anti-lebrikizumab antibodies was determined using a validated homogenous bridging ELISA. The assay validation and sample analysis were conducted at Genentech. Samples were co-incubated overnight with a mixture of biotin- and digoxigenin-labeled lebrikizumab before addition to a streptavidin coated plate. Subsequently, mouse anti-digoxin HRP was added and incubated for detection. The minimum reportable titer for asthmatic human serum was 1.30 titer units. The relative sensitivity of the assay was 78 ng/mL, which was assessed using a surrogate positive control, a monoclonal anti-idiotypic antibody against lebrikizumab. The assay can tolerate up to 50 μg/mL of lebrikizumab in the presence of 500 ng/mL of the surrogate positive control. Anti-lebrikizumab antibody analysis was conducted using a tiered approach: screening, confirmatory, titering. Anti-lebrikizumab antibody status for patients was defined following terms described in the literature [8].

### 2.3. Population PK model development and evaluation

Population PK analyses were conducted via nonlinear mixed effects modeling using a qualified installation of NONMEM, version 7.3 (ICON Development Solutions, Hanover, MD). First, a stable and parsimonious base model with body weight (BWT) effect included was developed to describe lebrikizumab serum concentration-time data without considering all other covariate effects. Determining a reasonable structure PK model, an inter-individual variability (IIV) model, and a residual error model were the key focus of the base model development. The one- and two-compartment models were tested as the structure PK model. The IIV was described using an exponential random effects model, under the assumption that the PK parameters were log-normally distributed. For the residual error model, proportional and combined additive and proportional models were tested. Model selection was driven by the data and guided by various goodness-of-fit criteria, including diagnostic scatter plots, plausibility and precision of parameter estimates, off-diagonal terms of the correlation matrix of the estimates <0.95, and Akaike information criterion (AIC) [9].

Second, a full covariate model emphasizing parameter estimation rather than stepwise hypothesis testing was developed by incorporating the effect of all pre-specified intrinsic and extrinsic covariate parameter relationships into the base model [10]. Determination of the pre-specified covariates was based on clinical relevance and interest on the clinical pharmacology profiling of lebrikizumab. These covariate-parameter relationships include baseline body weight as a predictor of clearance (CL), central compartment volume of distribution (Vc), peripheral compartment volume of distribution (Vp), and inter-compartmental clearance (Q); sex, age, race, and time-varying anti-drug antibody (ADA) as predictors of CL; and formulation (nonsecreting murine myeloma cells [NS0], phase 2 Chinese hamster ovary [CHO] cells, phase 3 CHO) as a predictor of the absorption rate constant (ka) and bioavailability (F). The effects of these pre-specified covariates were estimated simultaneously in the full covariate model.

The relationship between the typical value of a parameter (TVP) and m individual continuous covariate ($cov_{mi}$) was described using a normalized power model:

$$TVP = P1*(cov_{mi}/ref_{m})^{P2} \quad (1)$$

where P1 and P2 are the fixed-effect parameters, and $ref_m$ is the reference value of the covariate, which was commonly selected to be the approximate median value of the covariate. The relationship between TVP and n individual categorical covariate indicator ($cov_{ni}$) was described as follows:

$$TVP = P1 * P_n^{cov_{ni}} \quad (2)$$

where P1 and $P_n$ are the fixed-effect parameters.

Inferences about covariate effects were made based on parameter estimates and uncertainty (bootstrap 95% confidence intervals [CIs]) from the final full covariate model. The impact of covariates on lebrikizumab exposure (ie, average concentration at steady state, $C_{ss,avg}$, given Q4W SC dosing) was evaluated via simulation using the bootstrap distribution (approximate joint posterior distribution) of the model parameter estimates. In each bootstrap replicate the population PK model was re-estimated and $C_{ss,avg}$ was simulated for the reference individual and over a grid of different covariate values representative of the observed data. Each of the covariate effects were evaluated in a univariate fashion. Covariates were fixed at their reference values except when perturbed. Typical value simulations were used, so the resulting covariate effect distributions reflect parameter uncertainty for the reference patient and perturbed covariate settings, but do not reflect inter-individual or residual variability. A covariate effect distribution (bootstrap 95% CI) that resulted in a greater than ±20% change in $C_{ss,avg}$ from the reference or null value was used as a limit for defining a potentially clinically relevant covariate effect.

As a hypothesis-generating exercise, an exploratory post hoc analysis of covariate-parameter relationships was performed to investigate potential influential covariates not included in the full model. Exploratory diagnostics included graphical inspection of estimates of individual random effects from the full model vs. covariates pre-specified for the post hoc analysis. Pre-specified covariates for the post hoc analysis included disease indication (healthy subjects, asthma without ICS, asthma with ICS), serum periostin levels, blood eosinophil counts, biomarker subgroup, baseline creatinine clearance (CrCL), baseline aspartate aminotransferase (AST), baseline alanine aminotransferase (ALT), and geographic region as predictors of CL; and baseline body mass index (BMI) and baseline body surface area (BSA) as predictors of CL and Vc.

The precision of model parameters was investigated by performing a stratified non-parametric bootstrap procedure [11]. The predictive performance of the final full covariate model was further evaluated using a simulation-based visual predictive check (VPC) method [12].

### 2.4. Population PK model application

In addition to characterizing the PK properties of lebrikizumab and assessing the impact of potential clinically relevant covariates on lebrikizumab PK and exposure, the final full covariate population PK model was applied to predict steady-state exposure metrics for patients in phase 3 LAVOLTA I and LAVOLTA II studies, which were used to characterize exposure-response relationships of efficacy and PD biomarkers in uncontrolled asthma patients. Individual exposures were simulated under the nominal dosing regimen to which the patient was randomized in the study.

The following steady-state exposure metrics were evaluated: peak, trough, and time-averaged concentration ($C_{ss,max}$, $C_{ss,min}$, $C_{ss,avg}$, respectively) that would be achieved with Q4W SC dosing. The $C_{ss,avg}$ was calculated as the area under the concentration-time curve for a dosing interval at steady-state ($AUC_{ss}$) divided by the dosing interval ($\tau$). Accumulation ratio ($R_{ac(AUC)}$) was also calculated using $AUC_{ss}$ and $AUC_{0,\tau}$ after first dose.

### 2.5. Exposure-response analysis

The exposure-response analyses were performed based on data from moderate-to-severe asthmatics (n = 2148) who received placebo, lebrikizumab 37.5 mg or 125 mg Q4W in LAVOLTA I and LAVOLTA II studies. In the analysis, response endpoints included asthma exacerbation rate during the 52-week placebo-controlled period (primary endpoint), $FEV_1$ change from baseline at week 52 (key secondary endpoint), and FeNO change from baseline at week 52 (key exploratory PD biomarker). Asthma exacerbation definition and measurement scheme of $FEV_1$ and FeNO were previously presented in detail [4]. The model-predicted individual $C_{ss,avg}$ was used as the exposure metric. Graphical analysis (including placebo) vs. quartiles of exposure was constructed for each endpoint. The impact of covariate on the exposure-response relationship for each endpoint was also evaluated by stratifying or faceting graphical output. Covariates of interest included:

- Baseline biomarker subgroup: Low (baseline blood eosinophil count < 300 cells/μL AND baseline serum periostin level < 50 ng/mL); High (baseline blood eosinophil count ≥ 300 cells/μL OR baseline serum periostin level ≥ 50 ng/mL)
- Quadrants of baseline biomarker status: Low baseline blood eosinophils/Low baseline serum periostin; High baseline blood eosinophils/Low baseline serum periostin; Low baseline blood eosinophils/High baseline serum periostin; High baseline blood eosinophils/High baseline serum periostin
- Baseline blood eosinophil status: Low (<300 cells/μL); High (≥300 cells/μL)
- Baseline serum periostin status: Low (<50 ng/mL); High (≥50 ng/mL)
- Number of exacerbations during the last 12 months: no exacerbations; 1 exacerbation; 2 or more exacerbations
- Baseline asthma medication: daily ICS use ≥ 1000 μg fluticasone propionate dry powder inhaler (DPI) equivalent plus long acting 2-agonist (LABA) (yes/no)
- Baseline IgE status: Low(<150 IU/mL); Medium (≥150 and < 700 IU/mL); High (≥700 IU/mL)
- Baseline body weight status: Low (<77 kg); High (≥77 kg)

The rationale for the cut-offs to create categorical variables from continuous variables follows. The cut-offs for periostin and blood eosinophils have previously been investigated with the aim to identify patient populations in which asthma is likely driven by IL-13 and who might most benefit from lebrikizumab treatment [3,4]. For IgE, a cut-off of 150 IU/mL may be considered the upper limit of normal, while the cut-off of 700 IU/mL may be considered as high IgE levels, as also illustrated by the upper limit in the dosing table of the Xolair® label in the United States. The cut-offs for the number of exacerbations are consistent with those used in the LAVOLTA efficacy analyses, provide a balanced number of patients in each group, and separate more stable patients (with 0 exacerbations) from those considered at higher risk for adverse outcomes overall (with ≥ 2 exacerbations). The ICS cut-off ≥ 1000 μg is a well-accepted threshold for defining high-dose ICS [13]and tends to identify a more severe patient population. Finally, the cut-off for body weight was based on the observed median baseline body weight of lebrikizumab-treated subjects in LAVOLTA I and LAVOLTA II.

Asthma exacerbation rate was summarized for each exposure quartile using a mean unadjusted exacerbation rate, which was calculated by taking the total number of exacerbations observed during the treatment period divided by the total patient years at risk on treatment. The 95% CI of the mean unadjusted exacerbation rate was calculated using equations for the exact 95% CI of the mean of a Poisson distribution:

$$\left(\frac{\chi^2_{\alpha/2,\,2\cdot\sum N_i}}{2\cdot\sum T_i},\ \frac{\chi^2_{1-\alpha/2,\,2\cdot(\sum N_i+1)}}{2\cdot\sum T_i}\right) \quad (3)$$

where $\alpha$ is 0.05, $N_i$ is the number of exacerbations observed during the treatment period for individual i, and $T_i$ is the treatment duration in years for individual i.

For the remaining endpoints ($FEV_1$ and FeNO), the mean response for each exposure quartile was calculated using the observed data and the 95% CI of the mean was derived using the mean ± 1.96 × standard error (SE). Individuals with missing $C_{ss,avg}$ or response data were excluded from the analysis. If individuals had missing covariate data, they were kept in the exposure-response analysis, but excluded from any graphical output stratified by that covariate.

## 3. Results

### 3.1. Population PK model development and evaluation

The final population PK analysis dataset included a total of 13,281 PK observations from 2259 subjects. Table 2 summarizes the baseline demographic and laboratory covariates that were used in the modeling and exploratory post hoc analysis. Covariate distributions were similar between LAVOLTA I and II studies.

Lebrikizumab concentration data were well described by a linear two-compartment model with first-order absorption and elimination. IIV in CL, Vc, and ka were characterized by log-normal distribution and full variance-covariance matrix were estimated, but the IIV in Q and Vp were fixed to zero as these variances could not be reliably estimated. The residual error was described by a combined additive and proportional error model.

In the final full covariate model (final model), typical population PK parameters given the reference covariates (70 kg, 40 years old, male, Caucasian, phase 3 CHO formulation, and negative ADA) were 0.156 L/day (CL), 4.10 L (Vc), 1.45 L (Vp), 0.284 L/day (Q), 0.239 $day^{-1}$ (ka), and 0.856 (F) (Table 3). Elimination half-life ($t_{1/2}$) for the reference subject was 25.7 days. Final estimates of unexplained variability in CL, Vc, and ka were 33.3%, 36.3%, and 40.8%, respectively. Based on the bootstrap 95% CI results, most typical structural model parameters, covariate effects, and random effect variance terms were estimated with good precision.

The full covariate model indicated that body weight was the most significant predictor of lebrikizumab disposition, with a change in lebrikizumab CL by a factor (95% CI) of 0.77 (0.57, 1.0) and 1.57 (1.17, 2.04) for the 54 kg (5th percentile of the baseline body weight) and 110 kg (95th percentile of the baseline body weight) individual, respectively, when compared to the reference subject (70 kg). The impact of sex on CL was small, with a point estimate (95% CI) indicating an increase in CL by a factor of 1.06 (1.04, 1.09) in females compared to males. The impact of race on CL was also small, with point estimates (95% CI) indicating a small increase in CL vs. Caucasian by a factor of 1.07 (1.03, 1.11) for African-American or Black, 1.09 (1.05, 1.13) for Asian, and 1.11 (1.05, 1.17) for other races. ADA status had a minimal effect on CL, with CL for ADA positive subjects changed by a factor (95% CI) of 1.04 (0.996, 1.08) vs. ADA negative subjects. The 95% CI was indistinguishable from the null effect. Age effect on CL and formulation effect on lebrikizumab absorption (both F and ka) were negligible with narrow 95% CIs that included the null effect.

The impact of covariates on lebrikizumab exposure ($C_{ss,avg}$), was further assessed through simulation. As expected given the estimated effect of weight on CL, the results showed that body weight was the most influential covariate for $C_{ss,avg}$ (ie, $C_{ss,avg}$ decreased with increasing weight) (Fig. 1). The remaining covariates evaluated had minimal impact on lebrikizumab $C_{ss,avg}$ (95% CI of the covariate effect was within ±20% of the reference value) when compared to the reference individual, which indicated that they are unlikely to be clinically relevant (Fig. 1).

In the exploratory post hoc analysis, maximum a posteriori Bayes estimates of individual random effects (ETAs) for CL and Vc from the final model were plotted against the pre-specified covariates and inspected for trends (Supplementary Figure S1). No clear covariate-parameter relationships were observed (over the distribution of covariates in the dataset) after accounting for covariates included in the final population PK model.

Standard goodness-of-fit plots, including model predictions vs. observations, residuals vs. model predictions, and residuals vs time, revealed that the final model was generally consistent with the observed data and minimal systematic bias remained (data not shown). The model evaluation results provided evidence that both

**Table 2**
Summary of baseline demographics and other characteristics of the pharmacokinetic analysis data set (N = 2259).

| Continuous covariates | Median (Range) |
|---|---|
| Age (years) | 49.0 (18.0–75.0) |
| Body weight (kg) | 79.0 (40.0–141) |
| Serum periostin (ng/mL) | 51.0 (22.7–194) |
| Blood eosinophil count (cells/μL) | 230 (0.00–2830) |
| CrCL (mL/min) | 106 (34.8–275) |
| AST (U/L) | 20.0 (10.0–287) |
| ALT (U/L) | 20.0 (5.00–205) |
| BMI ($kg/m^2$) | 28.0 (16.7–51.9) |
| BSA ($m^2$) | 1.87 (1.28–2.67) |
| **Categorical covariates** | **N (%)** |
| ADA Status | |
| Negative | 2003 (89) |
| Positive | 228 (10) |
| No post-baseline samples | 28 (1) |
| Formulation | |
| NS0 | 72 (3) |
| CHO (Phase 2) | 652 (29) |
| CHO (Phase 3) | 1535 (68) |
| Race | |
| Caucasian | 1746 (77) |
| Black or African American | 217 (10) |
| Asian | 202 (9) |
| Other | 94 (4) |
| Sex | |
| Male | 849 (38) |
| Female | 1410 (62) |
| Biomarker Subgroup | |
| Biomarker-high | 839 (37) |
| Biomarker-low | 1420 (63) |
| CrCL Category (mL/min) | |
| ≥30 and < 60 | 72 (3) |
| ≥60 and < 90 | 598 (26) |
| ≥90 | 1567 (69) |
| Disease Indication | |
| Healthy | 64 (3) |
| Asthma without ICS | 311 (14) |
| Asthma with ICS | 1884 (83) |
| Geographic Region | |
| Asia | 116 (5) |
| Central and Eastern Europe | 679 (30) |
| Latin America | 117 (5) |
| North America | 1124 (50) |
| Western Europe plus rest of world | 223 (10) |

ADA = Anti-drug antibody status; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BSA = aspartate aminotransferase; CHO = Chinese hamster ovary cells; CrCL = creatinine clearance; ICS, inhaled corticosteroids. NS0 = nonsecreting murine myeloma cells. Baseline biomarker subgroup: Low (baseline blood eosinophil count < 300 cells/μL AND baseline serum periostin level < 50 ng/mL); High (baseline blood eosinophil count ≥ 300 cells/μL OR baseline serum periostin level ≥ 50 ng/mL).

**Table 3**
Final population PK model parameter estimates.

| PK Parameter (Unit)* | Estimate | %RSE | Bootstrap 95% CI |
|---|---|---|---|
| Structure model parameters | | | |
| Clearance, CL (L/day) | 0.156 | 5.76 | (0.145, 0.167) |
| Central compartment volume of distribution, Vc (L) | 4.10 | 11.4 | (3.64, 4.47) |
| Peripheral compartment volume of distribution, Vp (L) | 1.45 | 19.7 | (1.15, 1.77) |
| Intercompartment clearance, Q (L/day) | 0.284 | 35.7 | (0.202, 0.371) |
| Absorption rate constant, ka ($day^{-1}$) | 0.239 | 8.04 | (0.206, 0.282) |
| Bioavailability, F | 0.856 | 5.42 | (0.794, 0.916) |
| CL ~ BWT* | 1.00 | 3.63 | (0.938, 1.07) |
| Vc ~ BWT* | 0.814 | 23 | (0.517, 1.06) |
| Vp ~ BWT* | 0.692 | 74.5 | (-0.0421, 1.55) |
| Q ~ BWT* | 0.479 | 226 | (-0.965, 1.96) |
| CL ~ AGE* | 0.0241 | 105 | (-0.0153, 0.0608) |
| CL ~ Sex**: Female | 1.06 | 1.27 | (1.04, 1.09) |
| CL ~ Race**: Black or AA | 1.07 | 1.86 | (1.03, 1.11) |
| CL ~ Race**: Asian | 1.09 | 2.03 | (1.05, 1.13) |
| CL ~ Race**: Other | 1.11 | 2.62 | (1.05, 1.17) |
| ka ~ Formulation**: NS0 | 0.981 | 10.4 | (0.801, 1.2) |
| ka ~ Formulation**: CHO Phase 2 | 0.989 | 8.17 | (0.869, 1.11) |
| F ~ Formulation**: NS0 | 1.00 | 3.44 | (0.946, 1.07) |
| F ~ Formulation**: CHO Phase 2 | 0.973 | 1.95 | (0.939, 1.01) |
| CL ~ ADA**: positive | 1.04 | 2.02 | (0.996, 1.08) |
| **Inter-individual variability model parameters** | | | |
| IIV CL, $\omega^2_{CL}$ | 0.105 (%CV = 33.3) | 6.36 | (0.095, 0.115) |
| $COV_{CL\text{-}Vc}$ | 0.0832 (CORR = 0.728) | 9.56 | (0.0695, 0.0968) |
| IIV Vc, $\omega^2_{Vc}$ | 0.124 (%CV = 36.3) | 9.44 | (0.102, 0.149) |
| $COV_{CL\text{-}ka}$ | 0.00203 (CORR = 0.0159) | 966 | (-0.0171, 0.0171) |
| $COV_{Vc\text{-}ka}$ | 0.00439 (CORR = 0.0318) | 473 | (-0.028, 0.0309) |
| IIV ka, $\omega^2_{ka}$ | 0.154 (%CV = 40.8) | 40.6 | (0.079, 0.218) |
| **Residual error model parameters** | | | |
| Proportional error, $\sigma2_{proportional}$ | 0.0490 (%CV = 22.1) | 3.56 | (0.046, 0.0521) |
| Additive error, $\sigma2_{additive}$ (μg/mL) | 0.00154 (SD = 0.0393) | 71.1 | (1e-06, 0.00511) |

Typical estimates of the PK model parameters are presented for the reference covariates: BWT = 70 kg, AGE = 40 yr, male, Caucasian, CHO (phase 3) formulation, ADA negative. "PK parameters ~ covariate" represent the parameter describing the relationship between the covariate and the PK parameter. Power coefficient for continuous covariate (*) and scaling factor for categorical covariates (**). Detailed model structures described in Eq (1) (for continuous covariates) and Eq (2) (for categorical covariates) in Methods section. AA = African American; ADA = Anti-drug antibody status; BWT = baseline body weight (kg); CHO = Chinese hamster ovary cells; CI = confidence interval; CORR = correlation coefficient (r); COV = covariance; %CV = percent coefficient of variation; IIV = inter-individual variability (variance, $\omega^2$); NS0 = nonsecreting murine myeloma cells; %RSE = percent relative standard error (approximated by taking the standard error of the natural log of the estimate multiplied by 100); SD, standard deviation.

the fixed and random effects components of the final model were reflective of the observed data (VPC plots for LAVOLTA I and LAVOLTA II studies in Fig. 2, and VPC plots for all other studies in Supplementary Figure S2).

### 3.2. Population PK model application

Individual parameter estimates from the final model were used to simulate steady state exposure metrics ($C_{ss,max}$, $C_{ss,min}$, $AUC_{ss}$, and $C_{ss,avg}$) for patients in LAVOLTA I and II studies. The simulations were performed using the nominal dosing regimen the patient was randomized to in the study. Correlation analysis indicated that these steady-state exposure metrics were highly correlated (data not shown), which is anticipated given the linear PK of lebrikizumab. $C_{ss,avg}$ was therefore chosen as the primary exposure metric for evaluating exposure-response relationships. The steady-state exposure metrics are summarized in Supplementary Table S1 by dose cohort (37.5 mg or 125 mg Q4W SC). The mean (95% prediction intervals [PIs]) $C_{ss,avg}$ for the 37.5 mg and 125 mg dose groups were 6.62 μg/mL (2.82, 13.8) and 22.8 μg/mL (10.2, 41.9), respectively. The accumulation ratio of $AUC_{ss}$ to $AUC_{0,\tau}$ ($R_{ac(AUC)}$) was comparable for both regimens with a mean of 1.92 and 1.95 for 37.5 mg and 125 mg, respectively.

### 3.3. Exposure-response analysis: asthma exacerbation rate

The exposure-response relationship for exacerbation rate, in general, appeared to be flat or unclear across the exposure quartiles in the active treatment groups across various covariates subgroups. There was no clear exposure-response trend in either biomarker-high or biomarker-low subgroups (Fig. 3A), and similar findings were observed when viewing the results separately for LAVOLTA I and II studies (data not shown). Interestingly, when analyzed by quadrants of biomarker status (ie, eosinophil high-periostin high, eosinophil high-periostin low, eosinophil low-periostin high, eosinophil low-periostin low), the high-high biomarker subgroup demonstrated a clinically meaningful treatment effect compared to placebo, with a flat exposure-response trend across exposure quartiles in the pooled analysis (Fig. 4A).

When the exposure-response was analyzed by blood eosinophil high-low or periostin high-low groups individually, eosinophil-high or periostin-high subgroups also had greater treatment effects compared to the respective low groups, although the effects were smaller than in the biomarker high-high subgroup.

Other covariates (exacerbation history, baseline asthma medication, baseline IgE status, and body weight) had no clear effect on exposure-response relationship of exacerbation rate.

### 3.4. Exposure-response analysis: $FEV_1$ change from baseline at week 52

In general, the exposure-response relationship for $FEV_1$ showed a trend of increased response from exposure Q1 (1st quartile)-Q2 and then leveled off with some subsequent fluctuation from exposure Q2-Q4 (4th quartile), suggesting the 37.5 mg Q4W dose may not achieve the maximal $FEV_1$ response compared to the

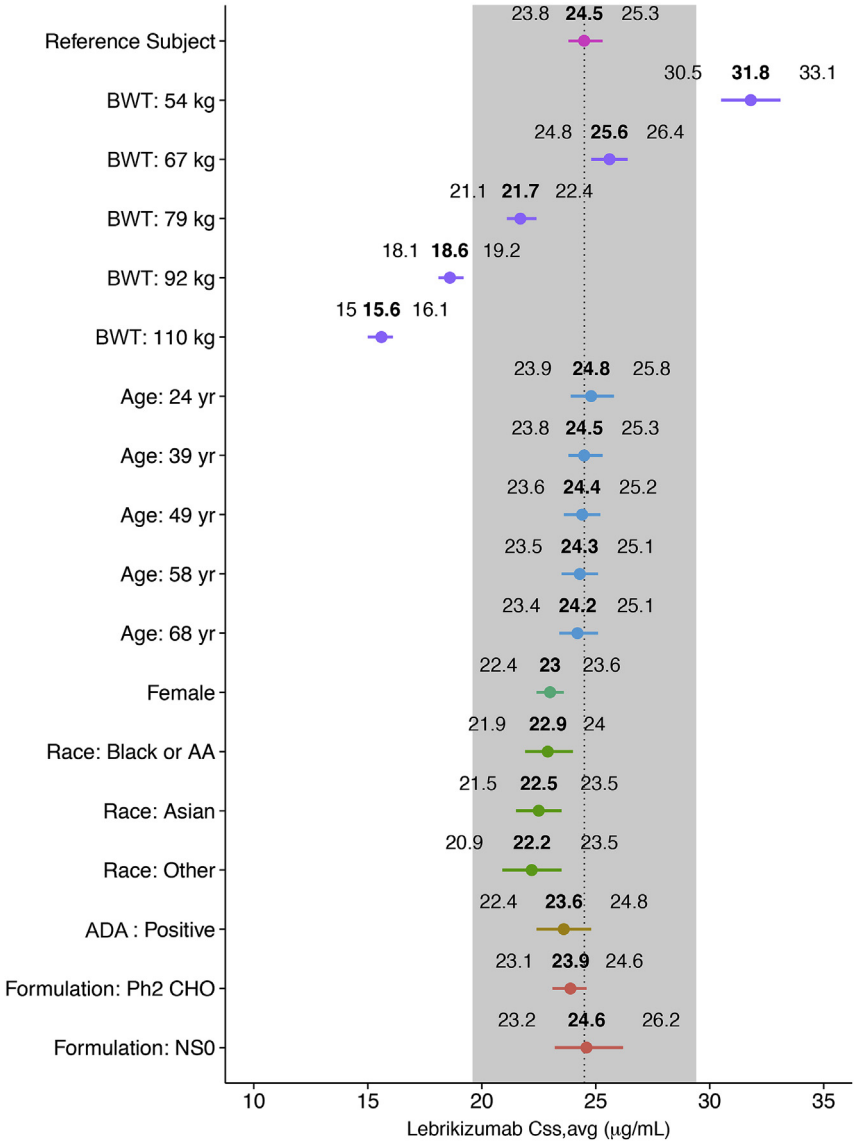


**Fig. 1.** Effects of covariates on lebrikizumab exposure ($C_{ss,avg}$). Final population PK model simulated $C_{ss,avg}$ values are based on a regimen of 125 mg SC administered every 4 weeks. Each point and horizontal line represent the median and 95% CI, respectively, of the bootstrap distribution of simulated $C_{ss,avg}$ adjusted for the covariate (values shown with median in bold). Covariates were fixed at the following reference values except when perturbed: body weight = 70 kg, age = 40 yr, sex = male, race = Caucasian, formulation = Phase 3 CHO, ADA = negative. Non-reference values at which body weight and age were evaluated represent approximate observed 5th, 25th, 50th, 75th, and 95th percentiles. The vertical dashed line is drawn at the median reference value (24.5), and the shaded region is ±20% of the median reference value chosen to represent an uncertainty range of clinical unimportance. AA = African-American; ADA, anti-drug antibody status; BWT, baseline body weight; CHO, Chinese hamster ovary cells; NS0, nonsecreting murine myeloma cells.

125 mg Q4W dose.

In the quadrant biomarker status analysis, the high-high and eosinophil high-periostin low subgroups both showed clear treatment effects compared to placebo (Fig. 4B). The high-high subgroup exposure-response trend saturated at exposure Q2-Q4. The eosinophil high-periostin low subgroup showed increasing response across Q1-Q4.

Biomarker high (Fig. 3B) and eosinophil high subgroups also had greater treatment effects compared to their respective low groups. Their effect sizes are similar to that of the high-high subgroup. The exposure-response trends in these subgroups were generally consistent with that of the high-high subgroup.

Other covariates (periostin, exacerbation history, baseline asthma medication, baseline IgE status, and body weight) had no clear effect on $FEV_1$ exposure-response relationship.

### *3.5. Exposure-response analysis: FeNO change from baseline at week 52*

Generally, the exposure-response relationship for FeNO showed a trend of increased response from exposure Q1-Q4, or saturated from Q2-Q4, suggesting the 37.5 mg Q4W dose, compared to the 125 mg Q4W dose, did not appear to reach the maximal FeNO response.

In the quadrant biomarker status analysis, the high-high and eosinophil high-periostin low subgroups both showed the greatest treatment effect (Fig. 4C). The high-high subgroup showed an increased response from Q1 to Q4. The eosinophil high-periostin low subgroup showed a generally flat but fluctuating response across Q1-Q4.

The biomarker high (Fig. 3C) and eosinophil high subgroups had

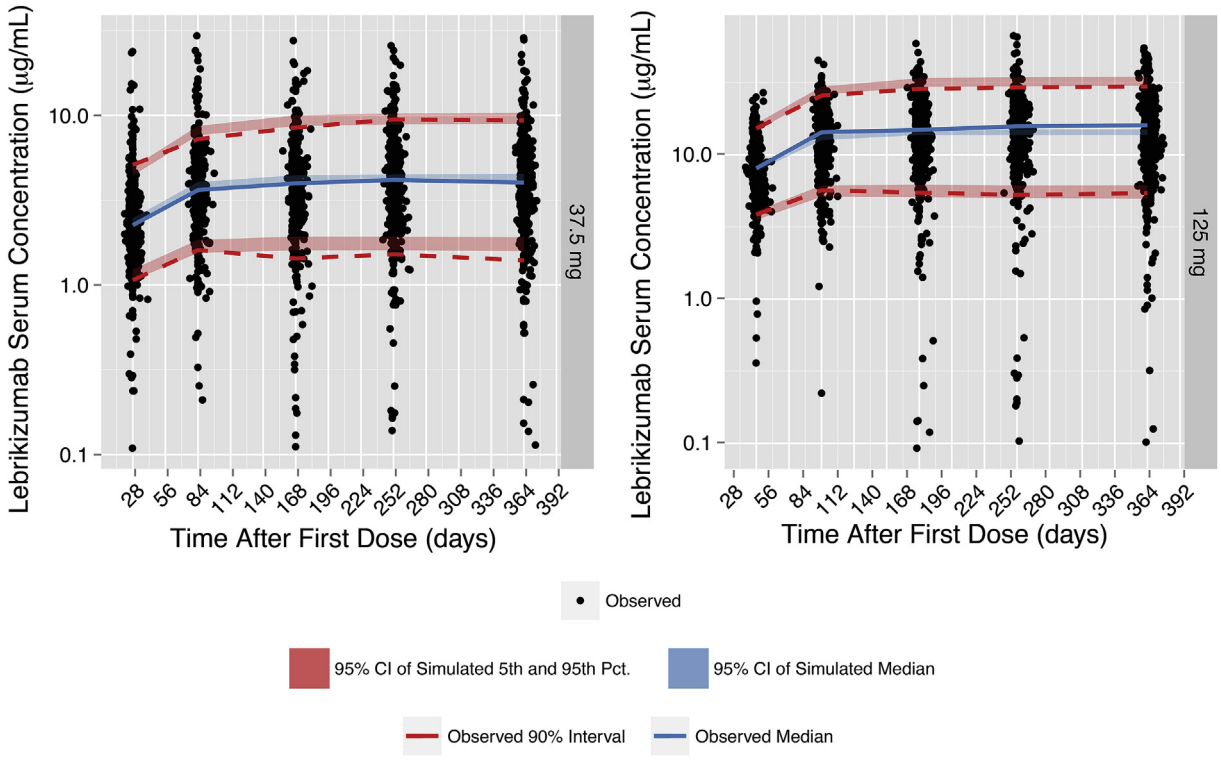


**Fig. 2.** Predictive check for final population PK model: LAVOLTA I and LAVOLTA II studies pooled and stratified by dose (left panel, 37.5 mg Q4W; right panel, 125 mg Q4W). Distributions of simulated lebrikizumab serum concentrations within each individual are compared to the actual observed distribution of concentrations from the population PK dataset at planned study visits for LAVOLTA I and LAVOLTA II studies pooled. Simulations were performed using the final population PK model. Results are presented on a semi-log plot. Pct, percentile.

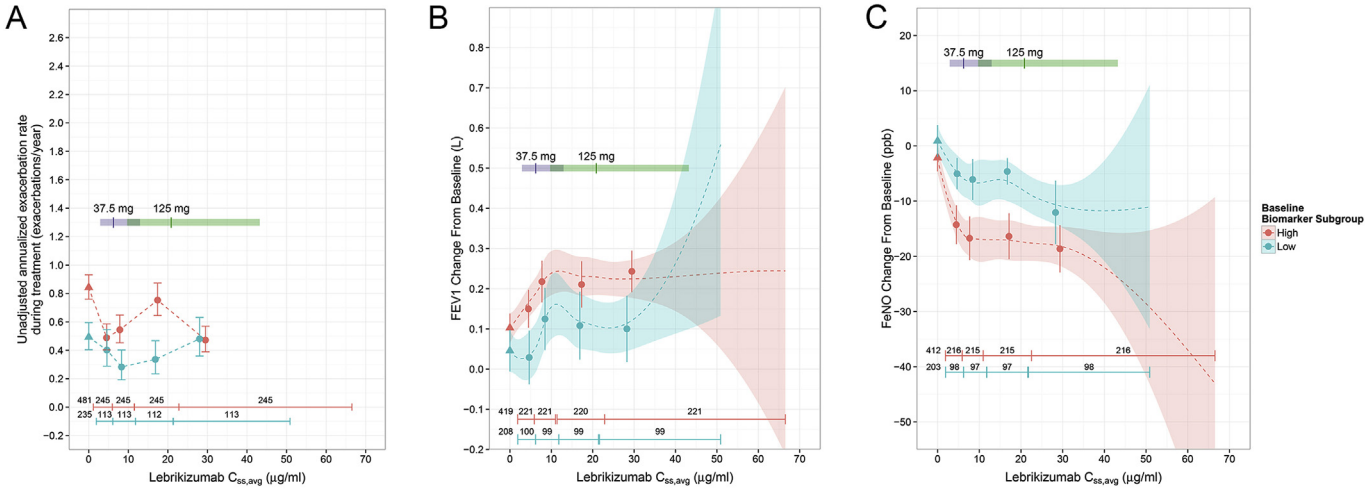


**Fig. 3.** Exposure-response relationships for exacerbation rate (panel A), $FEV_1$ (panel B), and FeNO (panel C): stratified by baseline biomarker subgroups, LAVOLTA I and II pooled. Points and error bars represent the mean response and 95% CI with each exposure quartile (circles) and placebo group (triangle). Mean response is plotted at the mean $C_{ss,avg}$ of the exposure quartile. Dashed blue/pink line is a line connecting mean data points (panel A) or a loess smooth of the individual observed data (panel B and C); the blue/pink band represents the 95% CI for the loess regression. Exposure ranges for the quartile groups are shown at the bottom of the figure as horizontal lines with ticks for minimum and maximum values. Numbers are number of subjects in the placebo and treatment exposure quartile groups. Vertical lines and horizontal bars at the top of the figure represent the median and 95% interval (2.5, 97.5 percentiles), respectively, of the distribution of individual predicted $C_{ss,avg}$ in each dose group.

greater treatment effects compared to the respective low groups. The eosinophil high subgroup demonstrated the greatest effect, similar to the high-high subgroup; and effect was smaller in the biomarker high subgroup. The exposure-response trends in these subgroups were generally consistent with that of the high-high subgroup.

Other covariates (periostin, exacerbation history, baseline asthma medication, baseline IgE status, and body weight) demonstrated no clear effect on FeNO exposure-response relationship.

## 4. Discussion

This study is the first comprehensive PK characterization of lebrikizumab based on data from 11 clinical trials and evaluation of the exposure-response relationship of efficacy and biomarker

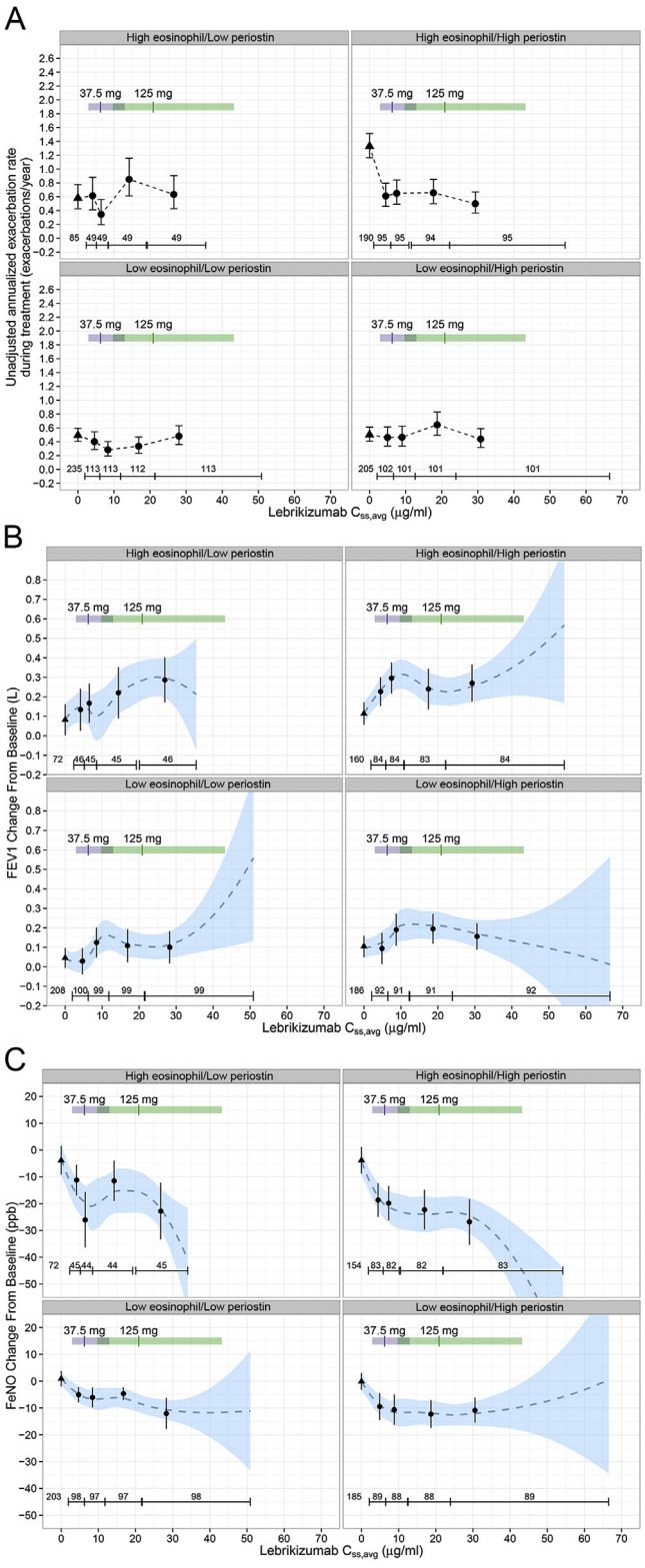


**Fig. 4.** Exposure-response relationship for exacerbation rate (panel A), $FEV_1$ (panel B), and FeNO (panel C): stratified by quadrants of biomarker status, LAVOLTA I and II pooled. Points and error bars represent the mean response and 95% CI with each exposure quartile (circles) and placebo group (triangle). Mean response is plotted at the mean $C_{ss,avg}$ of the exposure quartile. In panel A, dashed black line is a line connecting mean data points. In panel B and panel C, dashed blue line is a loess smooth of the individual observed data; the blue band represents the 95% CI for the loess regression. Exposure ranges for the quartile groups are shown at the bottom of the figure as horizontal lines with ticks for minimum and maximum values. Numbers are number of subjects in the placebo and treatment exposure quartile groups. Vertical lines and horizontal bars at the top of the figure represent the median and 95% interval (2.5, 97.5 percentiles), respectively, of the distribution of individual predicted $C_{ss,avg}$ in each dose group.

endpoints in the phase 3 LAVOLTA I and LAVOLTA II studies in moderate-to-severe uncontrolled asthma patients.

The goals of the population PK analysis were to characterize lebrikizumab PK in healthy volunteers and patients with asthma and to assess the effects of covariates on lebrikizumab PK and exposure. Lebrikizumab PK was determined to be linear and time-invariant within the dose range tested and was well described by a two-compartment model with first-order absorption and first-order elimination. The PK disposition characteristics of lebrikizumab were in general consistent with other therapeutic mAbs of the IgG4 class, including tralokinumab, another IgG4 mAb targeting soluble IL-13 without a mutation in the hinge region [14,15]. Elimination $t_{1/2}$ for the reference subject (70 kg, 40 years old, male, Caucasian, phase 3 CHO formulation, and negative ADA) was 25.7 days, which is consistent with estimates obtained from PK analyses of data from lebrikizumab phase 2 studies [5,7].

Lebrikizumab CL and Vc increased with body weight as power functions (ie, allometric scaling) with power coefficient estimates of 1.00 (95% CI: 0.938–1.07) and 0.814 (95% CI: 0.517–1.06), respectively. Point estimates also suggested that lebrikizumab Vp and Q increased with body weight but the 95% CIs were wide and included the null value of zero (Vp: 0.692 [95% CI: −0.0421–1.55]; Q: 0.479 [95% CI: −0.965–1.96]). The point estimates differed from expected allometric coefficients of 0.75 for physiologic processes (eg, CL and Q) and 1.0 for anatomical volumes [16]. This may be due in part to the relatively limited range of body weights in the analysis dataset which consisted of adult data only (90% interval: 54–110 kg). These findings are consistent with other population PK analyses of therapeutic mAbs in adult populations, where the effects of body weight were estimated rather than being fixed to allometric values and differences were noted [14]. Results from the final model indicated that body weight was the most influential covariate, while the effects of other covariates, including age, sex, race, time-varying ADA status, formulation, were unlikely to result in a clinically meaningful change in lebrikizumab exposure (Fig. 1).

The population PK model was used to predict the lebrikizumab exposures of individual subjects, which were used to characterize the exposure-response relationship of efficacy and biomarker responses in the LAVOLTA studies. There was no clear exposure-response trend for the exacerbation rate, which is consistent with the dose-response relationships of exacerbation rate in both LAVOLTA studies and previous phase 2 LUTE and VERSE studies [3,4].

Compared with exacerbation rate, $FEV_1$ and FeNO may be more sensitive endpoints to dose and exposure differences. The exposure-response analysis of $FEV_1$ in LAVOLTA studies showed an increased response from exposure Q1-Q2 and then leveled off with some subsequent fluctuation from exposure Q2-Q4 (Fig. 3). The response of $FEV_1$ had not reached maximum levels at the first/lowest exposure quartile (Q1). Given that Q1 is composed of a subset (50%) of patients from the 37.5 mg dose group, this 37.5 mg Q4W dose, compared with 125 mg Q4W, did not appear to achieve maximal response with regards to $FEV_1$ response. In the LUTE and VERSE studies, the improvement in $FEV_1$ was less pronounced for the 37.5 mg dose compared with the 125 mg dose, which also suggested that 37.5 mg was a partially effective dose [3]. In contrast, there was no clear dose-response relationship of $FEV_1$ in the LAVOLTA studies since the $FEV_1$ versus time profiles of the two doses were generally overlapping [4]. Similar to $FEV_1$, FeNO also showed a clear exposure-response trend but no dose-response trend in the LAVOLTA studies [4]. These results suggest that exposure-response

analyses are more sensitive than dose-response analyses in detecting trends in $FEV_1$ and FeNO responses in LAVOLTA studies.

Similar exposure-response quartile analyses were also performed for blood eosinophil change from baseline at week 52 (data not shown). An increase in the median blood eosinophil count was observed with lebrikizumab treatment and similar results have also been reported with tralokinumab and dupilumab (an anti-IL-4Rα mAb that inhibits both IL-4 and IL-13 signaling) [3–7,17–19]. The increase is hypothesized to be due to reduced migration from blood to tissues caused by the reduced chemotaxis. Although there appeared to be a trend towards a dose-dependent increase in median blood eosinophil change over time primarily in the biomarker high patients in LAVOLTAs [4], there was no clear exposure-response relationship for blood eosinophils at week 52 in the same patient population. The likely explanation is that only minimal separation of the blood eosinophil profiles for the two dose groups (37.5 mg and 125 mg Q4W) was observed at week 52, while the greatest separation of the profiles over time occurred in the middle of the 52-week placebo-controlled period. Graphical analysis of blood eosinophil increases over time stratified by exposure quartile groups indicated that there was an exposure-response trend in the biomarker high subgroup (Supplementary Figure S3).

Assessment of exposure-response and dose-response of the biomarker data (FeNO and blood eosinophil count) indicated that the IL-13 pathway was inhibited by lebrikizumab treatment. The fact that exposure-response trends in $FEV_1$ and FeNO were generally consistent supports that anti-IL-13 therapy has an effect on airflow obstruction and inflammation. However, the absence of consistent exposure-response trends and the observed differences in treatment benefit on $FEV_1$ versus exacerbation rate suggest that the underlying biology of airflow obstruction/airway inflammation and asthma exacerbations may be different, and the antibody levels needed to improve these outcomes may not be the same. This is also supported by results from phase 2a and phase 2b trials of tralokinumab showing improvement in $FEV_1$ but no significant effect on exacerbations in patients with severe uncontrolled asthma [17,18]. Alternatively, exacerbations may have different triggers and inhibition of the IL-13 pathway may only impact a subset of exacerbation events [20]. In addition, Type 2 cytokines have overlapping functions, and blocking IL-13 alone might not be sufficient or other mechanisms than Type 2 inflammation may play a role.

Interestingly, in the quadrant biomarker status exposure-response analysis, the high-high biomarker subgroup was the only one that demonstrated a clinically meaningful treatment effect for exacerbation rate compared to placebo (Fig. 4A). For $FEV_1$ and FeNO, both high-high and eosinophil high-periostin low subgroups had greater treatment effects compared to the other two eosinophil low subgroups, regardless of periostin levels (Fig. 4B and C). Overall, these data suggest that baseline blood eosinophil counts may be more informative in predicting response to anti-IL-13 therapy compared with baseline serum periostin levels in a global population. Biomarker strategies based on eosinophils generally have been used in the development of mAbs inhibiting the IL-5 pathway, such as mepolizumab, an IgG1 mAb approved for eosinophilic asthma. IL-5 is a key cytokine involved in eosinophil production and recruitment to inflammatory sites [21]. A post-hoc analysis of two mepolizumab clinical studies, DREAM and MENSA, showed that improvement in lung function was closely related to baseline blood eosinophil count: patients with a baseline eosinophil count of at least 500 cells/μL had the greatest increase from baseline in $FEV_1$ [22]. Since IL-13 also plays a role in eosinophil recruitment to tissues and eosinophil survival, blood eosinophil counts might also be a biomarker to predict treatment benefit with therapies targeting the IL-13 pathway.

## 5. Conclusions

In summary, the population PK analysis showed that lebrikizumab PK is as expected for a typical IgG4 mAb. Body weight is the most influential covariate on lebrikizumab PK; all other covariates tested either in the model or in the post hoc analysis were unlikely to be clinically relevant. The exposure-response trend of exacerbation rate was generally flat or unclear. The exposure-response trends of lung function ($FEV_1$) and a key PD biomarker (FeNO) were in general similar, suggesting that the 37.5 mg Q4W dose of lebrikizumab did not achieve the maximum responses in moderate-to-severe uncontrolled asthmatics compared to the 125 mg Q4W dose.

The differences in the exposure-response relationships between lebrikizumab and $FEV_1$/FeNO and between lebrikizumab and exacerbations suggest the antibody levels needed to improve these outcomes may not be the same. In addition, the role of IL-13 in airflow obstruction/airway inflammation and exacerbations may be different and therapies targeting multiple pathways may be required to effectively treat this heterogeneous disease and provide clinically meaningful benefits to asthma patients for both exacerbations and improvement in lung function.

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## Conflict of interest

RZ, WSP, JM, JO, JYJ, KP, CH, SV: Genentech employee and Roche shareholder.

YZ is former employee of Genentech.

NLD: Metrum Research Group employee.

## Author contributions

Conception and design: WSP, RZ, YZ, JM, JO, CH.

Collection and assembly of data: SV, KP.

Data analysis and interpretation: NLD, RZ, YZ, WSP, JYJ, JM, JO, CH.

All authors participated in manuscript writing, and approved the final version of the manuscript.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pupt.2017.08.010.

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