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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☆,☆☆

Rui Zhu [a, 1], Yanan Zheng [a, 1], Nathanael L. Dirks [b], Shweta Vadhavkar [a], Jin Yan Jin [a], Kun Peng [a], Cecile T.J. Holweg [a], Julie Olsson [a], John G. Matthews [a], Wendy S. Putnam [a, *]

[a] Genentech, Inc., South San Francisco, CA, USA
[b] Metrum Research Group, CT, USA

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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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* Corresponding author. Department of Clinical Pharmacology, Genentech, Inc. 1 DNA Way, South San Francisco, CA 94080, USA.
E-mail address: Putnam.Wendy@gene.com (W.S. Putnam).

[1] Rui Zhu and Yanan Zheng contributed equally to this work.

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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
τ	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