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ORIGINAL RESEARCH ARTICLE

Population Pharmacokinetics of Revefenacin in Patients with Chronic Obstructive Pulmonary Disease

Arthur Lo[1] · **Marie T. Borin**[1] · **David L. Bourdet**[1]

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Abstract

Background and Objectives Revefenacin is a lung-selective, long-acting muscarinic antagonist indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease. The objectives of this analysis were to evaluate the pharmacokinetics of revefenacin and its major metabolite (THRX-195518) in patients with chronic obstructive pulmonary disease, and identify significant covariates affecting revefenacin disposition using a population pharmacokinetic approach based on plasma concentration–time data obtained after single- and repeated-dose once-daily administration in three phase II and two phase III studies.

Methods Plasma concentrations of revefenacin and THRX-195518 following once-daily administration via nebulization at a dose levels ranging from 22–700 µg in 935 patients (488 men, 447 women; age 41–88 years) were analyzed using nonlinear mixed-effects modeling.

Results Plasma revefenacin pharmacokinetics was best described by a two-compartment model with first-order absorption and elimination. Pharmacokinetic parameters for THRX-195518 were estimated using a sequential approach, where the concentration–time profiles were fit to a combined model. The formation of the metabolite in each subject was estimated to be a fixed fraction of the individually estimated (post-hoc) clearance rate of revefenacin. Four statistically significant covariates were identified: for revefenacin, age on apparent clearance and body weight on apparent intercompartment clearance, for THRX-195518, age on apparent clearance and body weight on the fraction of revefenacin apparent clearance that was metabolized to THRX-195518.

Conclusions None of the identified statistically significant covariates were associated with a clinically meaningful effect on revefenacin or THRX-195518 exposure in patients with chronic obstructive pulmonary disease.

Registration ClinicalTrials.gov identifier number NCT03064113, NCT01704404, NCT02040792, NCT02459080, and NCT02512510

1 Introduction

Revefenacin is a long-acting, lung-selective muscarinic receptor antagonist formulated as a nebulized inhalation solution for use with a standard jet nebulizer for the once-daily maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). Clinical data demonstrate the clinical efficacy and safety of revefenacin in patients with COPD. In phase II and III studies, once-daily administration of revefenacin significantly improved the forced expiratory volume compared with placebo [1–3]. Revefenacin was also investigated in a 52-week safety study [4].

The pharmacokinetic (PK) properties of inhaled revefenacin were investigated in patients with COPD. In three phase II studies [1, 2] and two phase III studies [3], plasma revefenacin concentrations following inhaled administration were low (0.16 ng/mL) and declined rapidly from the initial maximum concentration, with a slow apparent terminal elimination phase. Limited accumulation for revefenacin and THRX-195518 in plasma was observed after repeated administration [2]. Renal elimination of revefenacin was very low after inhaled administration; < 1% of the dose was excreted in urine. Revefenacin was rapidly and extensively

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✉ Arthur Lo
alo@theravance.com

[1] Theravance Biopharma US, Inc., 901 Gateway Blvd, South San Francisco, CA 94080, USA

Key Points

The objectives were to evaluate the pharmacokinetics of revefenacin and its metabolite (THRX-195518) in patients with chronic obstructive pulmonary disease.

A population pharmacokinetic approach was used based on plasma concentration–time data from 935 subjects in three phase II and two phase III studies.

No clinically significant impacts of patient and disease characteristics on revefenacin and THRX-195518 systemic exposure were identified.

converted to THRX-195518 after inhaled administration. Revefenacin is approximately three- to ten-fold more potent than THRX-195518, which dissociates more rapidly from human M3 receptors [5]. The major metabolic pathway after intravenous (IV) or oral administration of revefenacin identified in a human absorption, distribution, and metabolism, and excretion study is the conversion of revefenacin to THRX-195518 via hydrolysis [6]. Revefenacin had low absolute bioavailability (2.8%) after oral administration and was eliminated primarily in feces after oral or IV administration, suggesting extensive hepatobiliary elimination [6].

This study elucidates the population pharmacokinetics of revefenacin and THRX-195518 in patients with COPD using a sequential modeling approach to first characterize revefenacin pharmacokinetics, followed by THRX-195518, and to identify significant covariates that impact the PK parameters of revefenacin and THRX-195518 in patients with COPD. The final population PK model in patients with COPD was used to determine the magnitude of effect of the intrinsic and extrinsic factors on the steady-state systemic exposures to revefenacin and THRX-195518.

2 Methods

2.1 Patient Population and Study Design

All participants gave written informed consent before any study-related procedures, and the protocols were approved by the appropriate institutional review board [Electronic Supplementary Material (ESM)] for each study site and were carried out in concordance with ICH Guidelines for Good Clinical Practice [1–3, 7]. Data for the analysis were obtained from three phase II studies (studies 1, 2, and 3) and two phase III studies (studies 4 and 5) in patients with COPD. The inclusion criteria for each study are outlined in the ESM. Participants in the phase II studies received revefenacin once daily as a nebulized solution at doses from 22 to 700 µg for 1, 7, or 28 days. Participants in the phase III studies received revefenacin once daily as a nebulized solution at 88 or 175 µg for 12 weeks. Pharmacokinetic sampling times are summarized in Table S1 of the ESM.

2.1.1 Study 1

Study 1 was a phase II, single-dose, randomized, double-blind, active- and placebo-controlled, four-period crossover study (NCT03064113) designed to examine the pharmacodynamic effects of two dose levels (350 and 700 µg) of revefenacin inhalation solution as a single dose administered in a population ($n = 32$, all with evaluable PK data) with moderate to severe COPD [2]. Study treatment administered in the four periods included the following: single doses of 350 and 700 µg of revefenacin via a nebulizer, active-control agent ipratropium bromide (500 µg), and placebo. Each subject underwent a washout of 7–12 days between dose administrations. Serial blood samples were collected from pre-dose to up to 24 h post-dose.

2.1.2 Study 2

Study 2 was a phase II, double-blind, randomized, five-period incomplete block, crossover study (NCT01704404) in which six dose levels of revefenacin inhalation solution (22, 44, 88, 175, 350, and 700 µg) and placebo were evaluated in a population ($n = 62$, 61 patients with evaluable PK data) with moderate to severe COPD [2]. Serial blood samples were collected from pre-dose to up to 24 h post-dose on days 1 and 7.

2.1.3 Study 3

Study 3 was a phase II, randomized, double-blind, placebo-controlled, parallel-group study (NCT02040792) [1] in which four dose levels of revefenacin inhalation solution (44, 88, 175, and 350 µg) and placebo for 28 days were evaluated in a population ($n = 355$, 34 patients where PK data were collected) with moderate to severe COPD. Serial blood samples were collected from pre-dose to up to 72 h post-dose on day 28.

2.1.4 Studies 4 and 5

Studies 4 and 5 were identical phase III, randomized, double-blind, active-controlled, parallel-group, multicenter studies (NCT02459080 and NCT02512510) [3] in which two doses (88 and 175 µg) of revefenacin inhalation solution or placebo were administered for 12 weeks in a population ($n = 1230$, 808 patients with evaluable PK data) with moderate to very severe COPD. Of these patients, 304 (37.6%)

were concomitantly taking long-acting β-agonist (LABA)/inhaled corticosteroid (ICS) therapy. Patients with moderate to severe hepatic impairment were excluded from the study. Blood samples were collected on days 1, 15, 29, 57, and 84.

2.2 Pharmacokinetic Sample Collection and Bioanalysis

Plasma samples from the three phase II and the two phase III studies were analyzed at Q2 Solutions (formerly Quintiles, Inc. and Advion Bioservices, Inc., Ithaca, NY, USA) using validated liquid chromatography with tandem mass spectrometry methods. The lower limit of quantification for revefenacin and THRX-195518 in plasma was 0.005 ng/mL and 0.05 ng/mL for the phase II studies and 0.0005 and 0.005 ng/mL, respectively, for the phase III studies. The lower limit of quantification for revefenacin in the phase III studies represents a ten-fold increase in assay sensitivity relative to the assay used for the phase II studies to allow for the quantification of revefenacin in the trough samples collected in the phase III studies.

2.3 Population Modeling

Data from all studies were pooled for the integrated population PK analysis using nonlinear mixed-effects modeling using the first-order conditional estimation method with interaction in NONMEM 7.2 (ICON, Dublin, Ireland) and PLT Tools (PLT Soft, San Francisco, USA). Models were compared using the mean value of the objective function computed as −2 times the log-likelihood.

One-, two-, and three-compartment models were considered to describe revefenacin and THRX-195518 concentration–time data [8]. The formation rate of THRX-195518 was defined in the model to be a fraction of the clearance rate of revefenacin from the central compartment. All models assumed lognormal distributions of the individual PK parameters, with a mixed residual error model. A study-specific additive residual error for revefenacin was used for the observations from phase III because of the ten-fold difference sensitivity in the assay.

A sequential approach was used whereby the revefenacin data were initially fit to the revefenacin model. Then, the THRX-195518 data were fit to the combined model where PK parameters for revefenacin for each subject were fixed to the individually estimated post-hoc PK parameters from the revefenacin model. Inter-individual error terms for the revefenacin PK parameters were included in the fit to the THRX-195518 data to minimize the effect of bias.

A simultaneous modeling strategy was also evaluated in addition to the sequential approach; the parameters for revefenacin and THRX-195518 were simultaneously estimated to investigate the potential bias of the sequential approach because of the presence of shrinkage in the post-hoc individual parameters of the revefenacin model. However, the simultaneous approach introduced the potential issue of the propagation of uncertainty in model and parameter estimates from/to revefenacin to/from THRX-195518 with the known risk of increasing run-time and model instability.

Inter-occasion variability was evaluated by comparing the measured plasma concentrations of revefenacin and THRX-195518 to determine the presence of any differences between study visits. Concentrations below the limit of quantification were discarded in this analysis (M1) as the increased sensitivity of the revefenacin assay in the phase III studies allowed for the characterization of trough concentrations in all patients. A sensitivity analysis was conducted by repeating the analysis for revefenacin using the likelihood maximization (M3) method [9].

2.4 Subject Covariate Analysis

Intrinsic covariates of age, weight, sex, race, smoking status, creatinine clearance, liver enzymes (alanine aminotransferase, aspartate aminotransferase, and total bilirubin), body mass index, and baseline forced expiratory volume in 1 s (FEV_1) were tested on the PK parameters of apparent revefenacin clearance (CL/F), apparent revefenacin volumes of the central (V_1/F) and peripheral (V_2/F) compartments, apparent revefenacin intercompartmental clearance (Q/F), the fraction of CL/F that is metabolized to THRX-195518 (F_{met}), apparent THRX-195518 clearance (CL_{met}/F), apparent THRX-195518 volumes of the central (V_3/F) and peripheral (V_4/F) compartments, and apparent THRX-195518 intercompartmental clearance (Q_{met}/F).

Continuous covariates were normalized to the population median values and modeled using the general equation:

$$\theta_i = \theta_{\text{Typical}} \left(\frac{\text{Cov}_i}{\text{Cov}_{\text{Median}}} \right)^{\theta_{\text{eff}}}$$

where θ_i is the value of the parameter for the ith individual, θ_{Typical} is the typical value of the parameter in the population, Cov_i is the value of the covariate for the individual, $\text{Cov}_{\text{Median}}$ is the median value of the covariate in the study population, and θ_{eff} is the effect of the covariate on the parameter.

Categorical covariates were modeled using the general equation:

$$\theta_i = \theta_{\text{Typical}} \times \theta_{\text{eff}}^{K_{\text{ind}}}$$

where K_{ind} is an indicator variable representing one form of the categorical variable, e.g., men are coded as 1 and women as 0.

2.5 Model Selection and Evaluation

Model selection was based on a comparison of the objective function value and visual inspection of goodness-of-fit plots. Significant parameter covariate relationships identified were included in an initial full PK model (a decrease of 6.63 points in the value of the objective function equivalent to a two-sided $\alpha = 0.01$). Covariates were subsequently excluded from the model using a stepwise deletion method in which the statistical significance of each parameter-covariate relationship was tested using a likelihood ratio test (an increase of 10.83 points in the value of the objective function, equivalent to a two-sided $\alpha = 0.001$). Evaluation of the model fit was conducted using a bootstrap analysis (200 replicates) and a visual predictive check of the final model using 1000 simulated data sets.

2.6 Simulation of Exposures in Phase III Studies

The steady-state exposure in each subject in the two phase III studies was simulated using the individual post-hoc parameter estimates from the final population PK model to compare exposures between smokers and nonsmokers, patients with and without concomitant medications with known potential drug–drug interactions, and between patients with and without LABA/ICS use. Nonlinear mixed-effects modeling was used to simulate the steady-state plasma concentrations at 0, 0.01, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16, and 24 h after the start of nebulization using individually estimated PK parameters (CL/F, V_1/F, Q/F, V_2/F) for each subject as determined by the final population PK model. The dose and interval were obtained from the study data. The duration of nebulization was not recorded in the phase III studies and was assumed to be 10 min for all patients based on observed dosing durations in prior studies. Steady-state exposure (AUC_{0-24}) was calculated using linear trapezoidal approximation and C_{max} was the maximum observed post-dose concentration in the simulated plasma concentration–time profile.

3 Results

A total of 10,043 and 10,717 measurable concentrations of revefenacin and THRX-195518, respectively, were utilized in this analysis. The median, minimum, and maximum number of observations from each patient were 10, 1, and 59, respectively, for revefenacin and 9, 1, and 75, respectively, for THRX-195518.

A fraction of pretreatment samples in the phase III studies collected from each subject on day 1 had quantifiable revefenacin concentrations (22%) and THRX-195518 concentrations (4%), the majority of which were near the lower limit of quantification. A sensitivity analysis was conducted with and without the inclusion of quantifiable pretreatment concentrations utilizing an additional term to estimate a residual additive error.

3.1 Patients

The baseline demographics and clinical characteristics of patients in this analysis are listed in Table 1. The PK analysis population comprised 935 patients aged 41–88 years, weight 38.5–192 kg, estimated creatinine clearances from 22 to 151 mL/min, and baseline FEV_1 values from 44 to 2962 mL. The study population was 52.2% men; 46% of patients were current smokers; 32.5% of patients in the PK analysis population were receiving concomitant LABA/ICS therapy. Pharmacokinetic sampling times used in the analysis are described by study in Table S1 of the ESM.

3.2 Revefenacin

Systemic revefenacin pharmacokinetics was best described by a two-compartment model with fixed first-order absorption (K_a) from the dosing depot (representing the lung). Terms used include relative bioavailability (F1) and distribution and elimination parameterized by CL/F, V_1/F, Q/F, and V_2/F with inter-individual variability (IIV) terms on CL/F, V_1/F, Q/F, V_2/F, and F1 with a combination additive and proportional residual error model for phase II study data and a separate proportional residual error model for phase III study data (Fig. 1). The F1 in the structural model included a separate categorical covariate term to represent observations from Study 1 to reflect the observed lower exposures, and a continuous covariate term to represent the relationship between dose and bioavailability.

In the final model (Table 2), the population estimate of CL/F was 668 L/h with an IIV of 56.2%; the typical V_1/F was estimated to be 867 L with an IIV of 26.9%; Q/F was estimated to be 2607 L/h with an IIV of 31.0%; and the population value of V_2/F was estimated to be 15,495 L/h with an IIV of 52.2%. First-order absorption was fixed at 200/h, the effect of Study 1 on F1 was 55.3% with an IIV of 33.7%, and the effect of the dose on F1 was 0.0987.

The analysis was repeated using the maximum likelihood (M3) method to assess the potential risk of bias. A sensitivity analysis conducted on the final structural model to compare the parameter estimates using the M1 and M3 methods did not show significant differences in the parameter estimates, indicating the absence of bias in the parameter values estimated with the M1 method. The corresponding η-shrinkage for the revefenacin model was 13.5% for CL/F, 42.5% for V_1/F, 33.7% for Q/F, and 46.8% for V_2/F.

Table 1 Baseline demographics and clinical characteristics for the pharmacokinetic analysis population

Abbreviation for continuous covariates	Characteristic	(*N* = 935)
AGE	Age, mean (SD), years	63.5 (8.72)
	Sex, male, %	52.2
	Race, white, %	90.3
WT	Body weight, mean (SD), kg	83.3 (21.8)
BMI	Body mass index, mean (SD), kg/m^2	29.0 (6.97)
CrCL	Creatinine clearance, mean (SD), mL/min	71.7 (20.7)
	Smoker (current), %	46.0
	Concomitant LABA/ICS, %	32.5
BLFEV1	Baseline forced expiratory volume in 1 s, mean (SD), mL	1330 (487)
BALT	ALT, mean (SD), IU/L	20.3 (11.5)
BAST	AST, mean (SD), IU/L	21.4 (9.38)
BTBIL	Total bilirubin, mean (SD), µmol/L	6.57 (3.83)
NEBTIME	Nebulization time, mean (SD), min	10.3 (2.08)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *LABA/ICS* long-acting beta-agonist or inhaled corticosteroid, *SD* standard deviation

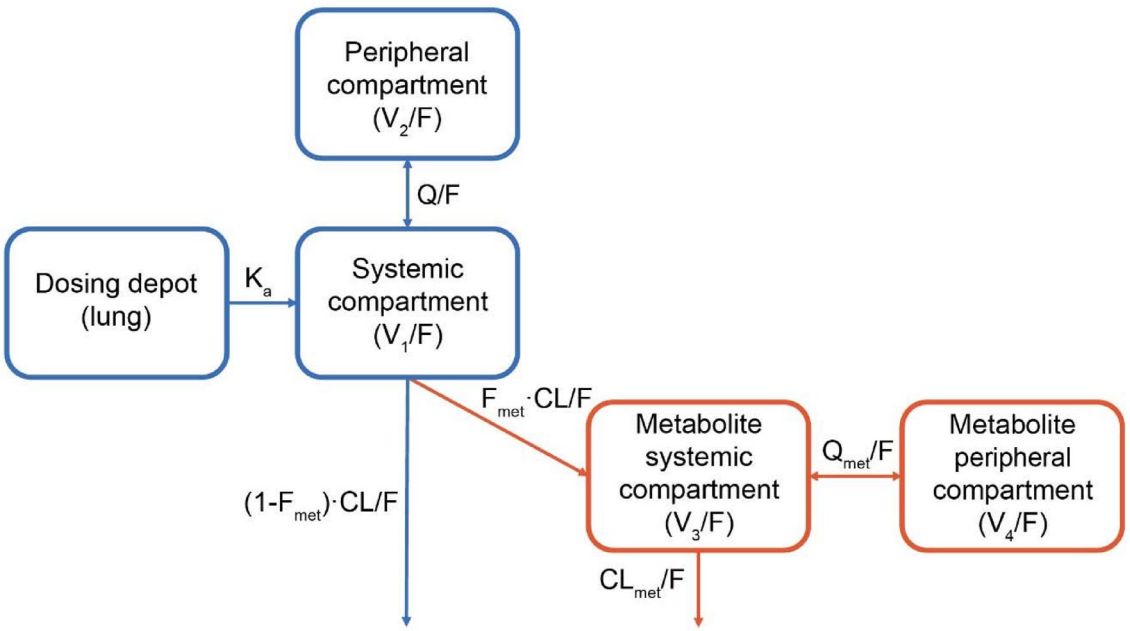

Fig. 1 Schematic of the revefenacin and THRX-195518 combined pharmacokinetic (PK) model. CL_{met}/F apparent THRX-195518 clearance, F_{met} fraction of revefenacin clearance that is metabolized to THRX-195518, K_a first-order absorption, Q/F apparent revefenacin intercompartmental clearance, Q_{met}/F apparent THRX-195518 intercompartmental clearance, V_1/F apparent revefenacin volume of the central compartment, V_2/F apparent revefenacin volume of the peripheral compartment, V_3/F apparent THRX-195518 volume of the central compartment, V_4/F apparent THRX-195518 volume of the peripheral compartment

3.3 THRX-195518

The appearance of the metabolite THRX-195518 in the systemic circulation was assumed to be a fraction of the revefenacin cleared from the systemic circulation and is structurally unidentifiable. It was not possible to simultaneously estimate F_{met}, V_3/F, and CL_{met}/F based on the measured concentration as the total amount of THRX-195518 formed per dose is unknown. The approach used to address the parameter identifiability problem was to estimate CL_{met}/F and V_3/F while fixing F_{met}. The value of F_{met} was chosen to match the total fraction of the dose recovered as THRX-195518 in

Table 2 Final pharmacokinetic model parameter estimates

	Description	Population estimate (% RSE)	Inter-individual variability (%)
Revefenacin	CL/F, L/h	668 (3.17)	56.2
	V_1/F, L	867 (3.77)	26.9
	Q/F, L/h	2607 (2.51)	31.0
	V_2/F, L	15,495 (4.88)	52.2
	K_a, L/h	200 (fixed)	0
	Study 1 effect on F1	0.553 (7.09)	33.7
	Dose effect on F1	0.0987 (4.80)	N/A
	Age effect on CL/F	−0.559 (26.0)	N/A
	Weight effect on Q/F	0.485 (12.4)	N/A
THRX-195518	CL_{met}/F, L/h	53.2 (1.84)	36.0
	V_3/F, L	20.4 (3.62)	52.1
	Q_{met}/F, L/h	36.3 (4.31)	0
	V_4/F, L	35.8 (5.44)	0
	F_{met}	0.21 (fixed)	0
	Correlation between CL_{met} and V_3	1.45 (7.46)	N/A
	Age effect on CL_{met}/F	−0.777 (13.1)	N/A
	Weight effect on F_{met}	−0.406 (18.1)	N/A

CL/F apparent clearance, CL_{met}/F apparent THRX-195518 clearance, *F1* bioavailability, F_{met} fraction of revefenacin clearance that is metabolized to THRX-195518, K_a first-order absorption, *N/A* not applicable, *Q/F* apparent revefenacin intercompartmental clearance, Q_{met}/F apparent THRX-195518 intercompartmental clearance, *RSE* relative standard error, V_1/F apparent revefenacin volume of the central compartment, V_2/F apparent revefenacin volume of the peripheral compartment, V_3/F apparent THRX-195518 volume of the central compartment, V_4/F apparent THRX-195518 volume of the peripheral compartment

the urine and feces (21%) following a single IV dose in the human absorption, distribution, and metabolism, and excretion study [6].

The model for THRX-195518 used the post-hoc individually estimated revefenacin PK parameters for each individual subject as the basis for the kinetics of THRX-195518 formation in the dataset. THRX-195518 pharmacokinetics was best described by a two-compartment model (Fig. 1) with a fixed value for F_{met} and PK characteristics parameterized by CL_{met}/F, V_3/F, Q_{met}/F, and V_4/F with IIV terms on CL_{met}/F and V_3/F with a combination additive and proportional residual error model for phase II study data and a separate proportional residual error model for phase III study data (Table 2). Inter-individual variability in the PK parameters CL_{met}/F and V_3/F was moderate (36.0% and 52.1%). The corresponding η-shrinkage for the THRX-195518 model was 30.5% for CL_{met}/F.

3.4 Covariate Analysis

Covariates of age, weight, sex, race, smoking status, creatinine clearance, body mass index, and baseline FEV_1 were tested for significance on the PK parameters CL/F, V_1/F, Q/F, V_2/F, CL_{met}/F, F_{met}, Q_{met}/F, and V_4/F. Additionally, the effects of baseline FEV_1 were tested on the PK parameters CL/F, V_1/F, Q/F, and V_2/F because of the potential impact of respirational capacity on the kinetics of revefenacin absorption. The effect of liver enzymes was included by the addition of alanine aminotransferase, aspartate aminotransferase, and total bilirubin as covariates on the formation and clearance of THRX-195518. Hepatobiliary elimination of revefenacin was assumed from the results of the absorption, distribution, and metabolism, and excretion study indicating the clearance of revefenacin via hepatobiliary elimination [6] and data from the hepatic impairment study demonstrating increased exposures to THRX-195518 in patients with moderate hepatic impairment [10].

The covariate analysis identified age as a statistically significant covariate on CL/F, and body weight was a significant covariate on Q/F of revefenacin. Age was identified as a statistically significant covariate on CL_{met}/F, and body weight as a statistically significant covariate on F_{met}.

For every 10% increase in age from 64 years, CL/F decreases by approximately 6%. In addition, for every 10% increase in weight from 81 kg, the Q/F increases by approximately 5%. To estimate the effect of age on revefenacin pharmacokinetics, a simulation of 2000 patients with the study median age of 64 years was compared with 2000 simulated concentration profiles of identical patients at 40 and 85 years of age. To estimate the effect of weight on revefenacin

pharmacokinetics, the simulation was repeated in patients with a median body weight of 81 kg and compared to otherwise identical patients with body weights of 50 and 150 kg.

There is considerable overlap in the steady-state revefenacin PK profile and exposure over the entire age and weight range of patients in the study (Fig. 2a). The $AUC_{0–24}$ in the median (64-year-old) subject following a 175-µg dose is predicted to be 0.332 ng·h/mL (covariance 74.8%). The corresponding predicted revefenacin exposures are 24% lower in a younger 40-year-old subject, and 18% higher in an older 85-year-old subject. The corresponding predicted revefenacin exposures are 3% lower in a 50-kg subject and the same as a 150-kg subject. A comparison of the individually predicted revefenacin exposures of all patients in the phase III patients does not indicate any significant differences across different age groups and weights (Fig. 2b). The effect of age and weight on revefenacin exposure is therefore considered to be minimal and does not warrant any dose adjustment. Effects of age and weight on THRX-195518 pharmacokinetics are further described in the ESM (Fig. S1a and b).

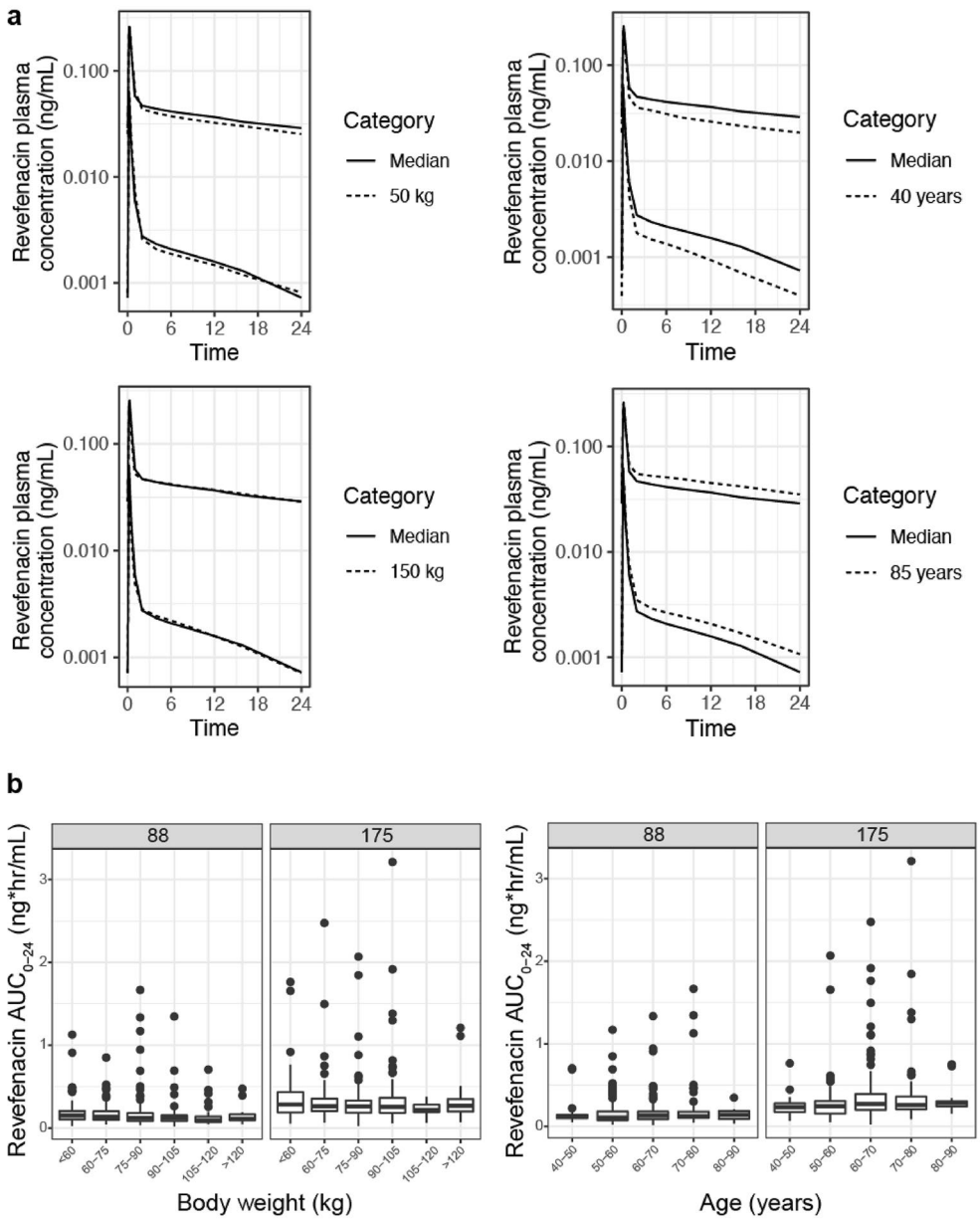

Fig. 2 Effect of age and weight on **a** individually predicted steady-state revefenacin plasma pharmacokinetic (PK) profiles [95% prediction interval (PI)] after a 175-µg dose and **b** exposures in patients from phase III studies. $AUC_{0–24}$ steady-state exposure

The effect of age, weight, sex, smoking status, and concomitant LABA/ICS therapy on exposure (AUC_{0-24} and C_{max}) was evaluated by comparing the individually predicted revefenacin and THRX-195518 exposures of all patients in the phase III studies. No clinically meaningful effect of age, weight, sex, smoking status, and concomitant LABA/ICS therapy was observed on exposure (AUC_{0-24} and C_{max}) (Fig. 3a, b), and therefore, these intrinsic and extrinsic factors do not warrant any dose adjustment.

3.5 Sensitivity Analysis

The final model was re-estimated using a lower and higher value for the rate of absorption, K_a, (100 and 1000/h vs 200/h in the final model) and did not result in an improvement of the fit based on the value of the −2 log-likelihood function ($p < 0.1$). The revefenacin and THRX-195518 AUC_{0-24} and C_{max} values predicted using the population PK model with and without the inclusion of quantifiable pretreatment

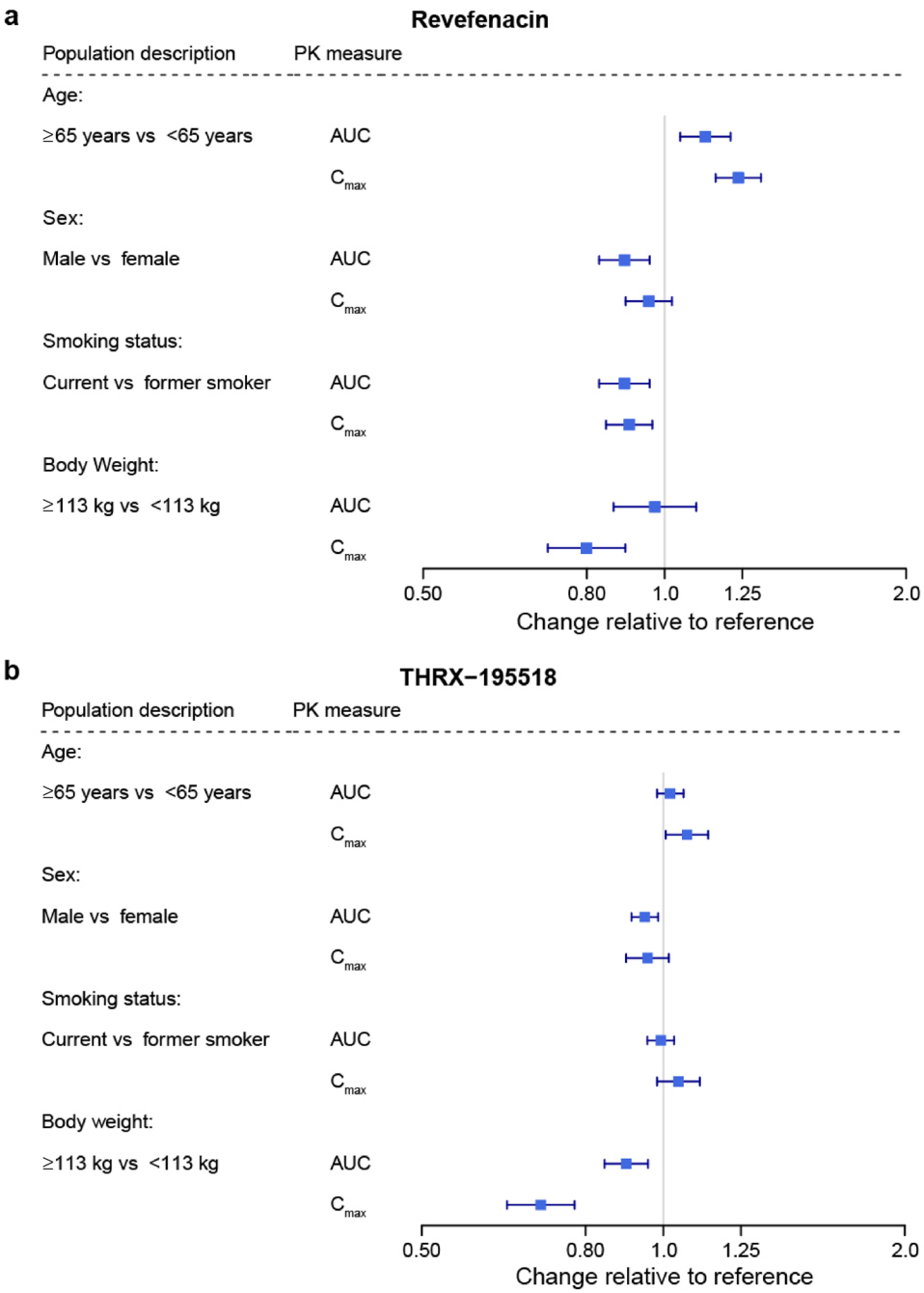

Fig. 3 Effect of age, sex, smoking status, and weight on the steady-state plasma **a** revefenacin and **b** THRX-195518 exposure. *AUC* area under the curve, C_{max} maximum exposure, *PK* pharmacokinetic

values showed minimal differences, with a point estimate of 0.0072 ng/mL for the residual additive error. The inclusion of the quantifiable pretreatment values reduced the mean predicted steady-state revefenacin AUC_{0-24} estimates by 8% at the 88-µg dose (0.170–0.157 ng h/mL) and by 3% at the 175-µg dose (0.329–0.319 ng h/mL), and the THRX-195518 AUC_{0-24} estimates were reduced by 7% at the 88-µg dose (0.426–0.396 ng h/mL) and by 1% at the 175-µg dose (0.859–0.849 ng h/mL). The mean predicted steady-state C_{max} estimates for revefenacin and THRX-195518 were nearly identical. Further analysis was conducted on data from the phase II studies only, which did not have quantifiable pretreatment concentrations. The resulting covariate effects determined by the phase II only model and phase II/III combined model were in agreement. Therefore, the inclusion of quantifiable pretreatment concentrations in the dataset did not significantly alter the results of the analysis.

3.6 Model Evaluation

3.6.1 Revefenacin

The predicted concentrations adequately match the observed concentrations at concentrations lower than 0.300 ng/mL (Fig. 4a). At higher concentrations associated with revefenacin doses ≥ 350 µg, the fitted model slightly under-predicts the plasma concentrations of revefenacin immediately following the end of drug nebulization. At the lower predicted concentrations, there is a group of observations where little to no revefenacin was expected, but detectable concentrations were measured (Fig. 4a). These observations reflect pre-dose trough samples collected in the phase III studies on days 15, 29, 57, or 84, where higher than expected concentrations of the drug were detected. These results may be due to sample handling or contamination issues; however, they were not removed from the PK analysis dataset because no attributable cause could be identified in the electronic records. The residual and weighted residual plots do not show any obvious trends (Fig. S2a and b of the ESM).

3.6.2 THRX-195518

The predicted THRX-195518 concentrations adequately match the observed concentrations at concentrations lower than 0.300 ng/mL (Fig. 4b). At higher THRX-195518 concentrations associated with revefenacin doses ≥ 350 µg, the fitted model slightly under-predicts the plasma concentrations of revefenacin. The residual and weighted residual plots do not show any obvious trends (Fig. S3a and b of the ESM). The bootstrap analysis indicated that the relationship of the estimated parameters from the final model is consistent with the estimates derived from 200 different datasets of the same size as the original dataset generated by sampling from the original dataset with replacement.

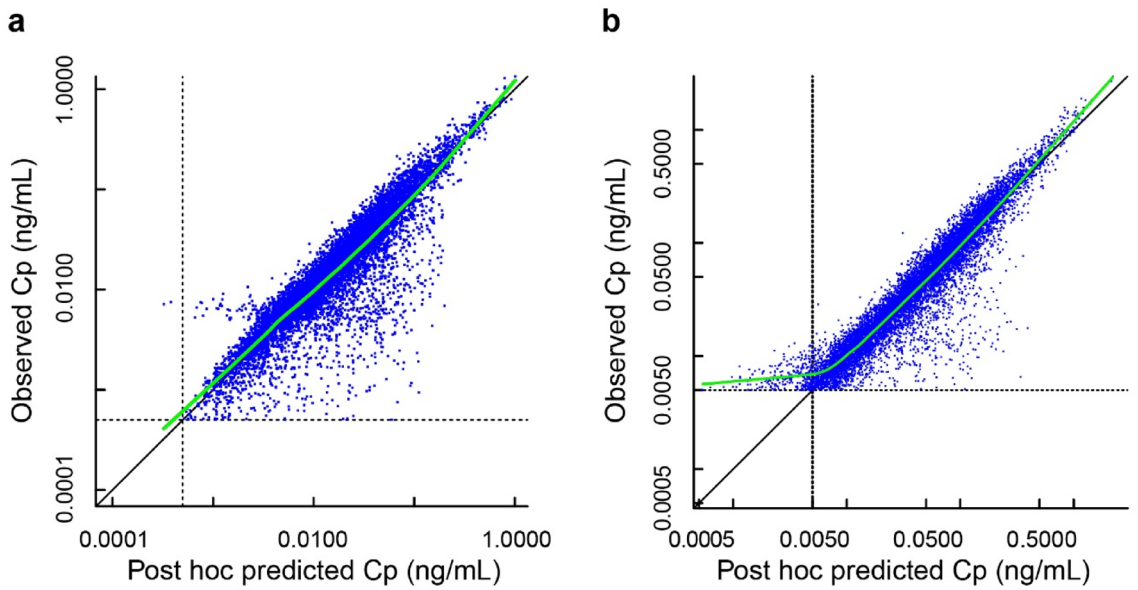

Fig. 4 Observed vs post-hoc predicted plasma concentrations for final revefenacin (**a**) and THRX-195518 (**b**) models. *Cp* plasma concentration

4 Discussion

A population PK approach was used to evaluate the effects of relevant demographic and clinical covariates and to explore clinical factors that might affect revefenacin exposure in individual patients with COPD. The impact of demographic and clinical covariates, including those previously identified as significant covariates (e.g., age, body weight, renal function, smoking status) for other inhaled muscarinic antagonists [11, 12], on the pharmacokinetics of revefenacin and THRX-195518 was assessed.

Across the clinical dose range, the PK profiles of revefenacin and THRX-195518 were both adequately described by a two-compartment open model with first-order clearance. A small dose effect on the fraction of revefenacin absorbed was identified, where the 175-µg dose was estimated to be 7% more absorbed than the 88-µg dose. Covariates including age, body weight, body mass index, sex, race, estimated creatinine clearance, baseline plasma alanine aminotransferase, aspartate aminotransferase, total bilirubin, smoking status, baseline FEV_1, and concomitant LABA/ICS therapy did not affect the pharmacokinetics of revefenacin or THRX-195518. Age and body weight were identified as statistically significant covariates for revefenacin (age on CL/F and body weight on *Q*/F), and for THRX-195518 (age on CL/F, body weight on THRX-195518 formation), but the sensitivity analysis suggested that there would be no clinically relevant impact on revefenacin or THRX-195518 exposure ($AUC_{0–24}$ or C_{max}) at steady state. Although increased age has been associated with a decline in hepatic function [13], the lack of a significant correlation between the markers of hepatic function and the PK parameters in the model suggests that age may affect clearance independent of liver function.

The results of the current analysis may be limited by the analysis population, which consisted of mostly white patients (90.3%). Future studies in other races may be helpful to generalize the current results across a larger population. Formal assessments of drug–drug interaction and concomitant medications were not conducted because of the phase III trial setting and lack of in vitro drug–drug interaction concerns identified for revefenacin.

Revefenacin is delivered directly to the lung and has poor oral absorption [6]. Thus, systemic levels of a parent drug and/or metabolite are not expected to significantly contribute to the lung (or local) PK effects of revefenacin administration. The systemic exposures of revefenacin and its major metabolite following inhaled administration in patients with COPD are low relative to concentrations necessary to antagonize muscarinic receptor function [14]. The low concentrations of revefenacin and THRX-195518 are expected to result in minimal systemic adverse effects of revefenacin consistent with the low observed incidence of antimuscarinic adverse events [1–3]. This observation is supported by the lack of exposure-response on heart rate, a biomarker for systemic M2-mediated antimuscarinic effects [1]. Additionally, revefenacin has exhibited a favorable safety profile in patients with COPD over a wide range of inhaled doses (up to 700 µg for 7 days), several-fold above the clinical dose of 175 µg/day [1–3]. Revefenacin (175 µg/day) was also shown to be well tolerated over 52 weeks of treatment [4]. Taken together, no dose adjustment is necessary based upon age, weight, sex, estimated creatinine clearance, baseline liver function tests, smoking status, and concomitant LABA/ICS therapy.

5 Conclusions

The sequential modeling approach resulted in a combined PK model that adequately characterized the pharmacokinetics of revefenacin and its major metabolite THRX-195518 in patients with COPD. No clinically significant impacts of patient and disease characteristics on revefenacin and THRX-195518 systemic exposure were identified, and thus no dose adjustments to account for intrinsic or extrinsic factors are necessary.

Declarations

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Conflict of Interest Arthur Lo and David L. Bourdet are employees of Theravance Biopharma US, Inc. Marie T. Borin is a consultant for Theravance Biopharma US, Inc.

Ethics Approval N/A.

Consent to Participate N/A.

Consent for Publication N/A.

Data Availability All authors had access to the data included in the article. The datasets generated during the current study are not publicly available but can be requested from the corresponding author.

Code Availability N/A.

Author Contributions AL designed the research, performed the research, analyzed the data, and wrote the manuscript. MB and DB designed the research, performed the research, and wrote the manuscript.

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