Electronic Supplementary Material

Clinical Pharmacokinetics

Population Pharmacokinetics of Revefenacin in Patients With Chronic Obstructive Pulmonary Disease

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Institutional Review Boards

Study 1: Pharma-Ethics Independent Research Ethics Committee (Irene, South Africa) and Central Regional Ethics Committee, Ministry of Health, Wellington, New Zealand)

Study 2: NHS-Health Research Authority, National Research Ethics Service (Manchester, UK) and Health and Disability Ethics Committees, Ministry of Health, (Wellington, New Zealand)

Study 3: IntegReview (Austin, TX, USA)

Studies 4 and 5: Quorum Review IRB (Seattle, WA, USA)

Inclusion Criteria for the Phase 2 and 3 Studies

Patients included in the Phase 2 studies were men or women of nonchildbearing potential, aged 40–75 years, with a current or former smoking history >10 pack-years and able to de monstrate the following respiratory criteria at screening: a ratio of forced expiratory volu me in 1 second (FEV1)/forced vital capacity (FVC) of <0.7 and FEV1 of 35%–80% of the predicted normal value after withholding short-acting bronchodilators for ≥6 hours and lo ng-acting bronchodilators for ≥24 hours.

Patients included in the Phase 3 studies were aged ≥40 years with a documented history of chronic obstructive pulmonary disease, a smoking history >10 pack-years, a post-ipratropi um FEV1/forced vital capacity ratio of <0.7 and a post-ipratropium FEV1 of <80% of pre dicted normal value but at least 700 mL, constituting criteria for moderate to very severe c hronic obstructive pulmonary disease.

Table S1. Pharmacokinetic data used from each study in the analysis

Study number	Drug dose (μg nebulization)	Number of treated patients	Pharmacokinetic sampling time points	Number of samples (Revefenacin, THRX-195518)	Study description
1	350, 700	32	Predose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 22, 24	896, 896	Phase 2 single-dose cross over study
2	22, 44, 88, 175, 350, 700	62	Day 1: predose, 0.25, 0.5, 1, 2, 3, 4, 6 Day 7: predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24	4287, 4287	Phase 2 multiple-dose cross over study
3	44, 88, 175, 350	355	Day 28: predose, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96	429, 429	Phase 2 multiple-dose study
4	88, 175	410[a]	Day 1, 15, 29, 57: predose, 1–30 mins postdose Day 84: predose, 1–30 mins postdose, 1–4 hrs postdose	3902, 3903	Phase 3 randomized control trial
5	88, 175	402[a]	Day 1, 15, 29, 57: predose, 1–30 mins postdose Day 84: predose, 1–30 mins postdose, 1–4 hrs postdose	3866, 3895	Phase 3 randomized control trial
Total		**1257**		**13380, 13410**	

Some patients have contributed to multiple profiles in Phase 2 studies, and some patients did not have sufficient data to be included.

hrs hours, *mins* minutes.

[a]Number of patients in safety analysis set who received revefenacin.

Effect of age and weight on THRX-195518 PK

For every 10% increase in age from 64 years, the CL_{met}/F decreases by approximately 8%. An 80-year-old subject will have about 16% lower CL_{met}/F as compared with a 64-year-old subject. For every 10% increase in weight from 81 kg, the F_{met} decreases by approximately 4%. A 64-year-old subject with an average weight of 120 kg will have about 15% lower F_{met} than a 64-year-old subject weighing 81 kg. To estimate the effect of age and weight on THRX-195518 PK, a simulation of 2000 patients with the study median age of 64 compared with 2000 simulated concentration profiles of identical patients at 40 and 85 years of age. To estimate the effect of weight on THRX-195518 PK, a simulation of 2000 patients with the study median weight of 81 kg was compared with 2000 simulated concentration profiles of identical patients with body weights of 50 and 150 kg. There is considerable overlap in the steady-state THRX-195518 PK profile and exposure over the entire age and weight range of patients in the study (**Figure S1a**).

The steady-state THRX-195518 exposure ($AUC_{0–24}$) in the median (64-year-old) subject following a 175 µg dose is predicted to be 0.797 ng*hr/mL (CV 50.7%). The corresponding predicted THRX-195518 exposures are 30% lower in a younger 40-year-old subject, and 24% higher in an older 85-year-old subject. The corresponding predicted THRX-195518 exposures are 21% higher in a 50 kg subject, and 24% lower in a 150 kg subject. A comparison of the individually predicted revefenacin exposures of all patients in the Phase 3 patients does not indicate any significant differences across different age groups and weights (**Figure S1b**). The effect of age and weight on THRX-195518 exposure is therefore considered minimal and does not warrant any dose adjustment of revefenacin.

Fig S1 Effect of age and weight on (**a**) individually predicted steady-state THRX-195518 plasma PK profiles (95% PI) after 175 µg dose and (**b**) exposures in patients from Phase 3 studies.

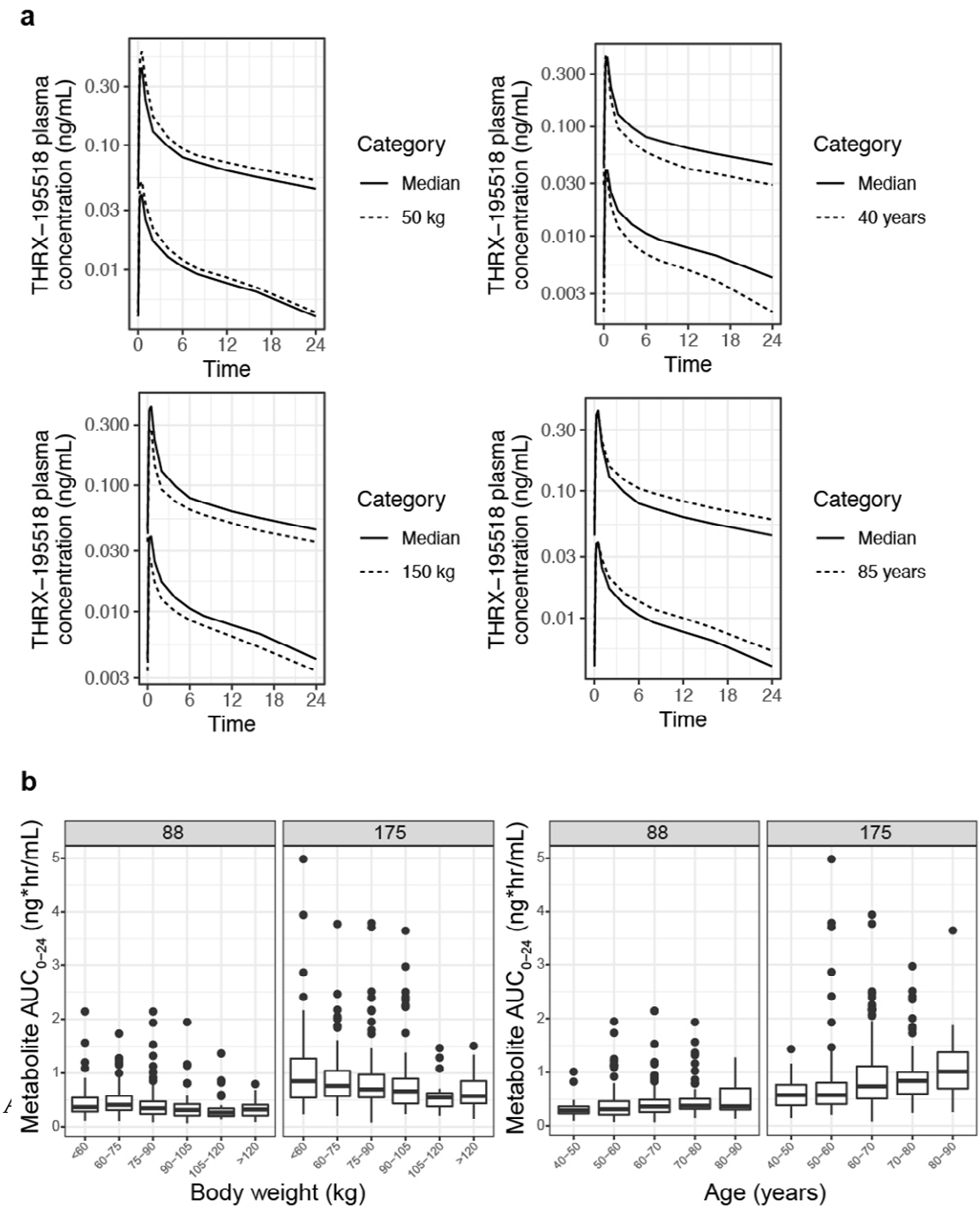
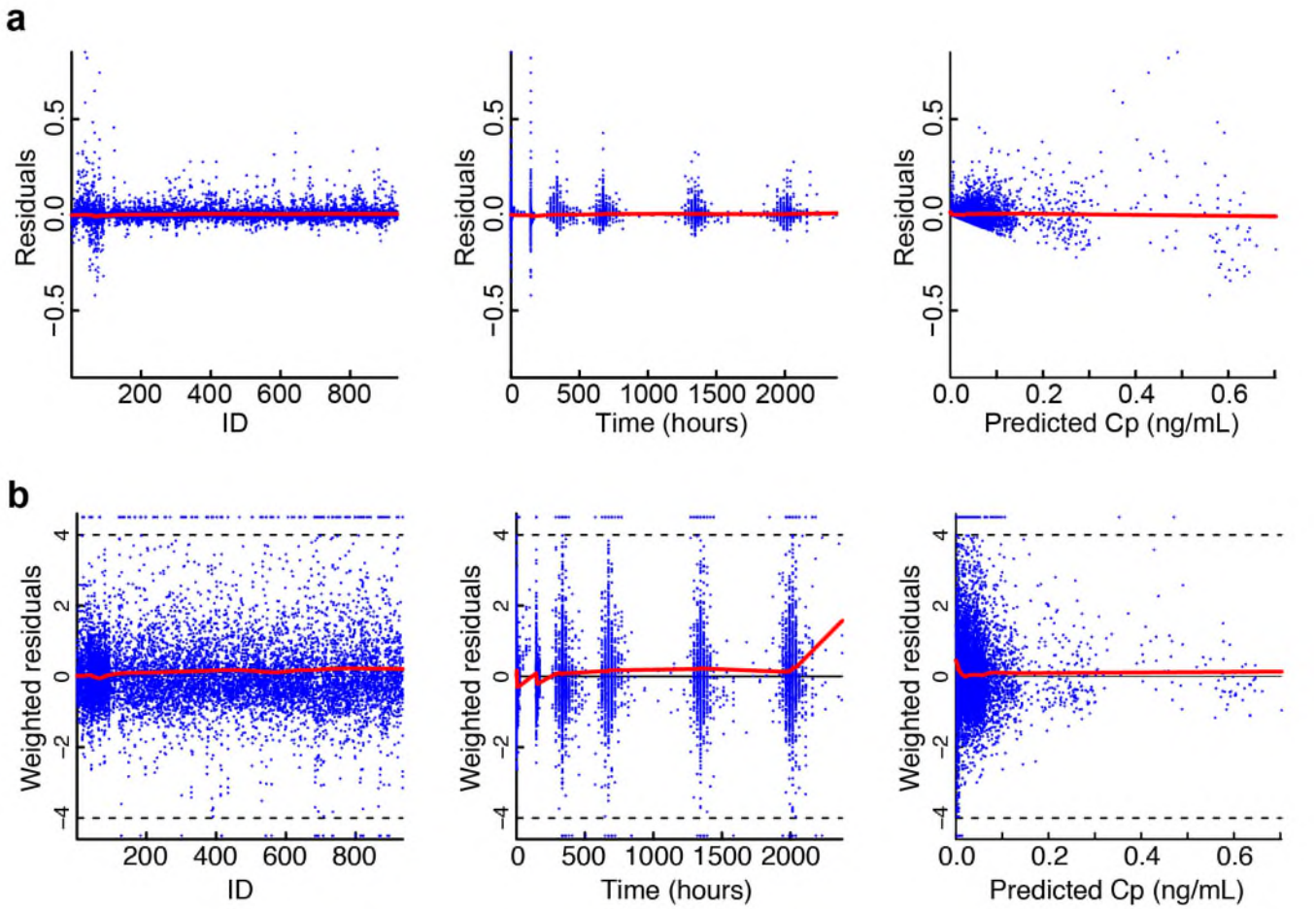
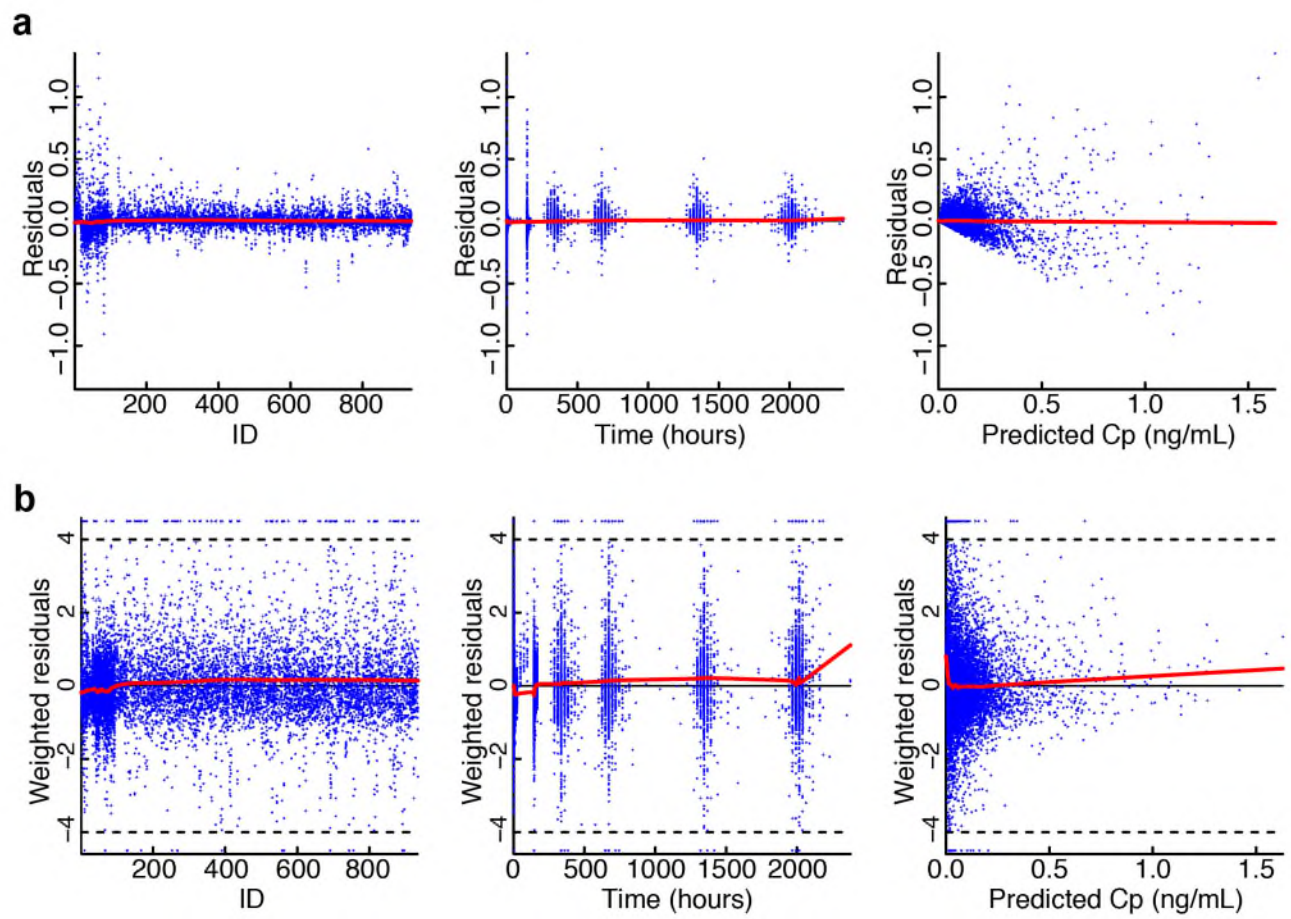


Fig S2 Goodness of population fit for final revefenacin model. (**a**) Residuals; (**b**) weighted residuals.



Cp plasma concentration, *ID* individual subject identifier.

Fig S3 Goodness of population fit for final THRX-195518 model. (**a**) Residuals; (**b**) weighted residuals.



Cp plasma concentration, *ID* individual subject identifier.