The Journal of Clinical Pharmacology
2023, 63(5) 593–603

DOI: 10.1002/jcph.2199

Pediatric Population Pharmacokinetic Modeling and Exposure–Response Analysis of Ambrisentan in Pulmonary Arterial Hypertension and Comparison With Adult Data

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Abstract

This study aimed to develop a population pharmacokinetic (PK) model of ambrisentan in pediatric patients (8 to <18 years) with pulmonary arterial hypertension (PAH) and compare pediatric ambrisentan systemic exposure with previously reported adult data. Association of ambrisentan exposure with efficacy (6-minute walking distance) and safety (adverse events) were exploratory analyses. A population PK model was developed using pediatric PK data. Steady-state systemic exposure metrics were estimated for the pediatric population and compared with previously reported data in adult patients with PAH and healthy subjects. No covariates had a significant effect on PK parameters; therefore, the final covariate model was the same as the base model. The pediatric population PK model was a 2-compartment model including the effect of body weight (allometric scaling), first-order absorption and elimination, and absorption lag time. Steady-state ambrisentan exposure was similar between the pediatric and adult population when accounting for body weight differences. Geometric mean area under the concentration-time curve at steady state in pediatric patients receiving ambrisentan low dose was 3% lower than in the adult population (and similar in both populations receiving high dose). Geometric mean maximum plasma concentration at steady state in pediatric patients receiving low and high doses was 11% and 18% higher, respectively, than in the adult population. There was no apparent association in the pediatric or adult population between ambrisentan exposure and change in 6-minute walking distance or incidence of ambrisentan-related adverse events in pediatric patients. The similar ambrisentan exposure and exposure–response profiles observed in pediatric and adult populations with PAH suggests appropriateness of body-weight–based dosing in the pediatric population with PAH.

Keywords

6-minute walking distance, ambrisentan, exposure–response, pediatrics, pharmacokinetic model, pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a rare, progressive disease with a poor prognosis, characterized by increased pulmonary arterial pressure leading to right ventricular heart failure and death.[1] The emergence of new treatments and the use of aggressive treatment approaches have led to recent improvements in the prognosis for pediatric PAH.[2] Few dedicated pediatric clinical trials have been completed,[3,4] with only 1 randomized controlled trial (investigating sildenafil)[5,6] and a number of pharmacokinetic (PK) studies.[7–9] Therefore, current treatment guidelines in pediatric patients are largely based on data from adult trials, small uncontrolled pediatric studies, and expert opinion.[2,10]

Current therapies for adult PAH include the endothelin receptor antagonist, ambrisentan, which has been shown to improve clinical symptoms, exercise capacity, World Health Organization functional class, and quality of life in adult patients with PAH, with an acceptable safety profile.[11] Ambrisentan 5 or 10 mg once daily is approved for the treatment of PAH in adults.[12] Ambrisentan has also shown promising efficacy outcomes in pediatric PAH and a similar safety

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Submitted for publication 5 May 2022; accepted 27 December 2022.

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ClinicalTrials.gov Identifier: NCT01332331; Study terminated

profile to that of the adult population in a retrospective cohort study[13] and the phase IIb randomized study AMB112529 (NCT01332331), which evaluated low- and high-dose regimens in a pediatric population aged 8 to <18 years.[14] However, this study was terminated in February 2019 owing to evidence of reductions in brain weight of juvenile rats treated with 20 mg/kg/day high-dose ambrisentan.[14]

Adult PK and PK/pharmacodynamic (PK/PD) data for ambrisentan have been previously characterized in healthy adults and adult patients with PAH using nonlinear mixed-effects modeling (NONMEM) (unpublished data on file, GSK, Collegeville, Pennsylvania). The aim of the current analysis was to develop a population PK model in patients with PAH aged 8 to <18 years (based on patient data from study AMB112529), using the previous adult population PK model as a starting point. Following development of the PK model, steady-state exposure was estimated in the pediatric population and compared with previously reported adult data. Exploratory analyses of the potential association of ambrisentan systemic exposure with efficacy and safety in pediatric patients were also conducted.

Methods

At each investigative site, the study was reviewed and approved by the institutional review board and/or local research ethics committee before commencement (all study sites had institutional review board approval) and was conducted in accordance with International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice ethical principles and the Declaration of Helsinki.[15]

Written informed consent was provided by each patient (or legal guardian) before participation. Information on investigator sites and ethics committees are provided in Table S1.

Objectives

The analyses were designed for the following primary objectives: to evaluate the predictive performance of the previously developed ambrisentan population PK model in adult patients, using data from pediatric patients (aged 8 to <18 years) in study AMB112529; to develop a population PK model using data from pediatric patients from study AMB112529 alone; and to compare systemic exposure metrics from pediatric patients in study AMB112529 with those from the adult population. Exploratory analyses evaluated the relationship between ambrisentan exposure and 6-minute walking distance (6MWD) change from baseline (CFB), and between ambrisentan exposure and incidence of adverse events (AEs; including serious AEs), in pediatric study AMB112529.

Pediatric Population: Study AMB112529

Study AMB112529 was a 6-month, randomized, open-label phase IIb study evaluating the safety, PK, and efficacy of high- and low-dose ambrisentan in pediatric patients with PAH aged 8 to <18 years (NCT01332331).[14] Patients were dosed orally once daily for 24 weeks after randomization to a high- or low-dose group. All patients received the low dose (2.5 or 5 mg, depending on body weight) for the first 2 weeks, after which the high-dose group was up-titrated to 5, 7.5, or 10 mg of ambrisentan (depending on body weight) if deemed appropriate by the investigator (Table 1). Safety was evaluated by monitoring treatment-emergent AEs, and efficacy outcomes included 6MWD and World Health Organization functional class.

Eligible patients had a current diagnosis of PAH (group 1) according to the Fourth World Symposium on Pulmonary Hypertension held in 2008 in Dana Point, California,[16] with 1 of the following PAH etiologies: idiopathic; heritable (familial); secondary to connective tissue disease; or persistent PAH despite surgical repair (≥6 months before screening) of atrial septal defects, ventricular septal defects, atrioventricular septal defects, and persistent patent ductus.

Data

Pediatric Population. Sparse plasma samples for PK analysis were taken from each patient (1 sample per visit) at weeks 4 and 12 (trough), weeks 8 and 16 (0.5-4 hours after dosing), week 20 (4-22 hours after dosing), and 24 hours after the last dose during study AMB112529. The PK data set included all randomized patients who received at least 1 dose of the study drug and for whom at least 1 PK sample of known time relative to dosing was obtained and analyzed. The exposure–response data set consisted of 6MWD CFB and safety from study AMB112529.

Adult Population. The adult population PK data set consisted of the complete PK data from 380 participants, including 41 healthy subjects and 339 patients with PAH, enrolled in 2 phase I studies (AMB-105, AMB-106), 1 phase II study (AMB-220, NCT00046319), 1 phase II long-term study (AMB-222, NCT00423592),[17] and 2 phase III studies as well as a long-term extension study (AMB-320 [ARIES-1], NCT00423748; AMB-321 [ARIES-2], NCT00423202; and AMB-320/321-E [ARIES-E], NCT00578786).[18] The exposure-response data set consisted of 6MWD CFB and safety from AMB-220, AMB-222, AMB-320, AMB-321, and AMB-320/321-E. See Table S2 for further details.

Table 1. Ambrisentan Body-Weight-Group–Based Daily Doses for Pediatric Study AMB112529[a]

	Low Dose		High Dose	
Body Weight (kg)	Starting Dose (mg)	Week 2 Onward (mg)	Starting Dose (mg)	Week 2 Onward (mg)
≥50	5	5	5	10
≥35 to <50	5	5	5	7.5
≥20 to <35	2.5	2.5	2.5	5

[a] More detail of weight bins and corresponding dosages used in study AMB112529 are reported in Ivy et al.[14]

Plasma Concentration of Ambrisentan

The concentration of ambrisentan in 50-μL human plasma samples containing sodium citrate was determined using validated analytical methods based on protein precipitation using acetonitrile containing internal standard BSF127041, followed by detection using high-pressure liquid chromatography with tandem mass spectrometric analysis (Applied Biosystems, Waltham, Massachusetts, USA; API-400, MDS Sciex, Redwood City, California) and quantification by positive ionization mode with TurbolonSpray interface with transition masses of 379 and 125. The lower and upper limit of quantification in plasma were 5 and 5000 ng/mL, respectively. The precision of the ambrisentan assay was ≤15%, and the accuracy of the assay was within ±15% of the actual value of ambrisentan. Further methodological detail is provided in Data S1.

Pediatric PK Model Development

The previously developed adult ambrisentan population PK model was the starting point for model development; this was a linear 2-compartment model with first-order absorption and elimination and absorption lag time (unpublished data on file, GSK). Parameters for the adult population PK model are shown in Table S3. In a prediction-corrected visual predictive check (pcVPC), the observed concentration versus time data from pediatric study AMB112529 were overlaid onto the 95% prediction intervals (PIs) from the adult PK model to confirm that data from the pediatric study were consistent with the adult model predictions. The pcVPC plot demonstrates that the majority of the observed ambrisentan PK data from the pediatric data lies within the 90% PI, indicating the adequacy of the adult final population PK model as a starting point.

Allometric body-weight scaling was applied to both apparent clearance (CL/F) and apparent volume of distribution parameters from the start of developing the pediatric model. Random-effect error structural models, including interindividual variability and residual errors, were evaluated. Details of the pharmacostatistical and covariate models are provided in Data S1.

Model Performance. The adequacy of the final pediatric population PK model was assessed through objective function value, and numerical- and simulation-based diagnostic plots (including pcVPC of 500 simulations).

Derivation of Ambrisentan Exposure

The final pediatric population PK model was used to compute individual estimates of steady-state systemic exposure metrics for the population following repeat dosing of daily ambrisentan. These were compared against the adult model-derived exposures in the adult population.

Individual estimates of area under the concentration-time curve (AUC) at steady state (AUC_{ss}) were calculated as:

$$AUC_{ss} = Dose_i \,/CL/F_i$$

where $Dose_i$ is the final daily dose for each subject and CL/F_i is the individual estimate of oral clearance. The parameter estimates from the final population PK model were used to simulate 500 data sets based on the covariates, sampling times, and dosing histories contained in the original data set. The model-derived and predicted CL/F estimates were used to derive AUC_{ss}. Median, 5th, and 95th percentiles were summarized. Similarly, 5th and 95th percentiles of the adult AUC_{ss} were derived for comparison with the adult population.

Concentration-time profiles were simulated using the parameter estimates from the final model to derive estimates of maximum plasma concentration at steady state ($C_{max,ss}$). Steady-state ambrisentan concentration-time profiles were predicted at 0, 0.5, 1, 1.5, and 2 hours and then hourly until 24 hours after dosing, and $C_{max,ss}$ for each patient in the population PK data set were derived using their respective doses.

Exposure–Response Analysis

Exposure–Efficacy in Pediatric and Adult Patients. An exploratory exposure–response analysis was conducted to assess the relationship between ambrisentan systemic exposure and efficacy (6MWD CFB), both in pediatric study AMB112529 and in the adult population. Ambrisentan individual post hoc AUC_{ss} (estimated exposures derived from the final population PK model) were plotted against 6MWD CFB at 12 and 24 weeks,

stratified by dose group. Potential association between exposure and 6MWD CFB was assessed visually.

Exposure–Safety in Pediatric Patients. An exploratory analysis was conducted to assess the relationship between ambrisentan exposure and the incidence of AEs related to ambrisentan (including serious AEs) in pediatric study AMB112529 (see Ivy et al[14] for a full description of the AEs experienced in study AMB112529). Ambrisentan individual post hoc exposures (AUC_{ss} and $C_{max,ss}$) were plotted against the incidence of any ambrisentan-related AE; a visual comparison assessed possible associations.

Software

Population PK analyses of ambrisentan plasma concentration–time data was done using NONMEM version 7.4.1 (ICON plc, Blue Bell, Pennsylvania) and the Importance Sampling Expectation Maximization method.[19] PDx-Pop version 5.2.0 was used as a NONMEM interface (ICON plc). The NONMEM model code is provided in Data S1. Data handling, summary statistics, exploratory diagnostics, exposure−response analyses, and postprocessing were conducted using R version ≥3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).[20]

Results

Pediatric Population PK Modeling

Demographics and Analysis Data. In study AMB112529, 39 of 41 patients (age range, 8-16 years) were included in the PK data set. One patient was excluded as no PK samples were taken, and the other was lost to follow-up after week 2, before the first PK sample was scheduled. The distribution of covariates and number of patients receiving ambrisentan by dose group in the population PK analysis are summarized in Table S4. Study AMB112529 also provided pediatric efficacy (ie, 6MWD) and safety measures for the exposure−response analysis.

The population PK analysis data set for study AMB112529 consisted of 211 observations from 39 pediatric patients with PAH, of which only 3% of the postdose observations were below the lower limit of quantification (<5 ng/mL). Ambrisentan plasma concentration-time data from the different body-weight groups showed similar exposure within low- and high-dose groups (Figure 1).

Predictive Performance of the Adult Population PK Model. The pcVPC plot demonstrated that the majority of the observed ambrisentan PK data from the pediatric study were within the 90% PIs of the previously developed adult population PK model, indicating the adequacy of the adult model in predicting the observed pediatric ambrisentan data from study AMB112529 (Figure S1). There were a few concentrations at early (4-8 hours) and later (16-20 hours) time points that were underpredicted.

Ambrisentan Pediatric Population PK Base Model. The base population PK model for the pediatric population (aged 8 to <18 years) was a 2-compartment model with first-order absorption and elimination and absorption lag time with body-weight effect (70-kg reference body weight and coefficients estimated) on CL/F, apparent volume of central compartment (Vc/F), apparent intercompartment clearance, and apparent volume of peripheral compartment (Vp/F). Body-weight effects were fixed to allometric coefficients (0.75 and 1 for the clearance and volume parameters, respectively); estimating the scaling parameters was also attempted, but it did not improve the fit of the model.

Effect of Covariates. A number of covariates were evaluated (in addition to body weight) on PK parameters. The following were included on CL/F: bilirubin, alkaline phosphatase, creatinine clearance, age, sex, race (White vs East Asian vs Other); the following were included on Vc/F: bilirubin, alkaline phosphatase, creatinine clearance; and dose (low/high) was included on absorption lag time.

As no covariates were statistically significant, the final covariate model remained the same as the base model, with body weight allometrically scaled. This was selected as the final pediatric population PK model.

Final Pediatric Population PK Model. The final population PK model in the pediatric population was a 2-compartment model with first-order absorption and elimination and absorption lag time. The selected final model incorporated the effect of body weight on the clearance and volume parameters.

Population PK parameter estimates from the final model are shown in Table 2. Parameter estimates for CL/F, Vc/F, absorption rate constant, and absorption lag time using the data from study AMB112529 were similar to those from the adult population PK model (Table S3). Despite Vp/F being statistically different from the adult population PK model, model-based sensitivity analysis using deterministic simulations showed that this difference was not expected to translate into clinically relevant differences in systemic exposure between pediatric and adult populations.

This final pediatric model adequately described the observed pediatric data with no obvious systematic bias in model predictions (Figure S2). The pcVPC of the final population indicated good overall agreement for the median as well as the 5th and 95th percentiles of ambrisentan concentrations

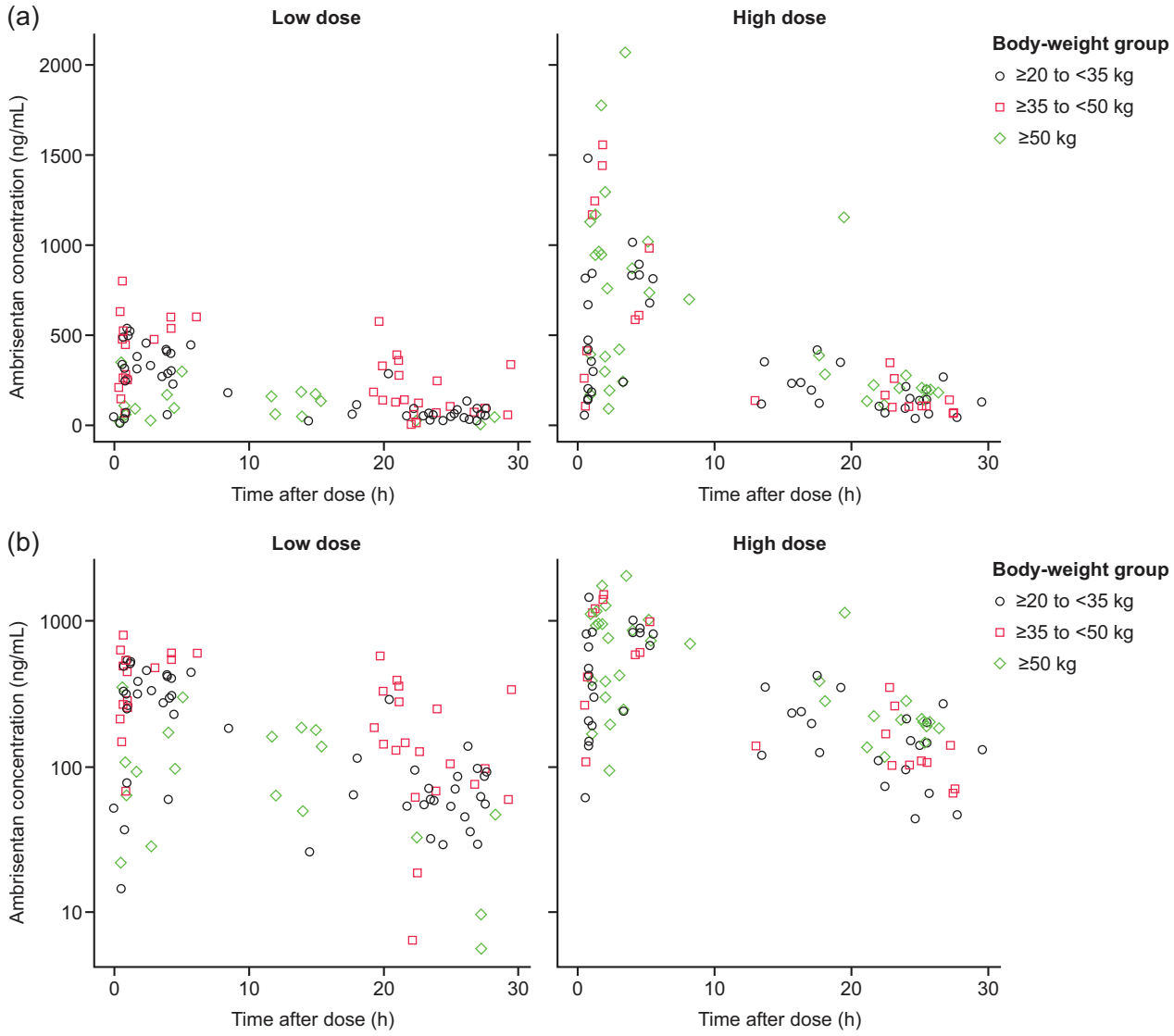

Figure 1. Observed ambrisentan concentration-time data, stratified by dose and body-weight groups in the pediatric study AMB112529 (a) linear and (b) log-linear.
h, hours.

between study AMB112529 observations and model-predicted data (Figure 2).

Comparison of Ambrisentan Exposure in the Pediatric and Adult Populations. Steady-state exposures derived from the final pediatric population PK model and the previously developed adult model confirmed similar exposure for ambrisentan in pediatric patients and adults when differences in body weight were accounted for (Table S5). Overall, there was good agreement between the model-derived average pediatric and adult ambrisentan AUC_{ss} and $C_{max,ss}$ for both the low- and high-dose groups (Figure S3). The geometric mean AUC_{ss} (95%CI) in pediatric patients receiving low doses (4.82 μg • h/mL [4.14-5.61]) was only 3% lower than the AUC_{ss} in the adult population receiving a low dose of 5 mg once daily (4.98 μg • h/mL [4.68-5.29]). The geometric mean AUC_{ss} (95%CI) in pediatric patients receiving high doses (9.15 μg • h/mL [8.41-9.96]) was similar to the AUC_{ss} in adult population receiving a high dose of 10 mg once daily (9.12 μg • h/mL [8.30-10.0]). The geometric mean $C_{max,ss}$ in pediatric patients receiving low and high doses was 11% and 18% higher than the $C_{max,ss}$ in the adult population receiving low and high doses of 5 and 10 mg once daily, respectively.

The geometric mean AUC_{ss} values in pediatric patients were similar across the evaluated weight groups for both the low and high doses except for the pediatric low dose ≥35 to <50-kg group, which had

Table 2. Parameter Estimates of the Final Pediatric Ambrisentan Population Pharmacokinetic Model

Parameter [Units]	Point Estimate	95% CI	%RSE		
CL/F [L/hr]	1.17	1.04–1.33	6.33		
Vc/F [L]	12.3	8.94–16.8	16.1		
Q/F [L/hr]	0.457	0.302–0.691	21.1		
Vp/F [L]	81.3	50.2–132	24.5		
Ka [hr^{-1}]	2.46	1.49–4.07	25.7		
tlag [hr]	0.525 FIXED	0.393–0.700	14.7		
Coefficient of body weight effect on CL/F and Q/F	0.75 FIXED	–	–		
Coefficient of body weight effect on Vc/F and Vp/F	1 FIXED	–	–		
Interindividual Variability		**Etabar (SE)**	**p-value**	**CV%**	**Shr%**
ω^2_{CL}	0.0477	–0.0000260 (0.0280)	0.999	21.8	19.0
Covar η_{CL}, η_{Vc}	–0.108	–	–	R = –0.621	–
ω^2_{Vc}	0.634	0.000878 (0.105)	0.933	94.1	16.5
Covar η_{CL}, η_{Q}	0.0776	–	–	R = 0.872	–
Covar η_{Vc}, η_{Q}	–0.119	–	–	R = –0.367	–
ω^2_{Q}	0.166	–0.000152 (0.0453)	0.973	42.5	29.6
Covar η_{CL}, η_{Vp}	–0.00121	–	–	R = –0.0167	–
Covar η_{Vc}, η_{Vp}	0.0429	–	–	R = 0.162	–
Covar η_{Q}, η_{Vp}	–0.00815	–	–	R = –0.0603	–
ω^2_{Vp}	0.110	–0.000389 (0.00729)	0.593	33.2	86.1
Covar η_{CL}, η_{Ka}	–0.0369	–	–	R = –0.167	–
Covar η_{Vc}, η_{Ka}	0.653	–	–	R = 0.812	–
Covar η_{Q}, η_{Ka}	0.0584	–	–	R = 0.142	–
Covar η_{Vp}, η_{Ka}	0.0664	–	–	R = 0.198	–
ω^2_{Ka}	1.02	0.0125 (0.119)	0.916	133	25.9
Covar η_{CL}, η_{tlag}	0.0156	–	–	R = 0.229	–
Covar η_{Vc}, η_{tlag}	–0.169	–	–	R = –0.680	–
Covar η_{Q}, η_{tlag}	–0.00599	–	–	R = –0.0471	–
Covar η_{Vp}, η_{tlag}	–0.00741	–	–	R = –0.0716	–
Covar η_{Ka}, η_{tlag}	–0.264	–	–	R = –0.838	–
ω^2_{tlag}	0.0973	0.000357 (0.0363)	0.922	31.2	26.4
Residual Variability		**95% CI**	**%RSE**		
Proportional error	0.210	0.152–0.268	14.2	45.8	

Etabar is the arithmetic mean of the η estimates and the p-value for the null hypothesis that the true mean is 0.
Residual error terms were estimated as thetas (point estimate is $\sqrt{\sigma^2}$).
CV% = 100* $\sqrt{\omega^2}$ or 100* is $\sqrt{\sigma^2}$ for log-normally distributed variability terms.
If $\omega^2 > 0.15$, CV% = 100* $\sqrt{\sigma^{\omega 2} - 1}$
Parameter estimates in this analysis are for the reference population which is a 70 kg patient with PAH.
%RSE, percent relative standard error of the estimate; CI, confidence interval; CL/F, apparent clearance; CV%, coefficient of variation; Ka, absorption rate constant; PAH, pulmonary arterial hypertension; Q/F, apparent intercompartmental clearance; SE, standard error; Shr, shrinkage; tlag, absorption lag time; Vc/F, apparent volume of central compartment; Vp/F, apparent volume of the peripheral compartment; ω^2_{CL}, variance of random effect of CL/F; ω^2_{Vc}, variance of random effect of Vc/F; ω^2_{Vp}, variance of random effect of Vp/F; ω^2_{Ka}, variance of random effect of Ka; $\omega^2_{Q/F}$, variance of random effect of Q/F.

29% higher exposure compared with the adult 5-mg dose (Figure S4). The range of individual AUC_{ss} values for this low-dose weight group were within the model predicted values for the adult population. Within the pediatric low-dose group, the $C_{max,ss}$ increased with the increasing body weight (Table S5). Within the pediatric high-dose group, $C_{max,ss}$ for the ≥35 to <50-kg group had a 33% higher geometric mean $C_{max,ss}$ compared with the adult 10-mg dose.

Model-derived and predicted ambrisentan AUC_{ss} versus body weight using the final pediatric population PK model is presented in Figure 3. For low and high doses, both model-derived and predicted ambrisentan AUC_{ss} in the pediatric population were within the observed adult range.

Exposure-Response Analysis

Exposure–Efficacy in the Pediatric and Adult Population. The exploratory exposure-efficacy analysis showed no clear associations between ambrisentan systemic exposure and 6MWD CFB at 12 and 24 weeks in the

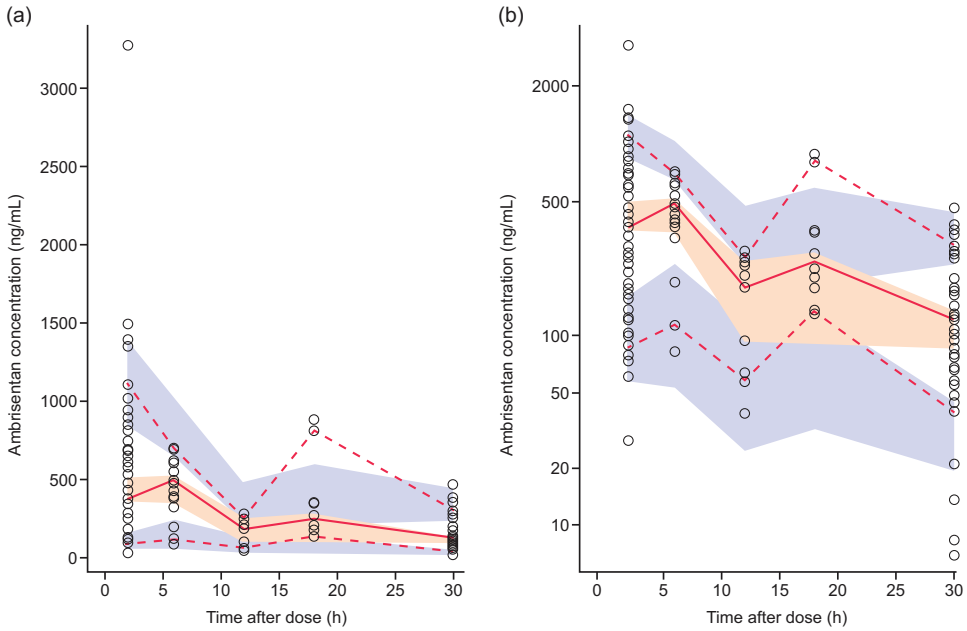

Figure 2. Prediction-corrected visual predictive check of the final pediatric population PK model using PK data from the pediatric study AMB112529 (a) linear and (b) log-linear.
Open circles, observations. Shaded areas represent 90% prediction interval of the median of predicted concentrations (pink) and 5th and 95th percentiles of the predicted data (blue) from the pediatric PK model. Solid line, median of the observed data from pediatric study AMB112529. Dashed line, 5th and 95th percentiles of the observed data from pediatric study AMB112529.
h, hours; PK, pharmacokinetic.

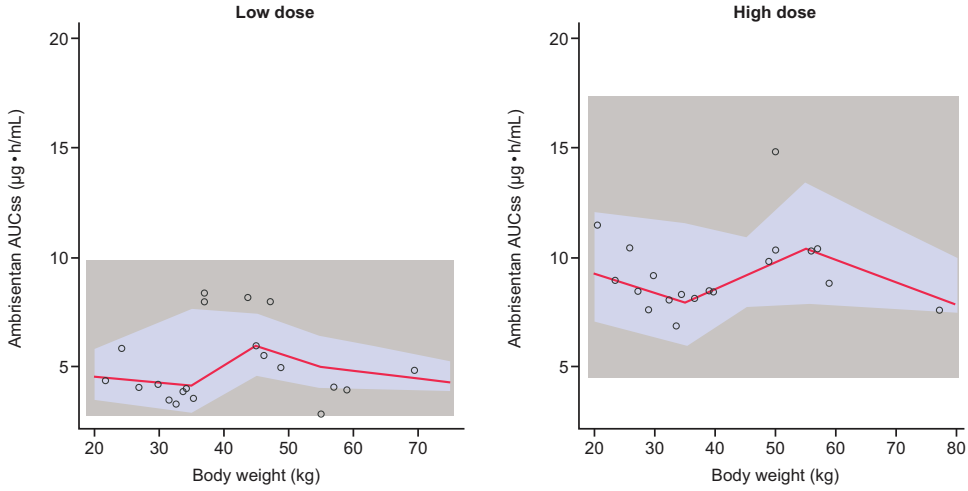

Figure 3. Model-derived and predicted AUC_{ss} versus body weight using the final pediatric population PK model.
Open circle, model-derived pediatric AUC_{ss}. Solid line, median of predicted pediatric AUC_{ss}. Blue shaded region, 90% prediction interval for predicted pediatric AUC_{ss}. Gray shaded region, 5th and 95th percentiles for adult model-derived AUC_{ss} at low dose (left) and high dose (right).
AUC_{ss}, area under the plasma drug concentration-time curve from predose to the end of the dosing interval at steady state; h, hours; PK, pharmacokinetic.

pediatric or adult population (Figure 4). The exposure–response evaluation was extended by graphically overlaying the pediatric and adult exposure–response data in addition to performing a nonparametric quantile analysis, which showed that most pediatric data lay within the adult quantiles data range (mean ± SD) at weeks 12 and 24. Furthermore, all pediatric data were within the variability range of adult data (unpublished data on file, GSK).

Exposure–Safety in Pediatric Patients. In another exploratory exposure–response analysis, plots of

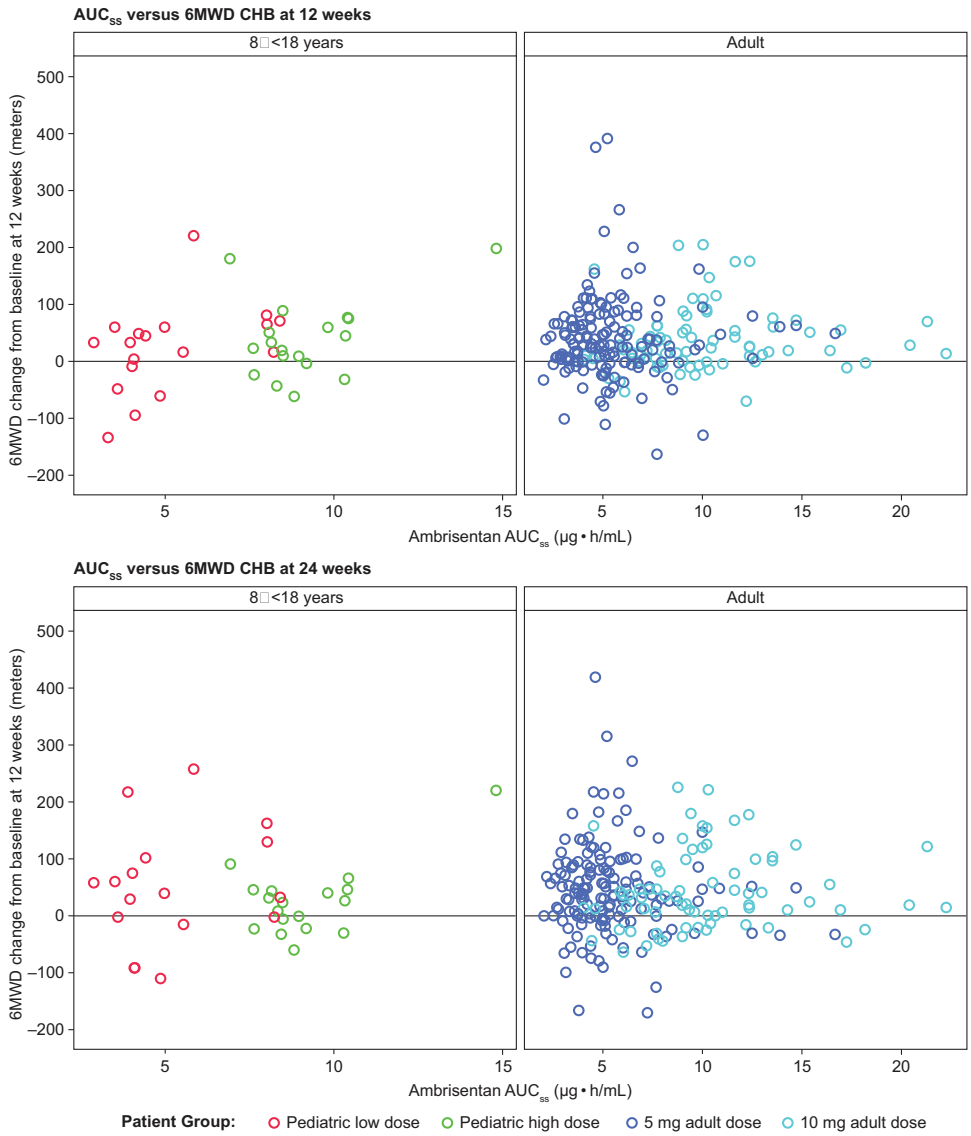

Figure 4. Predicted ambrisentan individual systemic exposure versus change in 6MWD in pediatric study AMB112529, and in the adult population, stratified by dose.
6MWD, 6-minute walking distance; AUC_{SS}, area under the plasma drug concentration-time curve from predose to the end of the dosing interval at steady state; CHB, change from baseline; h, hours.

ambrisentan systemic exposure against incidence of any AE related to ambrisentan in pediatric patients suggested no obvious association between ambrisentan exposure and the incidence of ambrisentan-related AEs (Figure 5).

Discussion

Here, we report the development of an ambrisentan population PK model in pediatric patients aged 8 to <18 years with PAH. The population PK model adequately described the pediatric data, showing no obvious systematic bias in model predictions. It was based on a 2-compartment model with first-order absorption and elimination with an absorption lag time that was previously established for ambrisentan in an adult population. The final pediatric population PK model adequately predicted the observed PK concentrations in the pediatric population (aged 8 to <18 years) from study AMB112529.

Overall, there was good agreement between the model-derived average pediatric and adult ambrisentan exposure (AUC_{ss} and $C_{max,ss}$) at both low and high doses of ambrisentan; the range of individual values in the pediatric population was well within the model-predicted values for the adult population. For both the low- and high-dose groups, the model-predicted pediatric ambrisentan AUC_{ss} for all body-weight groups

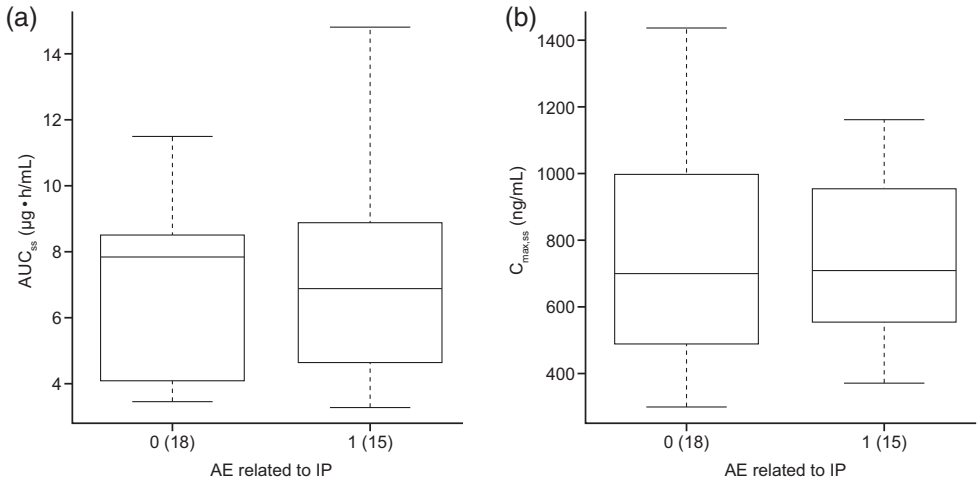

Figure 5. Ambrisentan exposures expressed as (a) AUC_{ss} and (b) $C_{max,ss}$ versus incidence of any AE related to ambrisentan in pediatric study AMB112529.

0 = no ambrisentan-related AE. 1 = ambrisentan-related AE.

AE, adverse event; AUC_{SS}, area under the plasma drug concentration-time curve from predose to the end of the dosing interval at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; h, hours; IP, investigational product (ambrisentan).

was within the range of model-predicted AUC_{ss} in adults, confirming that the body-weight–based dosing scheme in pediatric patients achieved exposures comparable to the adult population. This is consistent with a retrospective cohort study by Takatsuki et al,[13] which evaluated ambrisentan PK in 16 pediatric patients aged 3-15 years treated with body-weight–adjusted doses of ambrisentan (2.5-10.0 mg). The authors concluded that ambrisentan C_{max} and AUC in children were similar to that in the adult population.

However, differences in Vp/F were observed between the populations. This was anticipated due to variations in sample size (pediatric: 211 observations from 39 subjects; adult: 3126 observations from 380 subjects), and the difference in PK sampling (pediatric: sparse sampling of 1 plasma sample per visit; adult: intense sampling at numerous time points after dosing). Another variation was observed in the pediatric low-dose, ≥35 to <50-kg body-weight group, which had 29% higher geometric mean AUC_{ss} compared with the adult 5-mg dose group. This observed variation occurred despite the fact that the range of individual pediatric AUC_{ss} values were well within the model-predicted values for the adult population. One possible explanation for this observation could be that, in study AMB112529, patients in the ≥35 to <50-kg and ≥50-kg body-weight categories for the low-dose group received the 5-mg dose, which could have resulted in higher exposure in the ≥35 to <50-kg body-weight group compared with the ≥50-kg group. Additionally, this observation is based on a small sample size (N = 8), and therefore these results should be interpreted with caution. Furthermore, the higher AUC_{ss} is not expected to be clinically relevant with respect to safety following dosing in the pediatric population, as there is no obvious association between the predicted AUC_{ss} and the incidence of ambrisentan-related AEs in the pediatric population.

The final exposure-efficacy analyses in adults and pediatric subjects were in agreement, as neither analysis showed any strong relationships between ambrisentan systemic exposure and effects on 6MWD. The efficacy profile of ambrisentan in subjects aged 8 to <18 years was similar to that observed in adults with clinically relevant improvements in exercise capacity and symptoms as demonstrated by the 6MWD test.[14,21] The safety profile of ambrisentan in the pediatric population was also consistent with the known safety profile in adults.[14] The most frequently reported treatment-emergent AEs in the pediatric population were mild or moderate in severity and included headache, nausea, abdominal pain, and nasopharyngitis,[14] which is in line with the safety profile of ambrisentan in the adult PAH population.[18,21,22] The common exposure–response between the pediatric and adult populations suggests ambrisentan has a similar benefit–risk profile in both populations and, at similar exposures, extrapolation of efficacy data from adults to pediatric subjects (aged 8 to <18 years) with PAH is valid.

This study has a few limitations. First, the data from this study should be interpreted with caution as they are based on a PK model. Additionally, even though patients were dosed orally once daily for 24 weeks after randomization to either a high-dose or a low-dose group, we noted a profile that was more representative of twice-daily dosing (Figure 2). We believe that the

twice-daily–like profile is due to the sampling strategy. PK samples (1 plasma sample per patient per visit) were obtained at week 4 (trough), week 8 (0.5-4 hours after dosing), week 12 (trough), week 16 (0.5-4 hours after dosing), week 20 (4-22 hours after dosing), and 24 hours after dosing (trough). All the data on the same plot, presented by planned sampling time rather than actual sampling time, are provided in Figure 2. There was no evidence of delayed absorption or enterohepatic circulation of ambrisentan to explain the secondary peaks observed in Figure 2.

A number of treatments are available for PAH including bosentan,[7] macitentan,[23] prostacyclin analogs (treprostinil, selexipag, iloprost, beraprost, and epoprostenol),[24] riociguat, sildenafil,[25] and tadalafil.[9] Among these medications, bosentan is the only Food and Drug Administration–approved drug for use in pediatric patients, at dosages up to 31.25 mg twice daily (body weight 10-20 kg), 62.5 mg twice daily (body weight 20-40 kg), and 125 mg twice daily (body weight ≥40 kg).[7] Sildenafil, a phosphodiesterase type-5 inhibitor, is approved by the European Medicines Agency for children and adolescents (aged 1-17 years) with PAH, at dosages of 10 mg 3 times daily for body weight 8-20 kg, and 20 mg 3 times daily for body weight ≥20 kg.[25] Macitentan, an endothelial receptor antagonist,[23] and the inhaled prostacyclin analogs treprostinil and iloprost have been used off-label for the treatment of pediatric PAH.[24] Studies in pediatric patients with PAH using the phosphodiesterase type-5 inhibitor, tadalafil, have shown it is well tolerated at doses of up to 20 mg in children aged ≥2 years.[9]

Ambrisentan is now approved by the European Medicines Agency for use in children and adolescents (aged 8-17 years) with PAH, at dosages of 5–10 mg once daily based on body weight.[26] This was based on the totality of the analyses including disease exposure matching based on expectation of disease similarity as well as efficacy parameters albeit in a smaller population. Thus, ambrisentan was assessed in 38 pediatric patients with PAH (aged 3-15 years) who received ambrisentan either as add-on therapy (N = 23) or after transition from bosentan (N = 15), suggesting that ambrisentan in children had a similar PK profile to the adult population[13]; PK results from this study are consistent with those from study AMB112529.

Conclusions

In conclusion, ambrisentan plasma concentrations from study AMB112529 in the pediatric population (aged 8 to <18 years) were well interspersed with the previously reported adult data. The pediatric PK data were all adequately described with no obvious systematic bias in model predictions using a 2-compartment model with first-order absorption and elimination and an absorption lag time. Ambrisentan exposure was similar in the pediatric and adult populations, suggesting appropriateness of the body-weight–based dosing scheme in patients with PAH aged 8 to <18 years. Exposure–response (6MWD and safety) relationships were also similar in the adult and pediatric populations, with no clear exposure-efficacy and exposure-safety associations observed.

Acknowledgments

Editorial support (in the form of writing assistance, including preparation of the draft manuscript under the direction and guidance of the authors, collating and incorporating authors' comments for each draft, assembling tables and figures, grammatical editing, and referencing) was provided by Eithne Maguire, PhD, of Fishawack Indicia Ltd., part of Fishawack Health, and funded by GSK.

Funding

Study AMB112529 was funded by GSK (GSK study number 112529; ClinicalTrials.gov Identifier: NCT01332331). Analyses performed by ICON were funded by GSK.

Conflicts of Interest

MO was an employee of GSK at the time of the study and held shareholder status in the company. MAL and M. Beerahee are employees of GSK and hold shareholder status in the company. MMT and CF are employees of ICON; ICON received funding from GSK for the analysis of some of the data included in this article. M. Beghetti reports remunerations for lectures and/or consultancy from Actelion/Janssen, Acceleron, AOP, Bayer, Gossamer, Altavant, Eli Lilly and Company, GSK, and MSD, and research grants from Actelion and Bayer.

Data Availability Statement

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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