



Relative bioavailability of a pediatric dispersible tablet and adult film-coated tablet of macitentan in healthy volunteers

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Abstract

To compare the pharmacokinetic (PK) properties of the pediatric dispersible tablet formulation of macitentan and the adult film-coated tablet formulation of macitentan in healthy subjects. A randomized, open-label, single-dose, two-sequence, two-period, crossover, Phase 1 study was conducted in 12 healthy adults. Subjects were randomized to one of the two possible treatment sequences A/B or B/A on Day 1 under fasted conditions. Treatment A was a single 10 mg dose of macitentan (film-coated adult formulation) and Treatment B was a single 10 mg dose of macitentan, consisting of two 5 mg dispersible tablets (pediatric formulation). PK sampling over 216 hours was conducted, and PK parameters were derived using non-compartmental methods. For macitentan, geometric means ratio of peak plasma concentrations (C_{max}), plasma concentration-time curve from zero to the time of the last quantifiable concentration (AUC_{0-t}), and plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) were 1.140, 0.974, and 0.974, respectively. The corresponding 90% confidence intervals fell entirely within the referenced range of 0.8000 to 1.2500, which is used for evaluation of bioequivalence. These results indicate no significant differences between the pediatric dispersible tablet and the adult film-coated tablet. Both formulations were well tolerated. The pediatric dispersible tablet is biocomparable to the adult film-coated tablet formulation.

KEYWORDS

bioavailability, clinical trials, pediatrics, respiratory medicine

Abbreviations: AUC, area under the plasma concentration-time curve; $AUC_{0-\infty}$, AUC from zero to infinity; AUC_{0-t} , AUC from zero to the time of the last quantifiable concentration; CI, confidence interval; C_{max} , peak plasma concentration; EOP, end-of-period; EOS, end-of-study; ET, endothelin; GMR, geometric means ratio; PAH, pulmonary arterial hypertension; PK, pharmacokinetics; SD, standard deviation; $t_{1/2}$, terminal half-life.

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1 | INTRODUCTION

Pulmonary arterial hypertension (PAH) is a severe disease resulting from increased pulmonary vascular resistance causing increased pulmonary artery pressure. The endothelin (ET) isoform ET-1 plays a key role in the pathophysiology of PAH by activating two specific receptors, ET_A and ET_B. Stimulation of ET_A induces vasoconstriction, while engagement of ET_B causes vasodilation.¹⁻³

Macitentan is an orally active, non-peptide, potent ET receptor antagonist. Macitentan, brand name Opsumit® (macitentan 10 mg film-coated tablet), has been approved for the treatment of PAH at a dose of 10 mg once daily in the United States, European Economic Area, Canada, Australia, Switzerland, Japan, and additional countries in the Middle East, Asia, and Latin America. Macitentan acts on both ET receptors (ET_A and ET_B) and has been shown to significantly reduce morbidity and mortality among patients with PAH.⁴

Macitentan has been investigated in clinical studies in more than 500 healthy subjects and patients with essential hypertension, idiopathic pulmonary fibrosis, PAH, digital ulcers associated with systemic sclerosis, and patients with glioblastoma.

In the Phase 1 studies, subjects received single doses of macitentan up to 600 mg and multiple doses up to 30 mg once daily for 10 days. In the Phase 2 and 3 studies, patients received multiple doses of macitentan up to 10 mg once daily for up to 3.6 years. In two Phase 1 dose-escalation studies in oncology patients, multiple doses of macitentan up to 225 mg were administered, and one patient received multiple doses of 300 mg macitentan.

The plasma concentration-time profiles of macitentan in healthy subjects are described by slow absorption, with peak plasma concentrations (C_{max}) occurring about 8 hours after dosing. The apparent terminal half-life ($t_{1/2}$) is approximately 16 hours. Macitentan has two metabolites in plasma, one active metabolite (ACT-132577) and one inactive metabolite (ACT-373898). After multiple-dose administration, the pharmacokinetics (PK) of both macitentan and ACT-132577 were dose proportional over the tested dose range of 1-30 mg macitentan.⁵ Macitentan and its metabolites are mainly eliminated through urine and are highly bound (>99%) to plasma proteins.⁶

Analysis of the Phase 2 clinical data indicated no clinically relevant effect of age or sex on the PK of macitentan and ACT-132577. Plasma exposure to macitentan and its active metabolite ACT-132577 during a dosing interval did not differ significantly between PAH patients and healthy subjects.⁷

In the majority of pediatric patients, PAH presents as idiopathic PAH or PAH associated with congenital heart disease⁸ and occurs at all ages.⁹ There have been few clinical studies in the pediatric PAH population due to the limited number of patients worldwide, thus, this is still a disease with an unmet medical need. Since macitentan, based on its mechanism of action, may be an effective treatment in pediatric patients with PAH, dispersible tablets with lower dose loads (0.5, 2.5, and 5 mg) were developed for the entire pediatric age range because the available dose strength for adults was 10 mg only. A Phase 3 study assessing efficacy, safety, and PK of macitentan in children with PAH is ongoing. This study

will evaluate macitentan in comparison to standard of care with regard to delaying disease progression in children with PAH.

The primary objective of the present study was to compare the relative bioavailability of a pediatric dispersible tablet formulation of macitentan with that of the registered adult film-coated tablet of macitentan. The secondary objective was to evaluate the safety and tolerability of the two formulations of macitentan. The results of the study showed that the pediatric dispersible tablet is bioequivalent to the adult film-coated tablet formulation.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This was an exploratory, prospective, single-center, randomized, open-label, single-dose, two-period, crossover, Phase 1 study. The study enrolled healthy male subjects aged 18-45 years. Subjects were required to have a body mass index of 18.0-28.0 kg/m²; systolic blood pressure 100-145 mmHg, diastolic blood pressure 50-90 mmHg, and pulse rate 45-90 beats per min; and a normal 12-lead electrocardiogram (ECG). Key exclusion criteria included known allergic reactions or hypersensitivity to any excipient of the drug formulations; history or clinical evidence of alcoholism or drug abuse within three year period prior to screening; excessive caffeine consumption (defined as ≥800 mg per day at screening); smoking within three months prior to screening; treatment with another investigational drug within 3 months prior to screening; or participation in more than four investigational drug studies within 1 year prior to screening.

This study was approved by an independent ethics committee and was performed in accordance with the Declaration of Helsinki and with the laws and regulations of the Czech Republic. The study was registered at clinicaltrials.gov with identifier NCT02476864. Informed consent was obtained from all study participants. The study was conducted at CEPHA sro., Komenského 19, 323 00 Pilsen, Czech Republic in 2015.

2.2 | Intervention and randomization

As macitentan is approved at a dose of 10 mg for the treatment of PAH, a single oral 10 mg dose of the adult formulation was compared with a 10 mg pediatric dose. The inactive ingredients of the macitentan dispersible pediatric tablet formulation included: mannitol, croscarmellose sodium, isomalt, and magnesium stearate. Subjects were randomized to one of the two possible treatment sequences A/B or B/A (six subjects per sequence). Treatment A was a single 10 mg dose of macitentan on Day 1 (film-coated adult formulation, supplied by Actelion Pharmaceuticals Ltd. via the manufacturers Patheon Italia S.p.A.) and Treatment B was a single 10 mg dose of macitentan on Day 1, consisting of two 5 mg dispersible tablets (pediatric formulation, supplied by Actelion Pharmaceuticals Ltd. via the packager ALMAC Clinical Services). The adult formulation was

taken with 240 mL water. The pediatric formulation was suspended in a tablespoon of water, approximately 10-15 mL taken from the 240 mL, for 1 min. The subject was administered the suspended study drug, followed by drinking the remaining water. Both treatments were administered to the subjects on an empty stomach. Subjects remained fasted from at least 10 hours prior to each study drug administration until 4 hours thereafter. Smoking and consumption of any grapefruit or grapefruit juice was not permitted from screening until the end-of-study (EOS) examination. Drinking of alcoholic beverages and xanthine-containing beverages (eg, coffee, tea, cola, cocoa, Red Bull) was not permitted from at least 48 hours prior to clinic admission until the end-of-period (EOP)/EOS visit. The intake of water (tap or mineral) was ad libitum throughout the whole study, except for 1 hour before and after study drug administration.

The total observation period was 216 hours per period. Following the 216 hours assessment in the first period, there was an 11- to 14-day washout period. An EOP or EOS examination occurred between 216 and 288 hours after (last) study drug administration. The total duration of study for each subject was eight weeks (from screening to EOS).

2.3 | Statistical methods: sample size

No formal statistical hypothesis was set for this exploratory study. Therefore, the sample size was based on empirical considerations. Assuming a within-subject standard deviation (SD) on log scale of 0.079, 0.085, and 0.104 for $AUC_{0-\infty}$, AUC_{0-t} , and C_{max} of macitentan, respectively, it was estimated that, with a sample size of 12 evaluable subjects, the lower and upper bounds of the 90% confidence interval (CI) for the true means ratio 'dispersible tablet (pediatric) vs film-coated tablet (adult) formulations' would be approximately 0.96, 1.05 for $AUC_{0-\infty}$; 0.95, 1.05 for AUC_{0-t} ; and 0.94, 1.06 for C_{max} if the ratio was assumed to be one.

2.4 | Pharmacokinetic evaluations

2.4.1 | Sample collection and analytical methods

Blood samples (4 mL) were collected at predose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 24, 48, 72, 96, 120, 144, 168, and 216 hours post dose into Monovette® tubes containing ethylene diamine tetra-acetic acid. Within 30 min of collection, the tubes were centrifuged at approximately 1500g for 10 min at 4°C. All samples were stored in an upright position at below -20°C.

The plasma concentrations of macitentan and its active metabolite ACT-132577 were measured using a validated liquid chromatography with tandem mass spectrometry assay.¹⁰ For macitentan and ACT-132577, the lower limit of quantification was 1.00 ng/mL and the upper limit of quantification was 2000 ng/mL. Concentrations were calculated by interpolation from a calibration curve.

Precision and accuracy: the descriptive statistics of the quality control samples of macitentan showed that the inter-batch precision was $\leq 6.4\%$, whereas the inter-batch accuracy was in the range from 1.9% to 6.2%. The descriptive statistics of the quality control samples of ACT-132577 showed that the inter-batch precision was $\leq 5.5\%$, whereas the inter-batch accuracy was in the range from -0.4% to 4.3%.

2.4.2 | Primary pharmacokinetic endpoints

The primary PK endpoints were: area under the plasma concentration-time curve (AUC) from zero to the time of the last quantifiable concentration (AUC_{0-t}) for the pediatric and adult macitentan formulations, AUC from zero to infinity ($AUC_{0-\infty}$) of macitentan for the pediatric and adult macitentan formulations, and C_{max} of the pediatric and adult macitentan formulations.

2.4.3 | Secondary pharmacokinetic endpoints

The secondary PK endpoints were: time to maximum plasma concentration (t_{max}) for the pediatric and adult macitentan formulations, $t_{1/2}$ for the pediatric and adult macitentan formulations, and AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , t_{max} , and $t_{1/2}$ of the active metabolite, ACT-132577, for the pediatric and adult macitentan formulations.

2.4.4 | Analysis of pharmacokinetic endpoints

PK parameters were derived with non-compartmental methods using Phoenix WinNonlin version 6.4 (Certara, Princeton, NJ, USA). C_{max} , t_{max} , AUC_{0-t} , $AUC_{0-\infty}$, and $t_{1/2}$ were summarized by treatment using arithmetic mean, geometric mean, minimum, median, maximum,

TABLE 1 Descriptive statistics of demographic variables

Variable	Overall (N = 12)
Age, years	
Mean (SD)	26.1 (7.73)
Range	18-40
Weight, kg	
Mean (SD)	79.28 (9.347)
Range	63.1-99.0
Height, cm	
Mean (SD)	181.1 (6.76)
Range	170-193
BMI, kg/m ²	
Mean (SD)	24.18 (2.530)
Range	20.4-28.0

Abbreviations: BMI, body mass index; N, number of subjects; SD, standard deviation.

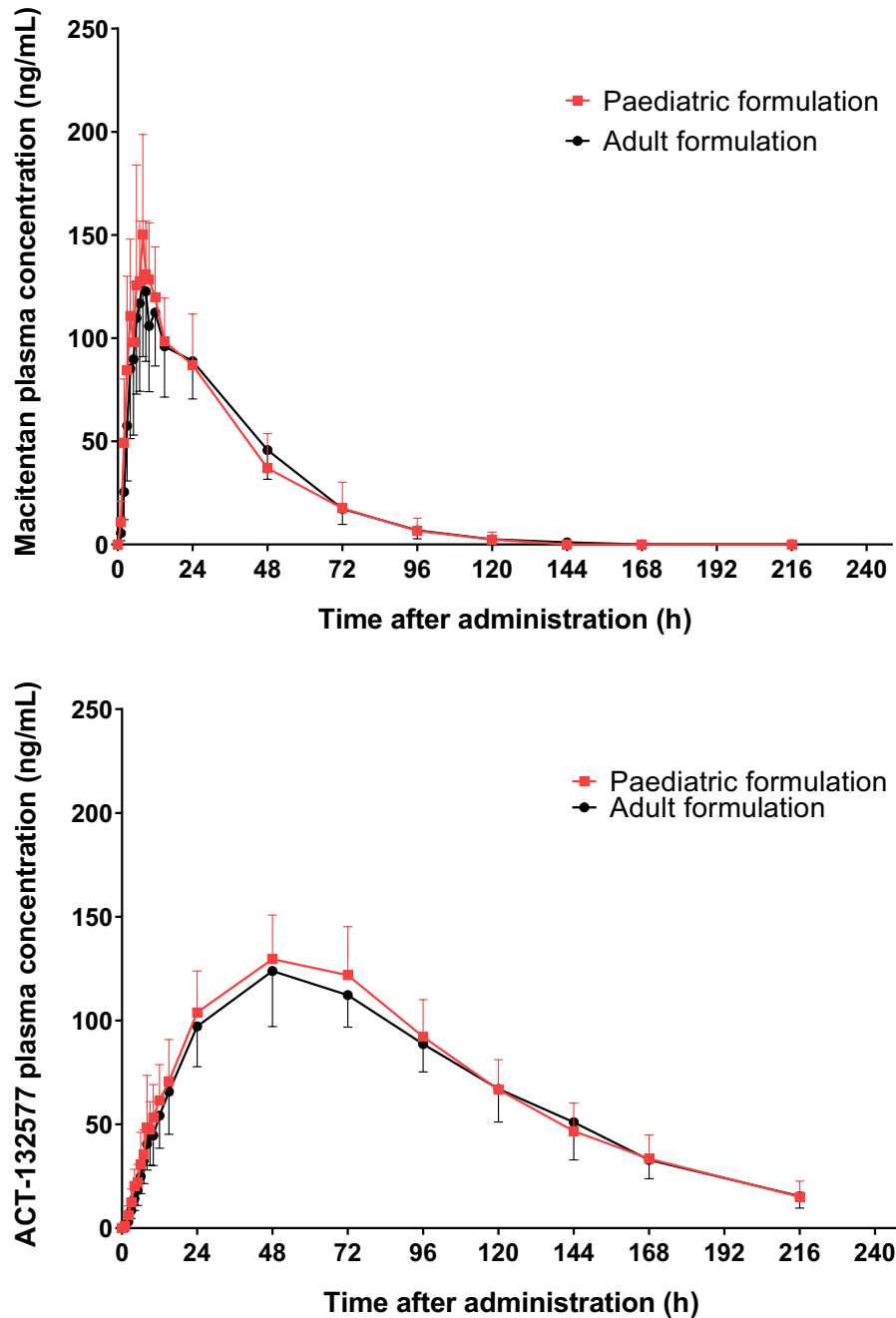


FIGURE 1 Arithmetic mean and standard deviation plasma concentration versus time profiles of macitentan (upper) and ACT-132577 (lower) after administration of adult macitentan formulation (Treatment A) and pediatric macitentan formulation (Treatment B) up to 216 hours (N = 12)

standard deviation (SD), standard error, coefficient of variation inter-subject (CV_b) and intra-subject (CV_w) in percent (%), and 95% confidence interval (CI) of the arithmetic and geometric means (for t_{max} the geometric mean and its 95% CI, CV_b , and CV_w were not calculated).

The pediatric and adult formulation treatments were compared via mixed-effects model using log-transformed values of the endpoint as dependent variable, treatment, treatment sequence, and period as fixed effect and subject nested within sequence as random effect. The geometric means ratio (GMR) (test/reference) and 90% CI were calculated from the corresponding back-transformed least-square means for period of the mixed-effects models. The difference in t_{max} between

pediatric and adult formulation treatments was explored using the non-parametric Wilcoxon signed rank test and Hodges-Lehmann estimates of the median differences (test-reference) and their 90% CIs.

2.5 | Safety and tolerability evaluations

Safety and tolerability assessments included the evaluation of treatment-emergent adverse events, serious adverse events, 12-lead ECG variables, clinical laboratory parameters (haematology and blood chemistry), vital signs (blood pressure and pulse), body weight,

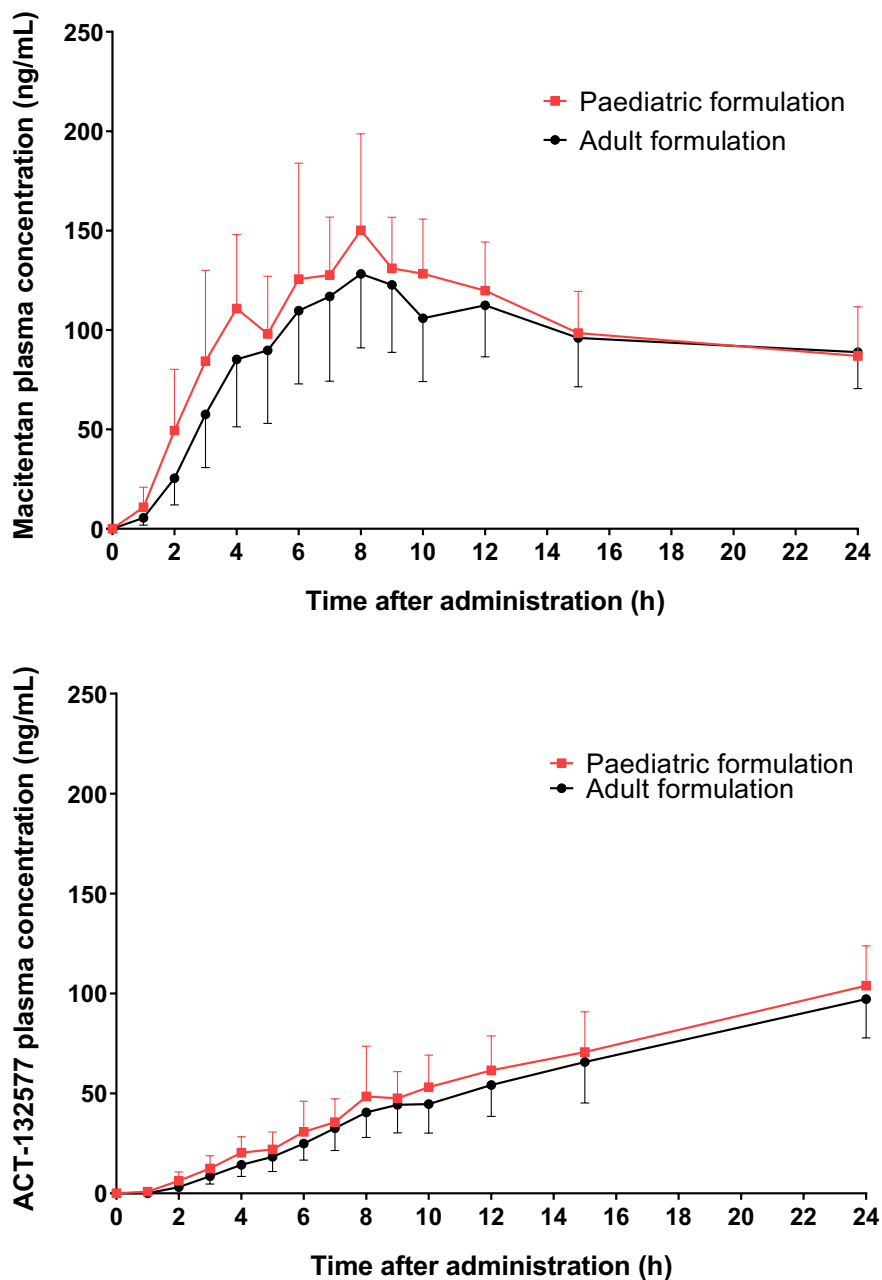


FIGURE 2 Arithmetic mean and standard deviation plasma concentration versus time profiles of macitentan (upper) and ACT-132577 (lower) during the first 24 hours after administration of adult macitentan formulation (Treatment A) and pediatric macitentan formulation (Treatment B) (N = 12)

and physical examination. Safety and tolerability data were summarized descriptively by treatment.

3 | RESULTS

3.1 | Study participants and data

All 12 healthy male subjects completed the study. The mean (SD) age was 26.1 (7.7) years, mean (SD) weight 79.3 (9.3) kg, and mean (SD) body mass index 24.2 (2.5) kg/m² (Table 1).

3.2 | Plasma concentration versus time profiles and PK parameters

The mean macitentan and ACT-132577 plasma concentration versus time profiles of the pediatric and adult formulations are presented in Figures 1-3. After administration of the adult tablet, macitentan and ACT-132577 peak plasma concentrations were reached with a t_{max} of 8.0 and 48.4 hours, respectively (Tables 2 and 3). Thereafter, plasma concentrations of both analytes declined slowly, as characterized by a $t_{1/2}$ of 16.7 and 43.8 hours for macitentan and ACT-132577, respectively. When administering the

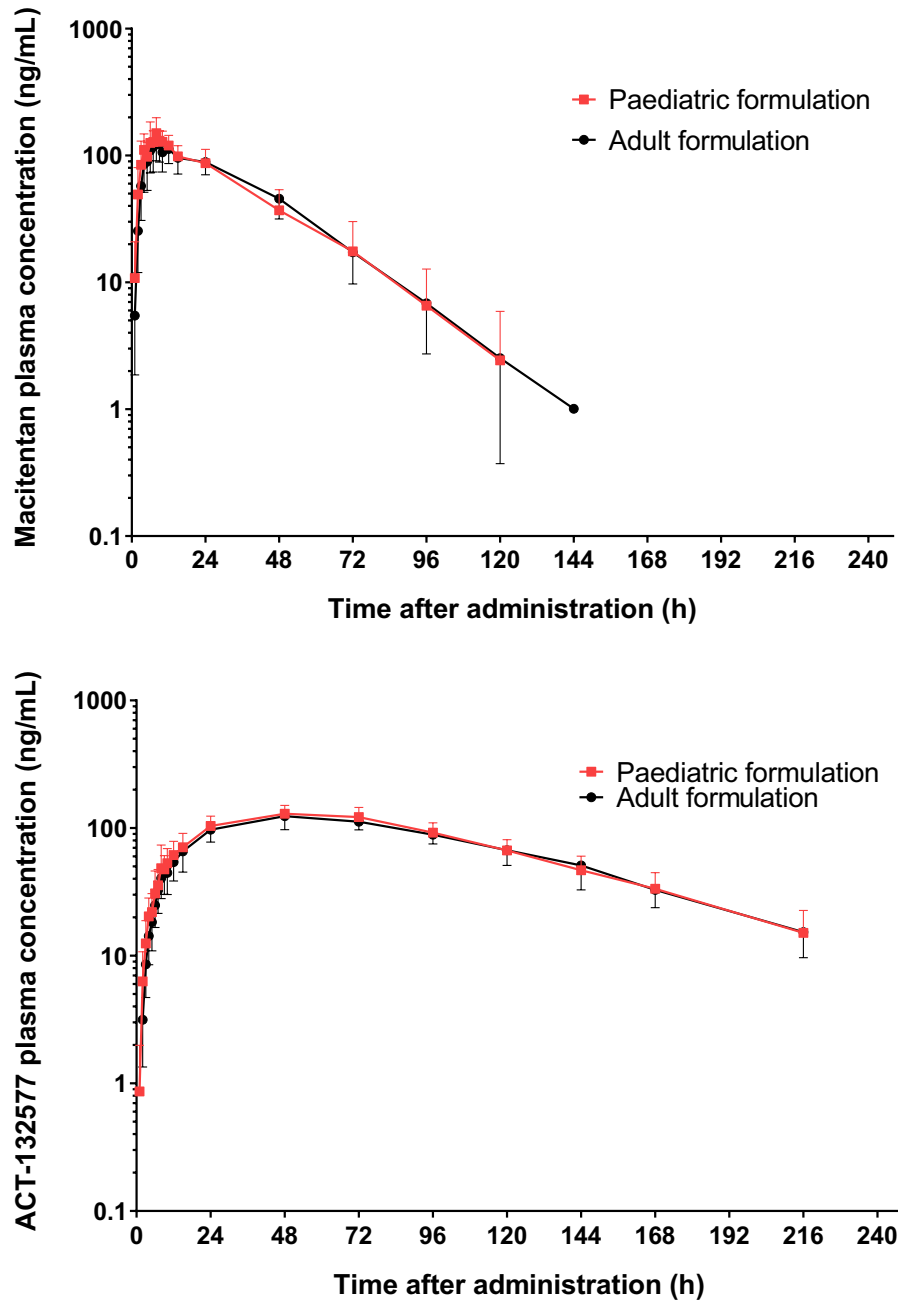


FIGURE 3 Arithmetic mean and standard deviation plasma concentration versus time profiles of macitentan (upper) and ACT-132577 (lower) after administration of adult macitentan formulation (Treatment A) and pediatric macitentan formulation (Treatment B) up to 216 hours - log scale (N = 12)

pediatric dispersible tablet, t_{max} did not change when compared with the values observed with the adult tablet. A slight increase in C_{max} of both macitentan and ACT-132577 was observed; however, total exposure expressed as AUC_{0-t} and $AUC_{0-\infty}$ was similar for both formulations and both analytes.

3.2.1 | Primary pharmacokinetic endpoints

For macitentan, GMRs of C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were 1.140, 0.974, and 0.974, respectively. The corresponding 90% CIs fell within the

referenced range of 0.8000 to 1.2500, which is used for evaluation of bioequivalence. These results indicate no significant differences between the pediatric dispersible tablet and the adult film-coated tablet. In addition, P -values for the effect of formulation on total exposure were >0.05 , further supporting that there were no differences between formulations.

3.2.2 | Secondary pharmacokinetic endpoints

For ACT-132577, GMRs of C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were 1.043, 1.037, and 1.033, respectively (Table 3). Similar to macitentan, the

TABLE 2 Summary of the pharmacokinetic parameters of macitentan by treatment

PK parameter	Geometric mean (95% CI) ^a		Geometric means ratio ^b (90% CI)/P-value
	Treatment A	Treatment B	
	Adult formulation (N = 12)	Pediatric formulation (N = 12)	
C_{max} , ng/mL	130.80 (110.20, 155.24)	149.12 (125.30, 177.48)	1.140 (1.0420, 1.2475)/.025
AUC_{0-t} , ng·h/mL	4829.45 (4125.42, 5653.62)	4705.52 (3814.47, 5804.72)	0.974 (0.9009, 1.0537)/.561
$AUC_{0-\infty}$, ng·h/mL	4873.86 (4168.05, 5699.18)	4747.47 (3852.50, 5850.35)	0.974 (0.9018, 1.0522)/.551
$t_{1/2}$, h	16.71 (14.74, 18.95)	16.36 (14.40, 18.58)	0.979 (0.9186, 1.0431)/.556
t_{max} , h	8.00 (7.0-12.0)	8.00 (6.1-12.0)	0.000 (-0.5000, 0.5000) ^c /1.000

Note: Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration-time curve from zero to infinity; AUC_{0-t} , area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; CI, confidence interval; C_{max} , maximum plasma concentration; N, number of subjects; PK, pharmacokinetic; $t_{1/2}$, terminal elimination half-life; t_{max} , time to maximum plasma concentration.

^aFor t_{max} , median (range) is shown.

^bTreatment B/Treatment A.

^cMedian (B - A).

TABLE 3 Summary of the pharmacokinetic parameters of ACT-132577 by treatment

PK parameter	Geometric mean (95% CI) ^a		Geometric means ratio ^b (90% CI)/P-value
	Treatment A	Treatment B	
	Adult formulation (N = 12)	Pediatric formulation (N = 12)	
C_{max} , ng/mL	127.38 (114.33, 141.92)	132.85 (119.38, 147.84)	1.043 (0.9618, 1.1309)/.369
AUC_{0-t} , ng·h/mL	14 438.15 (13 180.98, 15 815.23)	14 964.74 (13 443.43, 16 658.20)	1.037 (0.9861, 1.0895)/.222
$AUC_{0-\infty}$, ng·h/mL	15 420.35 (14 041.11, 16 935.07)	15 921.37 (14 089.67, 17 991.19)	1.033 (0.9760, 1.0923)/.328
$t_{1/2}$, h	43.814 (40.536, 47.357)	43.166 (38.618, 48.249)	0.985 (0.9180, 1.0573)/.710
t_{max} , h	48.39 (48.0-72.0)	48.00 (24.0-72.1)	-0.250 (-12.1000, 1.7700) ^c /.401

Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration-time curve from zero to infinity; AUC_{0-t} , area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; CI, confidence interval; C_{max} , maximum plasma concentration; N, number of subjects; PK, pharmacokinetic; $t_{1/2}$, terminal elimination half-life; t_{max} , time to maximum plasma concentration.

^aFor t_{max} , median (range) is shown

^bTreatment B/Treatment A

^cMedian (B - A).

corresponding 90% CIs also fell entirely within the referenced bioequivalence range of 0.8000 to 1.2500. Additionally, GMRs of $t_{1/2}$ for macitentan and ACT-132577 were close to 1 (0.979 and 0.985, respectively), and the 90% CIs were completely contained within the referenced bioequivalence range of 0.8000 to 1.2500. For all tests, P-values for the effects of formulation were >0.05, suggesting no difference between formulations.

Median differences in t_{max} between test and reference were 0 and -0.25 hours, respectively, for macitentan and ACT-132577.

3.3 | Safety and tolerability

Both formulations (pediatric macitentan formulation and adult macitentan formulation) appeared to be safe and well tolerated by the subjects and no difference in safety profile could be detected between formulations.

4 | DISCUSSION

The present study demonstrated that two pediatric dispersible tablets with a dose strength of 5 mg had equivalent bioavailability to one adult film-coated tablet of 10 mg macitentan. Analysis of macitentan and its active metabolite ACT-132577 concentrations, collected over a 216 hours time window after single-dose administration, indicated no differences in PK between the pediatric dispersible tablet and the adult film-coated tablet formulation. As the 90% CIs of the GMRs of C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ fell entirely within the referenced range of 0.8000 to 1.2500, which is used for evaluation of bioequivalence, it can be concluded that these formulations are bioequivalent.

The inclusion of healthy adult subjects was intended to reduce the variability in PK parameters and followed Food and Drug Administration¹¹ and European Medicines Agency guidelines.¹² Also, data from healthy subjects allow the extrapolation of the results to special populations, including children. Bioavailability comparisons

between adult and pediatric formulations should be performed in adults,^{11,13} as there can be no direct clinical benefit to children in these types of studies. Therefore, this study conformed to these various established guidelines for bioavailability studies of different formulations.

In this study, only one dose strength of a pediatric formulation was compared with the commercially available adult formulation. As macitentan will be dosed according to body weight category in children, tablets with a lower dosing strength are needed. Given that the PK of macitentan and ACT-132577 are dose-proportional up to 30 mg macitentan administered in multiple doses,⁵ and that there will be no significant changes in proportion of active and inactive ingredients, these results would also be applicable for alternative lower dose strength, without further clinical investigations.^{5,11} With the pediatric formulation being bio-comparable to that used in adults, no adjustments to account for switching the formulation have to be made when deciding on a dose for pediatric patients in clinical studies or therapeutic treatment. In the future, the pediatric formulation could also be used in other populations for which the adult formulation would not be practical (eg, people with swallowing problems).

Both formulations were well tolerated in this study.

The pediatric dispersible tablets evaluated in this study will be used in a pediatric Phase 3 study (AC-055-312, TOMORROW study), which will assess efficacy, safety, and PK of macitentan in children with PAH.

5 | CONCLUSION

The results of the study showed that the PK properties of the pediatric dispersible tablet of macitentan are comparable to those of the adult film-coated tablet formulation. Both formulations were well tolerated. Based on the study results, no adjustments have to be made when switching macitentan formulations.

ACKNOWLEDGEMENTS

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DISCLOSURE

PNS is an employee of Idorsia Pharmaceuticals Ltd. RS is an employee of the clinical research organisation Aixial sro., which performed the biostatistics for the study reported. SG is an employee of Idorsia Pharmaceuticals Ltd, which collaborated on the study reported and reports non-financial medical-writing support from Actelion Pharmaceuticals Ltd for the submitted work. IU was the Principal Investigator of the study that was sponsored by Actelion Pharmaceuticals Ltd. DC is an employee of Actelion Pharmaceuticals Ltd.

AUTHOR CONTRIBUTIONS

IU was responsible for the study implementation and had direct responsibility for the subjects. PNS was responsible for the PK analysis and for the interpretation of the data. SG was responsible for the bioanalytical activities. RS was responsible for the statistical analysis. DC was responsible for the interpretation of the data. All authors reviewed, contributed to, and approved the manuscript.

DATA AVAILABILITY STATEMENT

The data sharing policy of the Sponsor is available at <https://www.janssen.com/clinical-trials/transparency>. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at <http://yoda.yale.edu>.

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