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The pharmacokinetics, safety, and tolerability of mirabegron in children and adolescents with neurogenic detrusor overactivity or idiopathic overactive bladder and development of a population pharmacokinetic model–based pediatric dose estimation

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Summary

Introduction
Mirabegron, a selective β3-adrenoreceptor agonist, is a well-established alternative to antimuscarinics in adults with overactive bladder (OAB) symptoms and is under development for use in pediatric patients. Understanding drug pharmacokinetics (PK) in pediatric patients is needed to determine appropriate dosing. Conducting these studies is ethically complex, particularly as regulatory guidance requires that PK is assessed in pediatric patients with a therapeutic need for the drug. It is also vital to evaluate the safety/tolerability and palatability/acceptability of pediatric formulations.

Purpose
The purpose of the study was to characterize the PK of mirabegron in pediatric patients with neurogenic detrusor overactivity or idiopathic OAB, to provide a basis for a weight-based dosing algorithm, and to evaluate the safety, tolerability, and palatability/acceptability of the formulations.

Materials and methods
A preliminary population PK model constructed from adult data with allometric scaling was used to predict single weight-adjusted mirabegron doses. This was developed to achieve exposures in pediatric patients in two phase 1 studies that were consistent with steady state in adults following once-daily 25 mg ('low dose') and 50 mg ('high dose') dosing. In study 1, adolescents (12–<18 years) and children (5–<12 years) received a single tablet under fed or fasted conditions. In study 2, children (3–<12 years) received a single oral suspension dose under fed conditions. The PK data were used to assess the predictive value of the preliminary PK model and to update it to analyze mirabegron PK in pediatric patients. The safety/tolerability and palatability/acceptability of the formulations were evaluated.

Results
Forty-three patients comprised six study cohorts: adolescents, low-dose tablets, fed (n = 7); children, low-dose tablets, fed (n = 7); adolescents, high-dose tablets, fed (n = 8); children, high-dose tablets, fed (n = 6); children, high-dose tablets, fasted (n = 6); and children, high-dose oral suspension, fed (n = 9). The population PK model–based doses for tablets and oral suspension achieved exposures that were typically consistent with steady state in adults. The final population PK model was used to describe the PK for mirabegron in pediatric patients (Table). Both formulations were well tolerated, and there were no reports of bad taste or swallowing difficulties for the tablets, although some found the oral suspension unpleasant.

Conclusions
The single, weight-adjusted pediatric mirabegron doses were successfully predicted by population PK modeling to achieve drug exposures comparable with steady state in adults. The finalized PK model used to characterize the pediatric PK of mirabegron will be utilized to develop a weight-based dosing algorithm. The single mirabegron doses were well tolerated.

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Summary Table Pharmacokinetic parameters of mirabegron by cohort.

Parameter	Study 1					Study 2
	Cohort 1 Adolescents Low dose Fed Tablets (n = 7)	Cohort 2 Children Low dose Fed Tablets (n = 7)	Cohort 3 Adolescents High dose Fed Tablets (n = 8)	Cohort 4 Children High dose Fed Tablets (n = 6)	Cohort 5 Children High dose Fasted Tablets (n = 6)	Cohort 6 Children High dose Fed Oral suspension (n = 9)
AUC_{inf}, ng·h/mL	103 (83.7–158)	117 (80.6–208)	411 (150–573)	422 (288–715)	883 (724–1200)	537 (199–670)
C_{max}, ng/mL	3.85 (2.45–10.5)	5.24 (2.45–14.9)	29.7 (3.40–80.4)	38.1 (14.1–98.2)	58.4 (28.6–79.2)	16.7 (2.56–42.4)
t_{max}, h	5.03 (3.95–5.75)	4.17 (2.55–6.37)	4.48 (3.08–7.08)	4.28 (3.88–4.42)	3.95 (3.47–4.27)	3.93 (1.25–6.50)
$t_{1/2}$, h	45.0 (41.1–48.7)	44.5 (40.7–50.1)	42.7 (40.5–54.0)	42.2 (39.3–45.2)	43.0 (42.0–52.9)	42.7 (39.4–65.2)
CL/F, L/h	248 (158–320)	214 (120–310)	158 (131–333)	118 (70.0–174)	59.2 (41.7–97.7)	186 (146–502)
AUC_{24}, ng·h/mL	49.7 (40.2–76.1)	56.3 (38.8–100)	198 (72.2–275)	203 (138–344)	424 (348–577)	258 (95.7–322)

Data shown are median (range).
AUC_{24} = area under the concentration–time curve from 0 to 24 h, AUC_{inf} = area under the concentration–time curve from 0 to infinity, CL/F = apparent oral plasma clearance, C_{max} = maximum concentration of drug after administration, t_{max} = time at which C_{max} occurred, $t_{1/2}$ = half-life.

Introduction

Overactive bladder (OAB) syndrome affects ≤12% of children aged 5–10 years [1,2]. Neurogenic detrusor overactivity (NDO) is defined by involuntary detrusor contractions during filling cystometry in patients with a relevant neurological condition [2]. Pharmacotherapy options for pediatric patients with OAB symptoms or NDO are limited to antimuscarinics [1,3,4], although few clinical trials have been conducted [4–10]. Mirabegron, a β3-adrenoreceptor agonist, is an alternative to antimuscarinics in adults with OAB symptoms although data in pediatric patients are limited [11–15].

Understanding drug pharmacokinetics (PK) in pediatric patients is needed to determine appropriate dosing. However, the conduct of phase 1 PK studies in pediatric patients is ethically complex, particularly as drug safety in this population is often unconfirmed and as numerous blood samples may be required. In contrast with PK studies in healthy adults, regulatory guidance requires that PK is assessed in pediatric patients with a therapeutic need for the drug [16–18], which may necessitate normal medication interruption.

By using population PK modeling to determine PK parameters from sparse data [19–22], the phase 1 mirabegron pediatric studies could be conducted by administering a single dose to a small number of patients with limited blood sampling. Mirabegron PK data from adults permitted development of a preliminary PK model with allometric scaling, which was used to predict the single, weight-adjusted pediatric doses of mirabegron tablets and oral suspension required to achieve equivalent exposures to adults at steady state.

The purpose of the two phase 1 pediatric studies reported herein was to assess the safety and tolerability of mirabegron tablets and oral suspension, obtain PK data to confirm the predictive value of the preliminary PK model, and update the model to describe the pediatric PK of mirabegron. The palatability and acceptability of the two formulations were also evaluated.

Materials and methods

Study design

Two multicenter, open-label, single-dose phase 1 mirabegron studies were conducted in children and adolescents with NDO or idiopathic OAB. The studies were conducted in accordance with European Union recommendations [18] (patients had the indication to be treated with no inducement to enter the study for the patients or their parents/legal guardians). In study 1 (NCT02211846), children (5–<12 years) and adolescents (12–<18 years) with a diagnosis of NDO or idiopathic OAB according to International Children's Continence Society (ICCS) criteria [2] received a single mirabegron prolonged-release tablet. The study was conducted at nine centers from September 2014 to September 2015. In study 2 (NCT02526979), children with a diagnosis of NDO (3–<12 years) or idiopathic OAB (5–<12 years) according to ICCS criteria [2] received a single mirabegron dose using prolonged-release oral suspension. The study was conducted at three centers from December 2015 to December 2016. As the two studies had consistent methodology, data are reported collectively. Inclusion/exclusion criteria are provided in Supplementary Table 1.

Patients were enrolled into six cohorts, with the safety data from each cohort being reviewed before enrollment into the next cohort: adolescents, low-dose tablets, fed; children, low-dose tablets, fed; adolescents, high-dose tablets, fed; children, high-dose tablets, fed; children, high-dose tablets, fasted; and children, high-dose oral suspension, fed. Cohorts 1–5 were from study 1, and cohort 6 was from study 2. Cohort 5 was included to assess mirabegron safety at the higher exposure expected while fasting.

Screening occurred ≤28 days before dosing, with a subsequent washout of prohibited medications, if applicable (Supplementary Fig. 1). Before day 1, patients were asked to fast from midnight. Cohorts 1–4 and 6 received a light breakfast (low in fat and fiber) and were dosed within 1 h. Patients in cohort 5 remained fasted.

Patients were dosed according to body weight. Patients in the low-dose tablet cohorts weighing 20–<55 or ≥55 kg received 25 or 50 mg, respectively. Patients in the high-dose tablet cohorts weighing 20–<40 or ≥40 kg received 50 or 75 mg (25 + 50 mg tablets), respectively. Patients in the oral suspension cohort weighing 15–<20, 20–<30, 30–<40, or ≥40 kg received 40 mL (mirabegron 80 mg), 50 mL (100 mg), 55 mL (110 mg), or 65 mL (130 mg), respectively. The doses were predicted using an adult population PK model with allometric scaling to result in exposures equivalent to those in adults at steady state following once-daily mirabegron 25 or 50 mg dosing. The target exposures (area under the concentration–time curve over a dosing interval [AUC_{tau}]) were 69 ng·h/mL (low dose) and 188 ng·h/mL (high dose), respectively (Astellas, data on file). The model accounted for food intake (mirabegron bioavailability is greater under fasted conditions [23]) and also the 48% relative bioavailability of the oral suspension to the tablet previously demonstrated in adults (Astellas, data on file). The accumulation for a 24-h repeat dosing interval is ∼ 2-fold higher than following a single dose [24], so the doses were multiplied by two to achieve steady-state exposures.

Patients were allowed a light lunch (low in fat and fiber) >2 h after dosing in cohorts 1–4 and 6, and >4 h after dosing in cohort 5. Food or ingredients that may impact the absorption of mirabegron (high fat or fiber foods, chewing gum, or citrus fruit) were not permitted.

Independent ethics committee approval was obtained before starting the studies, which were conducted in accordance with Good Clinical Practice, International Committee on Harmonisation guidelines, and the ethical principles originating from the Declaration of Helsinki. Informed consent was provided by patients and/or their parents/legal guardians. Informed consent/assent was provided according to local law.

Assessments

Screening assessments included demographics, medical and OAB/NDO history, prior/concomitant medications, vital signs, electrocardiograms (ECGs), safety laboratory evaluations, and adverse events (AEs). Patients underwent 24-h Holter monitoring on a reference day (day −4 to −1, baseline) and on day 1 (before dosing).

Blood samples for PK analysis were obtained from each child (six samples) or adolescent (seven samples). Samples were taken on day 1 (0.5–2, 3–5, and 6–8 h after dosing for children; 0.5–2, 3–4, 5–6, and 7–8 h after dosing for adolescents), day 2 (24–32 h), and on another 2 days between days 3 and 7 (48–56, 72–80, 96–104, 120–128, or 144–152 h).

The occurrence and severity of AEs (classified using Medical Dictionary for Regulatory Affairs v16.0) were assessed throughout both studies. AEs of special interest included increased blood pressure (BP), tachycardia, QT prolongation, hypersensitivity reactions, cardiac arrhythmia, cardiovascular AEs, urinary retention, hepatotoxicity, and nervous system AEs (seizure, syncope). Safety laboratory evaluations (hematology, biochemistry, urinalysis) were conducted before dosing on day 1, on day 2, and at end of study (EoS) (assessment conducted during the last PK sample visit). Furthermore, 12-lead ECGs were conducted before and 1, 2, 4, and 6 h after dosing on day 1, and at EoS. Vital signs were assessed before dosing and 1, 2, 4, and 6 h after dosing on day 1, on day 2, and at EoS. Potentially clinically significant (PCS) criteria for study 1 were systolic BP (SBP) above the 95th age/sex/height percentile and ≥20 mmHg change from baseline, diastolic BP (DBP) above the 95th age/sex/height percentile and ≥15 mmHg change from baseline, and pulse rate above the 95th age/sex percentile and ≥15 bpm change from baseline. The same criteria were used for study 2, but with the 99th age/sex/height percentiles. Postvoid residual (PVR) volume was assessed in patients with idiopathic OAB by ultrasonography/bladder scan before dosing and 5 h after dosing. PVR volume was not assessed in patients with NDO as all were on clean intermittent catheterization.

A palatability and acceptability questionnaire using a visual analog scale was completed by the patient (or parent/guardian based on patient input) after tablet and suspension dosing. This exploratory endpoint was added as a protocol amendment to study 1, and therefore was not conducted for all patients.

Statistical methods

Six patients per cohort were expected to receive study drug, consistent with Food and Drug Administration guidance [17,19]. If six patients tolerated the dose, the lower limit of Clopper-Pearson 95% confidence interval (CI) for the dose tolerability rate would have been >60%, thereby supporting the statement that ≥60% of individuals taking the same dose under the same conditions would tolerate the dose. For the nine patients planned for inclusion in study 2, the lower limit of the 95% CI would be >70%.

The safety analysis set consisted of all patients who took study medication. The PK analysis set consisted of all patients who received study drug and who had concentration values for a sufficient number of time points to reliably calculate at least one PK parameter.

Patient demographic data were summarized with descriptive statistics using SAS® version 9.3 or higher (Cary, NC, USA).

A preliminary population PK model developed from data on mirabegron PK in adults (including food, dose, and formulation effects on bioavailability) adequately described the PK of mirabegron in adults after administration of the suspension and tablets under fed and fasted conditions. Weight (allometric scaling) was added to the PK parameters to provide scale for the pediatric patients and determine the doses to use. The model was later updated by pooling the adult and pediatric data and re-estimating the model parameters. The following parameters were estimated or derived using population PK modeling (NONMEM 7.3; ICON Development Solutions, Ellicott City, MD,

USA): the apparent oral plasma clearance (CL/F), area under the concentration–time curve from 0 to 24 h (AUC_{24}), the area under the concentration–time curve from 0 to infinity (AUC_{inf}), and the half-life ($t_{1/2}$). The maximum concentration of drug after administration (C_{max}) and the time at which C_{max} occurred (t_{max}) were observed and not model-derived.

Results

Patients

Forty-three patients received treatment and completed the studies (Supplementary Fig. 2). Patient demographic and baseline characteristics are shown in Table 1. Most patients across both studies were female (28/43, 65.1%), and the race of all patients was white. The mean ages of the children and the adolescents were 8.1 years (range 7–10 years in study 1; 4–10 years in study 2) and 14.5 years (range 12–17 years), respectively. In total, 26 patients (60.5%) had idiopathic OAB and 17 (39.5%) had NDO. For patients with NDO, spina bifida with closure surgery was the most common neurological condition and almost all were receiving antimuscarinic and/or mirabegron treatment at screening (94.1%).

Pharmacokinetics

Observed and model-predicted mirabegron plasma concentrations are shown in Fig. 1. Median AUC_{24} values (Table 2) were typically within the range of the adult steady-state values obtained during dosing with once-daily tablets of mirabegron 25 and 50 mg (Astellas, data on file). Although the median AUC_{24} values in patients who received low-dose tablets (fed conditions) or high-dose tablets or oral suspension (fed conditions) were not identical to the target values of 69 and 188 ng·h/mL, respectively, they were within range, and the span of individual values for each cohort included the target value. Conversely, the median AUC_{24} values for children who received high-dose tablets (fasted conditions) were higher than the target value (median: 424 ng·h/mL, range: 348–577 ng·h/mL). Median t_{max} and $t_{1/2}$ values were similar across all cohorts (approximately 4–5 and 42–45 h, respectively).

Children who received high-dose oral suspension had higher median AUC_{24}, AUC_{inf}, and CL/F values, and a lower median C_{max} than children who received high-dose tablets (fed conditions). Median C_{max} and CL/F values were higher and lower, respectively, in children than in adolescents within each tablet category (low and high dose, fed conditions). For the children who received high-dose tablets, median AUC_{24}, AUC_{inf}, and C_{max} values were higher and median CL/F values were lower for the patients dosed under fasted conditions compared with the patients dosed under fed conditions.

Safety and tolerability

Overall, five patients developed treatment-emergent AEs (TEAEs), all of which were mild in severity and did not require treatment (Table 3). No serious AEs were reported, and no patients discontinued because of an AE. Of the AEs of special interest, only ECG QT prolongation was reported in one child (cohort 2) and one adolescent (cohort 3).

There were no clinically relevant changes in vital signs in either study. Two patients met the PCS criteria for changes in SBP and DBP. Increases in mean pulse rate relative to baseline were observed across all cohorts, with nine patients meeting the PCS criteria. There were no clinically relevant changes in average heart rate relative to dosing time observed during the 24-h Holter measurements.

No clinically relevant changes in PVR volume were observed, and no post-dose PVR volumes were significantly elevated (exceeded the 20 mL threshold defined by the ICCS [2]).

Palatability and acceptability

There were no reports of bad taste or swallowing difficulties for the tablets, although some children found the oral suspension unpleasant (Supplementary Table 2).

Discussion

The phase 1 studies reported herein represent the first investigations evaluating mirabegron PK in pediatric patients. As well as focusing on the PK, this investigation also examined the safety, tolerability, and palatability/acceptability of the mirabegron tablet and oral suspension formulations used.

The single weight-based pediatric tablet and oral suspension doses selected using the preliminary population PK model were capable of generating exposures close to the target exposures in adults at steady state, which helped confirm that the model constructed from adult data could be successfully used to predict pediatric dosing. The higher-than-target exposures observed in children who received high-dose tablets under fasted conditions may be explained by the exposure targets being more relevant to the fed than fasted state, as during the studies on which the population PK model was based, patients were either fed or given no instructions regarding food.

The preliminary population PK model was updated with the data from these studies to characterize mirabegron PK in pediatric patients. Apparent oral plasma clearance was higher in children who received high-dose oral suspension versus high-dose tablets under fed conditions, a finding which is consistent with the lower relative bioavailability of the oral suspension to the tablet that has been previously demonstrated in adults (Astellas, data on file). The lower CL/F values in children compared with adolescents in cohorts that received the same dose level and fed state were expected because of clearance being related to body weight, as demonstrated by allometric scaling principles. The higher exposure and lower CL/F in the cohort of children who received high-dose tablets under fasted conditions versus fed conditions are consistent with the increased bioavailability of mirabegron in the fasted versus fed state previously confirmed in adults [23].

The C_{max} data obtained are difficult to interpret as sampling was sparse during the absorption phase and,

Table 1 Demographics and baseline characteristics (safety analysis set).

Parameter	Study 1					Study 2
	Cohort 1 Adolescents Low dose Fed Tablets ($n = 7$)	Cohort 2 Children Low dose Fed Tablets ($n = 7$)	Cohort 3 Adolescents High dose Fed Tablets ($n = 8$)	Cohort 4 Children High dose Fed Tablets ($n = 6$)	Cohort 5 Children High dose Fasted Tablets ($n = 6$)	Cohort 6 Children High dose Fed Oral suspension ($n = 9$)
Sex, *n* (%)						
Male	2 (28.6)	2 (28.6)	2 (25.0)	2 (33.3)	3 (50.0)	4 (44.4)
Female	5 (71.4)	5 (71.4)	6 (75.0)	4 (66.7)	3 (50.0)	5 (55.6)
Age in years						
Mean ± SD	14.9 ± 1.6	8.1 ± 0.9	14.1 ± 1.6	8.2 ± 0.8	9.3 ± 0.8	7.3 ± 2.2
Median	15.0	8.0	14.5	8.0	9.5	8.0
Range	13–17	7–9	12–16	7–9	8–10	4–10
Weight at day 1 (predose) in kg						
Mean ± SD	51.0 ± 7.5	31.2 ± 5.4	55.3 ± 14.0	26.7 ± 4.8	31.3 ± 5.3	26.0 ± 8.8
Median	50.2	31.7	53.3	25.4	30.3	25.0
Range	43.0–66.6	21.0–37.8	36.9–80.0	22.0–35.7	25.1–41.0	15.9–44.4
Height at screening in cm						
Mean ± SD	162.6 ± 8.3	133.9 ± 9.7	160.4 ± 10.4	131.6 ± 8.0	136.2 ± 8.8	125.8 ± 13.8
Median	164.0	135.3	157.5	131.3	135.3	130.0
Min-max	151.5–175.0	116.0–148.0	150.0–175.0	123.0–144.0	126.7–150.0	104.0–145.0
Diagnosis at screening, *n* (%)						
NDO	2 (28.6)	2 (28.6)	3 (37.5)	2 (33.3)	2 (33.3)	6 (66.7)
Idiopathic OAB	5 (71.4)	5 (71.4)	5 (62.5)	4 (66.7)	4 (66.7)	3 (33.3)
OAB/NDO medication at screening, *n* (%)	2 (28.6)	3 (42.9)	3 (37.5)	3 (50.0)	3 (50.0)	7 (77.8)
NDO	2/2 (Both mirabegron)	2/2 (1 Mirabegron; 1 mirabegron + solifenacin)	2/3 (1 Mirabegron; 1 mirabegron + tamsulosin)	2/2 (Both mirabegron)	2/2 (1 Mirabegron; 1 solifenacin)	6/6 (3 Solifenacin; 1 mirabegron; 1 mirabegron + solifenacin; 1 oxybutynin)
OAB	0/5	1/5 (Tolterodine + desmopressin)	1/5 (Solifenacin)	1/4 (Solifenacin)	1/4 (Solifenacin)	1/3 (Solifenacin)
Time since OAB diagnosis in months, mean ± SD[a]	25.8 ± 34.6	23.5 ± 13.5	53.3 ± 32.5	32.6 ± 10.5	32.2 ± 13.3	25.2 ± 22.5

(*continued on next page*)

Table 1 (*continued*)

Parameter	Study 1					Study 2
	Cohort 1 Adolescents Low dose Fed Tablets ($n = 7$)	Cohort 2 Children Low dose Fed Tablets ($n = 7$)	Cohort 3 Adolescents High dose Fed Tablets ($n = 8$)	Cohort 4 Children High dose Fed Tablets ($n = 6$)	Cohort 5 Children High dose Fasted Tablets ($n = 6$)	Cohort 6 Children High dose Fed Oral suspension ($n = 9$)
Medical condition of patients with NDO, *n* (%)[b]						
Spina bifida with closure surgery	1 (14.3)	1 (14.3)	2 (25.0)	2 (33.3)	2 (33.3)	5 (55.6)
Sacral agenesis/hypoplasia	—	1 (14.3)[c]	—	—	—	1 (11.1)[c]
Syringomyelia	—	—	—	—	—	1 (11.1)[c]
Congenital system anomaly	1 (14.3)	—	—	—	—	—
Tethered cord syndrome	—	1 (14.3)[c]	—	—	—	—
Myelitis transversa	—	—	1 (12.5)	—	—	—

In study 1, one patient in cohort 3 and two patients in cohort 5 deviated from the protocol. The patient in cohort 3 received a lower dose of mirabegron than defined by the protocol based on her weight, and the two patients in cohort 5 had higher heart rate than permitted by the exclusion criteria. A further six protocol deviations were noted after hard lock of the database. Four patients had mean SBP greater than the 95th percentile at screening according to age and height. Two patients had pulse rate >100 bpm at screening. The data from the patients with protocol deviations were not excluded and are not considered to have impacted the overall results/conclusions. There were no protocol deviations in study 2 (cohort 6).
NDO = neurogenic detrusor overactivity, OAB = overactive bladder, SBP = systolic blood pressure, SD = standard deviation.

[a] Among patients with idiopathic OAB.

[b] Among patients with NDO. Patients may have had more than one condition.

[c] Same patient.

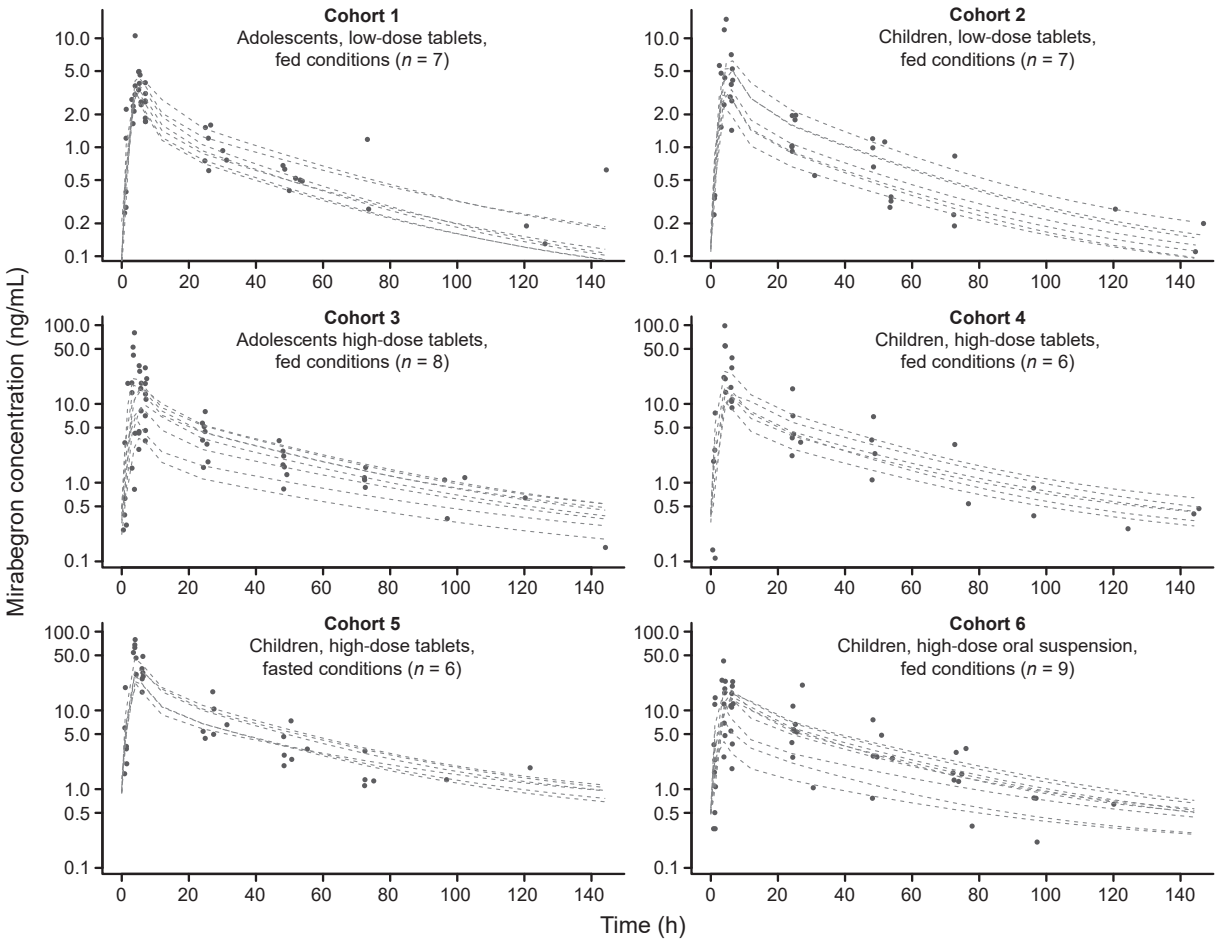

Fig. 1 Observed and model-predicted plasma concentrations of mirabegron (pharmacokinetics analysis set). Data shown are individual observed concentrations (points) and model-predicted concentrations (dashed lines). Cohorts 1–5 were from study 1, and cohort 6 was from study 2.

Table 2 Pharmacokinetic parameters of mirabegron by cohort (pharmacokinetics analysis set).

Parameter	Study 1					Study 2
	Cohort 1 Adolescents Low dose Fed Tablets (n = 7)	Cohort 2 Children Low dose Fed Tablets (n = 7)	Cohort 3 Adolescents High dose Fed Tablets (n = 8)	Cohort 4 Children High dose Fed Tablets (n = 6)	Cohort 5 Children High dose Fasted Tablets (n = 6)	Cohort 6 Children High dose Fed Oral suspension (n = 9)
AUC_{inf}, ng·h/mL	103 (83.7–158)	117 (80.6–208)	411 (150–573)	422 (288–715)	883 (724–1200)	537 (199–670)
C_{max}, ng/mL[a]	3.85 (2.45–10.5)	5.24 (2.45–14.9)	29.7 (3.40–80.4)	38.1 (14.1–98.2)	58.4 (28.6–79.2)	16.7 (2.56–42.4)
t_{max}, h[a]	5.03 (3.95–5.75)	4.17 (2.55–6.37)	4.48 (3.08–7.08)	4.28 (3.88–4.42)	3.95 (3.47–4.27)	3.93 (1.25–6.50)
$t_{1/2}$, h	45.0 (41.1–48.7)	44.5 (40.7–50.1)	42.7 (40.5–54.0)	42.2 (39.3–45.2)	43.0 (42.0–52.9)	42.7 (39.4–65.2)
CL/F, L/h	248 (158–320)	214 (120–310)	158 (131–333)	118 (70.0–174)	59.2 (41.7–97.7)	186 (146–502)
AUC_{24}, ng·h/mL	49.7 (40.2–76.1)	56.3 (38.8–100)	198 (72.2–275)	203 (138–344)	424 (348–577)	258 (95.7–322)

Data shown are median (range).
AUC_{24} = area under the concentration–time curve from 0 to 24 h, AUC_{inf} = area under the concentration–time curve from 0 to infinity, CL/F = apparent oral plasma clearance, C_{max} = maximum concentration of drug after administration, t_{max} = time at which C_{max} occurred, $t_{1/2}$ = half-life.
[a] C_{max} and t_{max} are observed, all other parameters are model based.

Table 3 Treatment-emergent adverse events (safety analysis set).

Parameter	Study 1					Study 2
	Cohort 1 Adolescents Low dose Fed Tablets (n = 7)	Cohort 2 Children Low dose Fed Tablets (n = 7)	Cohort 3 Adolescents High dose Fed Tablets (n = 8)	Cohort 4 Children High dose Fed Tablets (n = 6)	Cohort 5 Children High dose Fasted Tablets (n = 6)	Cohort 6 Children High dose Fed Oral suspension (n = 9)
TEAE, n (%)	1 (14.3)	1 (14.3)	1 (12.5)	0	1 (16.7)	1 (11.1)
Drug-related TEAE, n (%)	0	0	1 (12.5)	0	0	0
TEAE details	Pyrexia, vomiting	ECG QT prolonged[a]	ECG QT prolonged[b]	N/A	Vomiting	Pyrexia

AE = adverse event, ECG = electrocardiogram, N/A = not applicable, OAB = overactive bladder, QTcB = QT interval corrected for heart rate by Bazett's formula, QTcF = QT interval corrected for heart rate by Fridericia's formula, TEAE = treatment-emergent AE.

[a] A 9-year-old female with idiopathic OAB receiving mirabegron 25 mg by tablet experienced a mean QTcB >450 ms 4 h after dosing. This event was deemed to be not related to study drug by the investigator.

[b] A 15-year-old female with idiopathic OAB receiving mirabegron 75 mg by tablet. The ECG showed a mean increase of QTcB >30 ms versus baseline at 4 h after dosing (448.33 versus 407.83 ms, respectively) which was considered to be clinically significant by the investigator. The mean QTcF increased 29.4 ms versus baseline at 4 h after dosing (432.7 versus 403.3 ms, respectively). This AE was considered to be possibly drug-related by the investigator—the only TEAE to be deemed so in either study.

consequently, there was high variation between patients. In addition, the C_{max} values observed after administration of the single doses during the present studies would be higher than during normal daily dosing, as higher single doses were administered to target steady-state exposures and account for the accumulation that occurs at steady state. T_{max} and $t_{1/2}$ values were consistent across all cohorts at approximately 4–5 and 42–45 h, respectively, which are similar to the values obtained during a single-dose adult PK study [25].

The final population PK model, updated with the pediatric data from these studies, will be used to develop a weight-based dosing algorithm for future studies with pediatric patients. In addition, as adult dosing is often appropriate for adolescents [26], the model can also be used to determine a body-weight cutoff above which an adult dose is appropriate.

Mirabegron was well tolerated at the tested doses, with only one TEAE that was considered to be drug related. This adolescent, who received a high dose of mirabegron under fed conditions, experienced QT prolongation (QT interval corrected for heart rate by Bazett's formula [QTcB] increase >30 ms from baseline at 4 h after dosing). Given the high variability between patients and restrictive definitions for change, the authors consider that this result was not of clinical importance. Furthermore, the corresponding mean increase in QT interval corrected for heart rate by Fridericia's formula did not meet the criteria for QTc interval change (29.4 ms from baseline to 4 h after dosing). This is consistent with the fact that the QTcB method is known to overestimate the duration of cardiac repolarization at high heart rates [27]. During a thorough, four-arm, two-way crossover, active- and placebo-controlled study with 352 randomized healthy adults, daily dosing of mirabegron 50 or 100 mg (supratherapeutic dose) did not cause any relevant prolongations in individual subject-specific corrected QT intervals [28]. The higher mirabegron exposures in children who received high-dose tablets under fasted conditions did not result in any additional safety issues compared with dosing under fed conditions.

Increases in mean pulse rate were consistently observed for all cohorts and nine (20.9%) patients met the PCS criteria for pulse rate. It is difficult to draw any meaningful conclusions about the clinical significance of these findings because of the burdensome study design (e.g. clinic visits, numerous blood draws, and fasted conditions for cohort 5), the lack of a placebo group, the low number of patients, and the high data variability. Additional studies involving placebo groups may be required to determine the clinical significance of these results, although previous mirabegron studies involving pediatric patients with OAB have not reported any clinically significant changes in vital signs [11,13].

Limitations of these two single-dose studies include the lack of a placebo group which, although would have added perspective to the safety and tolerability data, was not possible due to the ethical considerations of taking frequent blood draws for PK analysis from patients who did not receive any drug. By design, the number of patients was low, although there were particularly few with NDO. This is unsurprising, given the low prevalence of NDO, which likely reflects the reducing frequency of neural tube defects [29].

Conclusions

These data represent the first investigation of mirabegron PK in pediatric patients. Overall, a population PK model based on adult exposure data successfully predicted the single, weight-adjusted pediatric doses required to achieve drug exposures comparable with steady state in adults during daily treatment. The final population PK model, updated with the PK data from these studies, will be a suitable foundation for a weight-based pediatric dosing algorithm for use in future studies. The results of this investigation also showed that mirabegron had a favorable safety profile and satisfactory palatability/acceptability. The ongoing phase 3 study in pediatric patients with NDO will collect additional PK data, as well as determine the

safety and efficacy of mirabegron in this population (NCT02751931).

Author statements

Acknowledgments

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Ethical approval

Independent ethics committee approval was obtained before starting the studies, which were conducted in accordance with Good Clinical Practice, International Committee on Harmonisation guidelines, and the ethical principles originating from the Declaration of Helsinki.

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Competing interest

Søren Rittig has received personal fees from Astellas for services as an advisor and lecturer at investigator meetings, and his institution received payment from Astellas for participating in the studies reported herein. Małgorzata Baka-Ostrowska has received personal fees from Astellas for services as a clinical advisor and principal investigator, and her institution received payment from Astellas for participating in the studies reported herein. Camilla Tøndel's institution received payment from Astellas for participating in the studies reported herein. Johan Vande Walle has received personal fees from Astellas and Ferring for services as a lecturer and participating in advisory boards, and his institution received payment from Astellas for participating in the studies reported herein. Birgitta Kjaeer, Paul Passier, Brigitte Bosman, and Stacey Tannenbaum were employees of Astellas at the time of the study. Otto Stroosma is an employee of Covance-Chiltern, contracted by Astellas. As employees of the sponsor, Birgitta Kjaeer, Paul Passier, Brigitte Bosman, and Stacey Tannenbaum were involved in the design of the studies; the collection, analysis, and interpretation of data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Data sharing statements

Study 1: studies conducted with product indications or formulations that remain in development are assessed after study completion to determine if individual participant data can be shared. The plan to share individual participant data is based on the status of product approval or termination of the compound, in addition to other study specific criteria described on www.clinicalstudydatarequest.com under "Sponsor Specific Details for Astellas."

Study 2: access to anonymized individual participant level data will not be provided for this trial as it meets one or more of the exceptions described on www.clinicalstudydatarequest.com under "Sponsor Specific Details for Astellas."

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpurol.2019.10.009.