9 November 2017
EMEA/H/C/002388
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Betmiga

mirabegron

Procedure no: EMEA/H/C/002388/P46/008

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ●CanaryWharf●London E14 4HB ●United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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1. Introduction

On March 2017, the MAH submitted a completed paediatric study for Betmiga (mirabegron), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Betmiga (mirabegron) was approved in adults for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in patients with overactive bladder (OAB) syndrome in EU in 20th December 2012.

A Paediatric Investigation Plan (PIP) has been agreed with the EMA for the development of mirabegron for the treatment of OAB and neurogenic detrusor overactivity (NDO) in the pediatric population. The following reference numbers apply to the latest agreed PIP:

- For OAB:
    - EMA PIP number: EMEA-000597-PIP02-10-M05
    - EMA Decision Number: P/0287/2016, dated 04 Nov 2016
- For NDO:
    - EMA PIP number: EMEA-000597-PIP03-15-M03
    - PDCO Opinion at Day 60: EMA/PDCO/737452/2016, dated 27 Jan 2017

The PIPs are agreed to be completed by March 2024.

This document provides a critical assessment of the results of Study 178-CL-203.

The pediatric development program for mirabegron in the treatment of NDO and OAB includes the following 4 completed phase 1 studies, in addition to phase 3 studies that are yet to be started/completed:

1. A relative bioavailability study in healthy young male and female adults (18 years to< 26 years) to compare the tablet and suspension formulation (2 mg/mL) when dosed under fasting and fed conditions (Study 178-CL-201)
2. A single ascending-dose study using tablets (Study 178-CL-202) in children and adolescents with NDO or OAB (5 years to < 18 years).
3. This single dose study in children with NDO or OAB (3 years to < 12 years) with the oral suspension of 2 mg/mL (Study 178-CL-203)
4. A single-dose relative bioavailability study in healthy adult subjects to compare the 2 mg/mL and 8 mg/mL oral suspension formulations, including assessment of the effect of food on the pharmacokinetics of the 8 mg/mL oral suspension (Study178-CL-208).

The results of the above mentioned studies will be used to determine the doses for future studies in the pediatric population.

The results from Study 178-CL-201 demonstrated that the relative oral bioavailability of the oral suspension was approximately 2-fold lower than that of the tablet and showed that single doses of 50 mg mirabegron oral suspension under fed and fasted conditions in healthy young male and female subjects were generally considered safe and well tolerated.

In Study 178-CL-202, prolonged-release mirabegron tablets were investigated in a pediatric population for the first time. The single low and high doses were predicted to result in exposure levels comparable to the exposure in adults at steady state following 25 mg and 50 mg mirabegron once daily, respectively. The results showed that mirabegron exposures and pharmacokinetic parameters were in line with dose, age and food state in each cohort (5 cohorts: low dose adolescents fed condition, low dose children fed condition, high dose adolescents fed condition, high dose children fed condition, high dose children fasted condition). The single dose administration in this study was sufficient to reach similar exposure to that in adults at steady state. Based on the available data, mirabegron had an acceptable safety profile and was well tolerated at single doses of up to 75 mg in adolescents and children with OAB and NDO.

Assessor´s comment
EMEA-C2-000597-PIP03-15-M03 compliance report was discussed at the 16-19 May (2017) PDCO meeting. Feedback from the applicant has been requested in relation to the use of descriptive reporting of mirabegron PK in studies 178-CL-202 and 178-CL-203 as population pharmacokinetics was agreed to be used with the Committee.

No multiple-dose phase I study for evaluating steady state concentrations in the paediatric population has been planned/informed.

2.2. Information on the pharmaceutical formulation used in the study

Mirabegron 2 mg/ml prolonged-release granules for oral suspension was used in the Study 178-CL-203.

Oral suspensions have been developed for those pediatric patients who cannot be dosed with tablets. To obtain more acceptable volumes of dosing compared to the 2 mg/mL oral suspension, a 4-fold higher strength oral suspension (8 mg/mL) was developed.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for Study 178-CL-203. This study is included in the paediatric clinical development program as detailed in agreed PIPs (EMEA-000597-PIP02-10-M04; EMEA-000597 -PIP03 -15-M01).The data submitted do not influence the benefit-risk balance of mirabegron and therefore does not have further regulatory consequences.

2.3.2. Clinical study: Study 178-CL-203

A Multicentre, Open-label, Single Dose, Phase 1 Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Mirabegron Oral Suspension in Pediatric Subjects from 3 to Less than 12 Years of Age with Neurogenic Detrusor Overactivity (NDO) or Overactive Bladder (OAB)

Description

The study explored the pharmacokinetics, safety, tolerability, acceptability and palatability of mirabegron prolonged-release granules for oral suspension following a single dose targeted to obtain comparable exposure to once-daily 50 mg of mirabegron prolonged-release tablets at steady state, when administered to adults under undefined food conditions.

Methods

Objectives

Primary: To evaluate the pharmacokinetics of mirabegron oral suspension after single dose administration in children with NDO or OAB

Secondary:

- To evaluate the safety and tolerability of mirabegron oral suspension after single dose administration in children with NDO or OAB
- To evaluate the palatability and acceptability of mirabegron oral suspension after single dose administration in children with NDO or OAB

Assessor´s comment
Single doses of prolonged-release granules for oral suspension (2 mg/ml) will be administered to children aged 3 years and above. Doses will be adjusted by body weight and targeted to obtain exposure levels comparable to 50 mg prolonged-release tablets at steady state in adults. The PK, safety, tolerability, palatability and acceptability will be studied.

Study design

This was a multicenter, open-label, single-dose study in the children with NDO from 3 to less than 12 years of age and in children with OAB from 5 to less than 12 years of age. Nine male and female children were enrolled in the study, including 6 NDO and 3 OAB subjects.

Informed consent and screening took place maximally 28 days prior to dosing. When eligibility of the subject was confirmed, washout of prohibited medication, if applicable, started. After washout, a 24-h heart rate assessment (24-h Holter) was done – hereafter referred to as reference day. If no washout was required, the screening visit and the reference day for the 24-h Holter could be combined. The reference day was scheduled 1 to 4 days prior to dosing (day -4 to -1).

In the morning of day 1, all subjects were admitted to the clinic in fasting condition (last meal intake before midnight). Subjects had a light breakfast, their eligibility check was performed and if eligible, a blood sample for safety labs was drawn if necessary. Subjects were dosed within 1 h after completion of the light breakfast and were allowed to have a light lunch not sooner than 2 h after dosing.

Pharmacokinetic sampling was initially performed on day 1, and during follow-up 3 pharmacokinetic samples were taken according to the pharmacokinetic sampling scheme (1 sample on day 2 and 1 sample in 2 of the following intervals: day 3 [48-56 h], day 4 [72-80 h], day 5 [96-104 h], day 6 [120-128 h], day 7 [144-152 h]). The visit for taking the last pharmacokinetic sample (day 4 to 7) was also used to conduct the end of study (EoS) assessments for that subject.

Table 1 Schedule of Pharmacokinetic Sampling

Day 1 (Dosing Day)	Day 2 (PK Sample)	Day 3-7: 2 Pharmacokinetic Samples Collected on 2 Separate Days Listed Below
0.5-2, 3-5, 6-8 h postdose	24-32 h	Day 3: 48-56 h Day 4: 72-80 h Day 5: 96-104 h Day 6: 120-128 h Day 7: 144-152 h

The screening, the day 1, and the day 4 to 7 visits had to be performed at the clinic. Visit details and any potential changes in the subject's condition and/or concomitant medication were recorded in the source records and sent to the investigator by the qualified home healthcare service.

Rescreening was not permitted.

Figure 1 Study Flow Chart

Screening						Dosing		Follow-up		
Day -28 (Maximum Window to Day -1)				Day -4 to Day -1		Day 1		Day 2	Day 3 to Day 6	Day 4 to Day 7
Obtain informed consent	→	Screening Check inclusion / exclusion criteria / washout	→	Reference day 24-h Holter (Heart rate)	→	Check remaining exclusion criteria Receive single dose	→	PK & safety	PK	PK & EoS

End of study (EoS) was defined as the subject's last protocol-defined assessment. Start of study was defined as the signing of the informed consent by the first subject.

PK: pharmacokinetics

† When the subject was NOT using prohibited medication that required washout, the reference Holter may have been applied at screening. If prohibited medication needed to be washed out, the reference Holter was applied on day -4 to -1 after washout of the prohibited medication. The wash-out period was 5 times the half-life of the prohibited medication.

‡ Wash-out started after the eligibility of the subject was confirmed.

§ During follow-up, 3 pharmacokinetic samples were taken according to the pharmacokinetic sampling scheme – 1 sample on day 2 and 1 sample in 2 of the following intervals: day 3: 48-56 h, day 4: 72-80 h, day 5: 96-104 h, day 6: 120-128 h, day 7: 144-152 h.

¶ EoS assessments on the last pharmacokinetic sampling day; depending on the intervals chosen, at day 4, 5, 6 or 7.

Assessor´s comment

Sparse sampling scheme was applied with individual pharmacokinetic samples to be collected at 6 separate time-windows post-dose. Samples from all subjects were required in the interval 0.5 to 32 hours post-dose (4 samples).Two additional samples were schemed to be taken between day 3 and day 7. In adults, the mirabegron terminal elimination half-life (t1/2) is approximately 50 hours.

Study population /Sample size

Male or female children with NDO from 3 to less than 12 years of age, and male and female children with OAB from 5 to less than 12 years of age with documented diagnosis according to the International Children's Continence Society(ICCS) criteria of NDO, or Idiopathic OAB and body weight of ≥ 15.0 kg were included in the study. The study was designed to keep the number of pediatric subjects as low as possible. It was expected to dose 6 subjects with NDO or OAB. To fulfill an FDA Written Request stipulating to enroll at least 6 subjects with NDO, 3 NDO subjects were added to the already recruited group of 3 NDO and 3 OAB subjects. In total, 6 subjects with NDO and 3 subjects with OAB were enrolled.

When the protocol amendment came into effect, 6 subjects (3 NDO and 3 OAB) had already been dosed. Therefore, to allow for 6 NDO subjects in the study, the sample size was adjusted to reflect 9 planned subjects (6 with NDO).

All analyses as described were performed for all subjects and for NDO subjects only.

Assessor´s comment
Nine patients were recruited in the study. The inclusion of 3 additional patients to fulfil an FDA Written Request is acknowledged.
In accordance with FDA request, all analyses were performed for all subjects and for NDO subjects only.

Treatments

Mirabegron 2 mg/ml prolonged-release granules as oral suspension was given orally with a glass of water.

Subjects reported to the clinic in fasting condition (last meal before midnight) and were dosed within 1 h after completion of the light breakfast and were allowed to have a light lunch > 2 h after dosing.

The dose level for Study 178-CL-203 was targeted to result in an exposure equivalent to that in adults after a 50 mg prolonged-release tablet once daily (target value AUC24 was 188 ng•h/mL) and was based on modeling and simulation predictions using data obtained in studies 178-CL-201 (tablets and oral suspension dosed in healthy young subjects under fasted and light meal food conditions) and 178-CL-202. The model adequately estimated the AUC observed in Study 178-CL-202. To determine the doses for Study 178-CL-203, a simulation was performed in which for every virtual patient (based on body weight samples from the National Health and Nutrition Examination Survey database) the optimal dose was estimated. Visualization of the plotted doses versus body weight allowed selection of possible weight cut-offs. Subsequently, various weight-based scenarios were investigated for accuracy in reaching the AUC target. For the administration of the suspension, 4 weight ranges were defined.

Table 2 Doses for Study 178-CL-203

Weight Range (kg body weight)	Oral Suspension Dose (mL)†	Corresponding Dose of Mirabegron (mg)
15 - 19 kg	40 mL	80 mg
20 – 29 kg	50 mL	100 mg
30 – 39 kg	55 mL	110 mg
> 40 kg	65 mL	130 mg

† Strength: 2 mg mirabegron/mL suspension

Assessor´s comment
Doses were based on body weight and targeted to result in an exposure equivalent to that in adults after a 50 mg prolonged-release tablet once daily (steady state). Four weight ranges were chosen based in modelling and simulation predictors from studies 178-CL-201 and 178-CL-202.
In the study 178-CL-201 bioavailability of the oral suspension was shown to be approximately 2-fold lower than that of the tablets in healthy adults.
Single doses of mirabegron prolonged-release tablets (25, 50 or 75 mg) were administered to paediatric population in study 178-CL-202, already evaluated in procedure no. EMA/H/C/002388/P46. Paediatric patients were divided into two age-groups (i.e. 12 to less than 18 years and 5 to less than 12 years). Doses administered were dependent on body weight. For the low dose and for the high dose cohort, weight categories were defined and patients received a dose (either 25, 50 or 75 mg) based on

the weight categories. In general, similar PK was seen when children were compared with adults at steady-state. Exposure and PK parameters were dependent with dose, age and food state. Exposition was higher in children versus adolescents, which was expected due to the lower body weights.
Patients with an age range between 3 and below 12 under light fed conditions have been considered for this 178-CL-203 study. This seems to be appropriate in view of the results of the study 178-CL-202 (age and food stage as covariates). Doses were estimated from simulations based on weight using data obtained in study 178-CL-202. Fifteen kilograms was selected as the low cut-off, corresponding to an age of 3 years. The lowest age and body weight in study 178-CL-202 were 7 years and 21 kilograms respectively.
It seems that 178-CL-202 and 178-CL-203 studies are to be used to determine the doses for phase II/III studies in the paediatric population. This approach is considered in principle adequate whenever a justification is provided for using one-dose versus multiple-dose concentrations for the comparison with steady-state levels in adults.
Volumes to be used are within 40 and 65 ml which is much more than desired. Higher strength, i.e. 8 mg/ml oral suspension, might have been used. Nevertheless, prolonged release tablets would be a more suitable formulation for the older children.

Outcomes/endpoints

Pharmacokinetics

The pharmacokinetic variables assessed were AUC_{inf}, Cmax, tmax, $t_{1/2}$, CL/F, Vz/F, AUC_{24}, AUC_{last}.

Safety

All safety and tolerability variables were secondary endpoints. Safety and tolerability were assessed by evaluation of the following variables:

- Nature, frequency and severity of TEAEs
- Clinical laboratory evaluations (haematology, biochemistry, urinalysis)
- Vital signs (including 24-h Holter heart rate)
- ECGs (including interval measurements)
- Physical examination (only date of assessment was collected in the eCRF. Clinically significant findings at screening were reported as medical history, clinically significant findings after screening were reported as AEs)
- Liver Safety Monitoring and Assessment
- Postvoid residual volume (PVR)
- Palatability and Acceptability

Statistical Methods

Two populations were used for the analyses, the safety analysis set (SAF) and the pharmacokinetics analysis set (PKAS).

– The safety analysis set (SAF) consisted of all patients who took the dose of study medication.

– The pharmacokinetic analysis set (PKAS) consisted of subjects from the SAF population for whom sufficient plasma concentration data was available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

No imputations of missing data were considered and all values were included in the analyses regardless of being a potential outlier or not.

Individual subject mirabegron plasma concentrations were listed and summarized for each time interval for the total group and additionally for NDO subjects only. “Spaghetti plots” and individual subject drug concentration-time profiles were produced. Noncompartmental analysis of pharmacokinetic data was performed. Pharmacokinetic parameters were analyzed descriptively. No inferential analyses were conducted.

Changes from Planned Analyses

- It was initially planned to calculate mean plasma concentrations for mirabegron. This was not done, because intervals instead of times were specified for pharmacokinetic sampling, resulting in variation in actual sampling times between subjects.
- By-subject displays of heart rate measured by the 24-h Holter were planned relative to clock-time and in addition relative to dosing time. The individual averaged 24-h Holter data were plotted relative to clock-time only, since plotting individual heart rate relative to dosing time would not have provided additional information.
- Noncompartmental analysis was done for descriptive reporting of mirabegron pharmacokinetics in this study report; however, population pharmacokinetic modelling is still planned for future dose optimization and PK characterization.

Summary of safety variables were presented for the SAF, for the total group and additionally for NDO subjects only. No formal statistical testing was performed on these data.

Assessor´s comment

Population pharmacokinetics was agreed with the PDCO to characterise the pharmacokinetic profile of mirabegron in children as well as the determination of AUC with individual prediction as a primary endpoint. This is not the case as only descriptive reporting of mirabegron PK has been presented. The MAH states that population pharmacokinetic modelling is planned for future PK characterization. Dosage from the present study is based on modeling and simulation predictions using data obtained in studies 178-CL-201 and 178-CL-202. No inferential analyses of data from study 178-CL-203 are presented at the moment. Company should clarify in relation to the pharmacokinetic modelling planned for future dose optimization and inform about phase 3 studies already initiated within the paediatric development plan, if it is the case, and the rational for the dosing in children and adolescents.

Results

Recruitment / Number analysed

Subject Disposition

Ten subjects signed informed consent and were assessed for eligibility. Nine subjects were eligible and 1 NDO subject was excluded before intake of study drug due to screen failure (prolonged QTc).

All 9 eligible subjects received the study drug, completed the study and were included in the PKAS and SAF.

Table 3 Listing of Study Drug Dosing, SAF

Subject ID	Sex	Diagnosis	Age (years)	Weight on day 1 (kg)	Oral Suspension Dose (mL)†	Corresponding Dose of Mirabegron (mg)
	F	OAB	5	22.8	50	100
	M	NDO	10	44.4	65	130
	F	NDO	4	15.9	40	80
	M	OAB	8	31.4	55	110
	M	OAB	7	20.5	50	100
	F	NDO	5	17.0	40	80
	F	NDO	8	31.0	55	110
	M	NDO	10	25.0	50	100
	F	NDO	9	26.0	50	100

NDO: neurogenic detrusor overactivity; OAB: overactive bladder; SAF: safety analysis set
†Strength: 2 mg mirabegron / mL suspension

The total study population comprised of 6 subjects with NDO and 3 subjects with OAB. Overall, 5 subjects were female and 4 subjects were male.

Table 4 Summary of Demographics and Baseline Characteristics for the Total Study Population, SAF

Parameter Category / Statistics	Total (n = 9)
Diagnosis	
NDO	6 (66.7%)
OAB	3 (33.3%)
Sex, n (%)	
Male	4 (44.4%)
Female	5 (55.6%)
Race, n (%)	
White	9 (100.0%)
Black or African American	0
Asian	0
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islander	0
Other	0
Ethnicity, n (%)	
Not Hispanic or Latino	9 (100.0%)
Hispanic or Latino	0
Age, years	
Mean (SD)	7.3 (2.2)
Median	8.0
Min - Max	4 - 10
Weight on day 1(kg)	
Mean (SD)	26.00 (8.78)
Median	25.00
Min - Max	15.9 – 44.4
Height (cm)	
Mean (SD)	125.77 (13.82)
Median	130.0
Min - Max	104.0 – 145.0
BMI on day 1 (kg/m^2)	
Mean (SD)	15.99 (2.35)
Median	15.15
Min - Max	13.9 – 21.1

All subjects who took the dose of study medication (safety analysis set, SAF)
BMI: body mass index (weight [kg]/height [m^2]); Max: maximum; Min: minimum; NDO: neurogenic detrusor overactivity; OAB: overactive bladder

All 9 subjects have been on antimuscarinic therapy or mirabegron for the treatment of OAB or NDO in the month before screening.

Assessor´s comment
Patients in treatment with mirabegron were included in the study if the concomitant treatment had been suspended at least twelve days before the reference day.

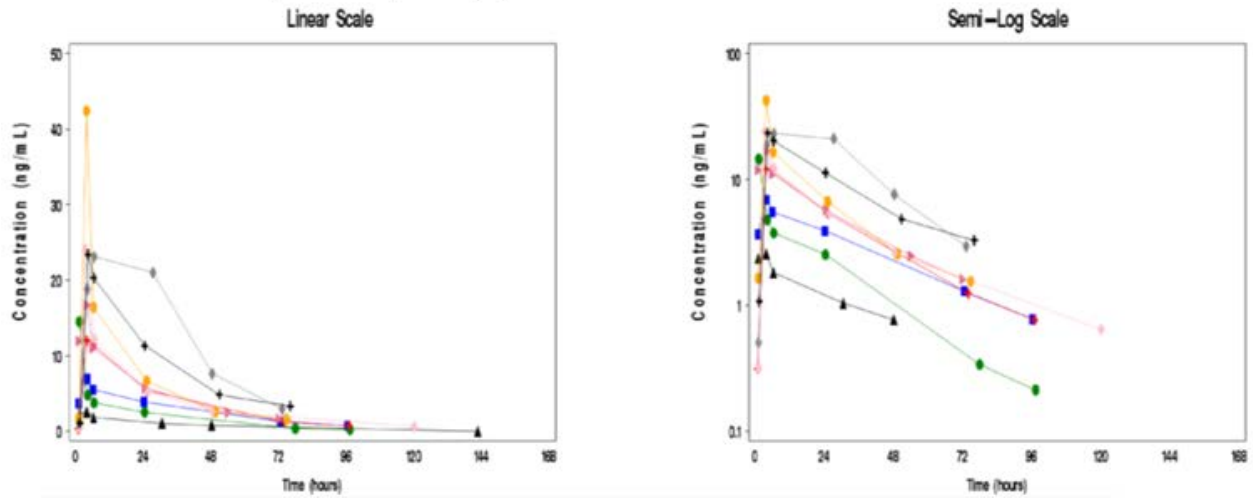
Pharmacokinetic results

The pharmacokinetic data were analysed using noncompartmental analysis based on actual sampling times. No subject was excluded from calculation of any pharmacokinetic parameter.

Plasma Concentrations of Mirabegron

Except for the last sample in a subject with OAB, all mirabegron plasma concentrations were quantifiable, allowing the calculation of all primary and additional pharmacokinetic parameters in all subjects.

Figure 2 Individual Subject Plasma Concentration Profiles of Mirabegron in the Total Population (PKAS)



Plasma Pharmacokinetic Parameters of Mirabegron

Descriptive statistics for mirabegron pharmacokinetic parameters following a single dose of mirabegron under light-meal fed conditions are presented in Table 2.

Table 5 Plasma Pharmacokinetic Parameters of Mirabegron in the Total Population (PKAS)

Parameter Statistic	Total (n = 9)
AUC_{inf} (ng•h/mL)	
Mean (SD)	464.1 (288.9)
%CV	62.3
Median	431.5
Min – Max	99.7 - 1005
C_{max} (ng/mL)	
Mean (SD)	18.41 (11.72)
%CV	63.7
Median	16.70
Min – Max	2.56 - 42.4
$t_{1/2}$ (h)	
Mean (SD)	25.99 (5.800)
%CV	22.3
Median	23.92
Min – Max	16.2 – 33.4
t_{max} (h)	
Median	3.930
Min – Max	1.25 - 6.50
AUC_{24} (ng•h/mL)	
Mean (SD)	226.9 (136.2)
%CV	60.0
Median	222.2
Min – Max	39.7 - 467
AUC_{last} (ng•h/mL)	
Mean (SD)	414.3 (263.6)
%CV	63.6
Median	375.9
Min – Max	62.8 - 936
CL/F (L/h)	
Mean (SD)	338.0 (281.5)
%CV	83.3
Median	231.7
Min – Max	109 - 1003
V_Z/F (L)	
Mean (SD)	13726 (14036)
%CV	102.3
Median	9591
Min – Max	2561 - 48272

All subjects from the safety analysis set for whom sufficient plasma concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom date and time of dosing and sampling were known (pharmacokinetics analysis set [PKAS]). All subjects in the PKAS provided data for each parameter.

%CV: coefficient of variation; Max: maximum; Min: minimum

The intersubject variability was as high as observed before in pediatric subjects and adults. The mean AUC24 for the total population (227 ng•h/mL) was similar to the target value obtained in adults at steady state under fed conditions following administration of 50 mg of mirabegron once daily (188 ng•h/mL).

Overall, the range of observed exposures (AUCinf from 99.7 to 1005 ng•h /mL for the total population) was included in the ranges observed in the phase 3 studies in adults for the 50 mg dose (Study 178-PK-015 AUCtau ranged from 29 to 1082 ng•h/mL over the 6 studies using the 50 mg dose). It can therefore be concluded that the dosing strategy in this study was appropriate to reach exposures similar to those in adults dosed with 50 mg mirabegron.

Slightly higher mean AUC24 was observed for the NDO population (265 ng•h/mL versus 227 ng•h/mL for the total population).The higher proportion of female subjects in the NDO population compared to the total population (4/6 versus 5/9) may have contributed.

Pharmacokinetic conclusions

Pharmacokinetic Conclusions for the Total Population

- Mirabegron reached Cmax at a median tmax of 3.93 h, and was eliminated with a mean t1/2 of 26.0 h.
- Mean values for the exposure parameters Cmax, AUC24, and AUCinf amounted to 18.4 ng/mL, 227 ng•h /mL, and 464 ng•h /mL, respectively.
- Mean apparent total systemic clearance after extravascular dosing (CL/F) and apparent volume of distribution during the terminal elimination phase after extravascular dosing (Vz/F) amounted to 338 L/h and 13726 L, respectively.

Assessor´s comment
Pharmacokinetic results are exploratory and no sound conclusions can be drawn from them further than defining median parameters derived from a limited number of patients. Targeted exposures were reached and remained within the ranges observed in adult studies with 50 mg doses at steady-state, but direct comparisons are limited as steady state was not reached in the study.
Intersubject variability was high and in line with that observed before in children and adults.

Safety results

Nine children, ranging from 4 to 10 years of age, diagnosed with NDO (6 subjects) or OAB (3 subjects), were exposed to a single dose of mirabegron oral suspension, strength 2 mg/mL. The volumes administered ranged from 40 to 65 mL solution, corresponding to 80 to 130 mg mirabegron.

Adverse Events

There were no deaths, serious treatment-emergent adverse events (TEAEs) or any adverse event leading to withdrawal from the study.

One TEAE (pyrexia) was reported in an 8-year-old girl with NDO dosed with 55 mg mirabegron. The girl showed the highest exposure for mirabegron (AUCinf of 1005 ng•h/mL) in the total population. The fever was observed 5.53 hours after dosing, around the time of the highest plasma concentration of mirabegron. The subject received paracetamol and recovered. The TEAE was mild in intensity and assessed as not related to study drug by the investigator.

Clinical Laboratory Evaluations

There were no clinically significant changes in any laboratory parameters after dosing.

No effects of mirabegron on liver function parameters were observed. One subject met PCS criteria for liver function. In the 10-year-old boy with NDO, the AST was > 2 times the ULN at baseline and on day 2 and met the PCS criteria. The respective events at baseline were reported as pretreatment AEs (increased ALT and increased AST). There was no further relevant increase in ALT or AST versus

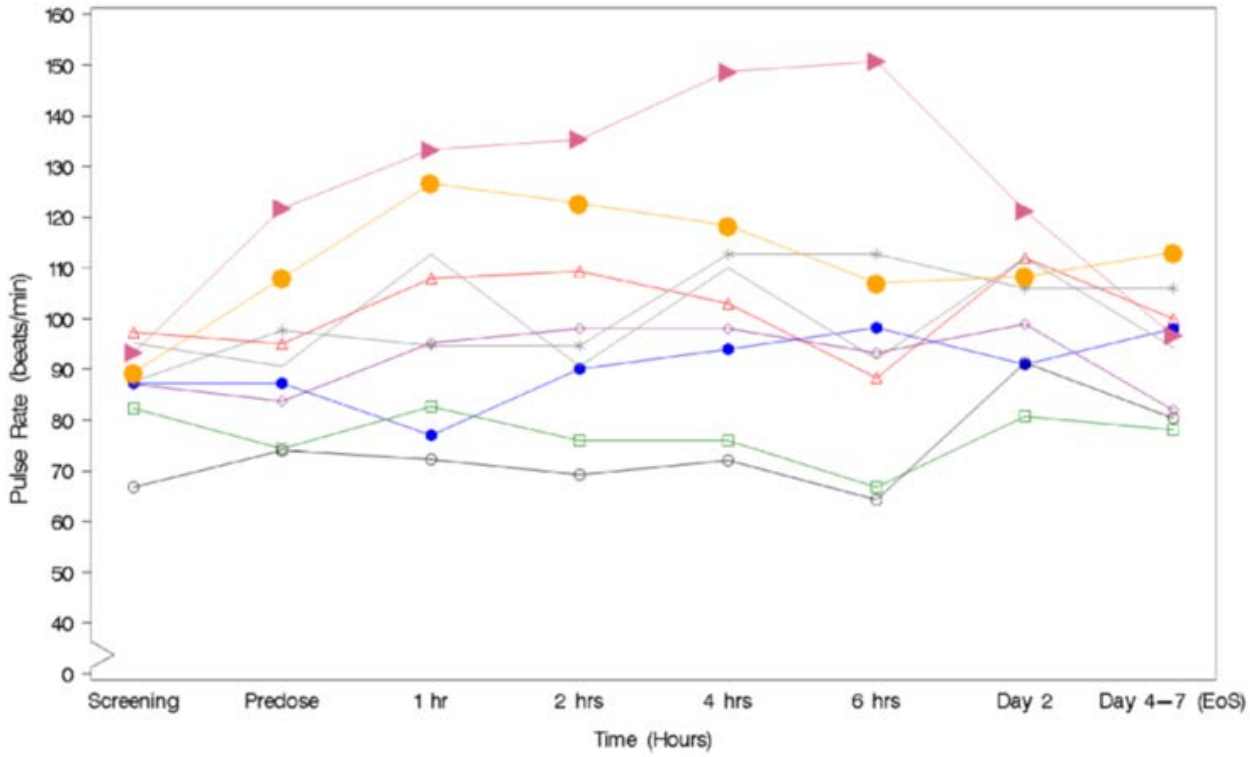
baseline in this subject. Both AEs were mild in intensity and resolved. No further investigation (serology) was performed to identify the cause of the increase in liver enzymes.

Vital signs

Three subjects with NDO showed vital signs meeting potentially clinically significant criteria, 2 subjects for pulse rate (one of which was reported to suffer from pyrexia at the same time) and 1 subject for both systolic blood pressure (SBP) and diastolic blood pressure (DBP). Overall, in these 3 subjects no clear relationship of vital sign values with mirabegron plasma concentrations was observed.

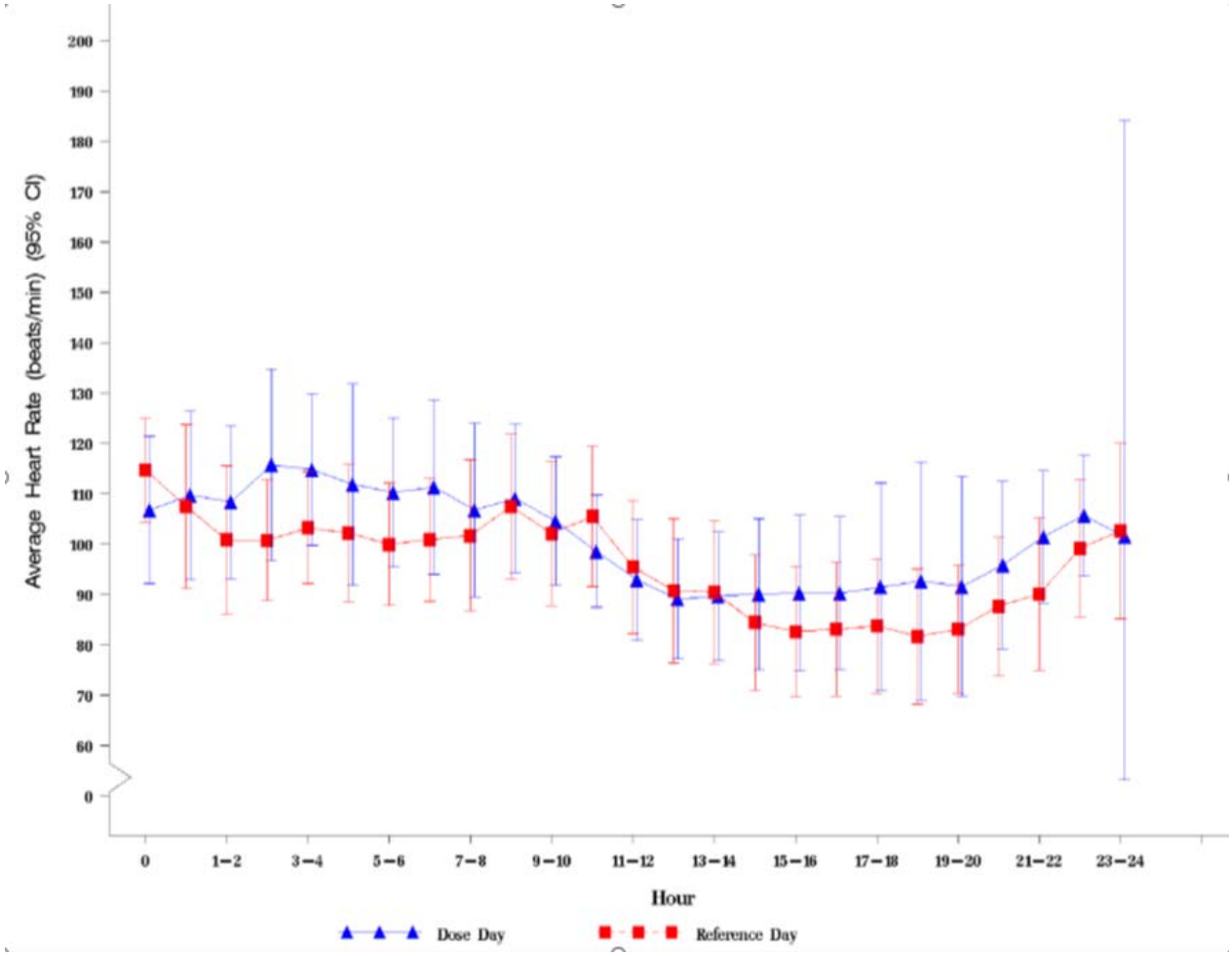
No clinically relevant changes were observed in mean SBP or DBP. An increase in mean pulse rate was observed after dosing.

Figure 3 Individual Pulse Rate Values in the Total Population, SAF



The mean changes from predose were 7.8 bpm, 6.0 bpm, 11.1 bpm, 4.5 bpm, 9.9 bpm and 1.8 bpm at time points 1 h, 2 h, 4 h, 6 h, day 2 and day 4 to 7, respectively. The time-matched mean difference between reference and dosing day in the 24-h Holter recording showed a peak value of 16.3 bpm in the 2 to 3 h interval after dosing. However, there was a tendency for higher heart rates on the dosing day even before dosing, compared to the reference day.

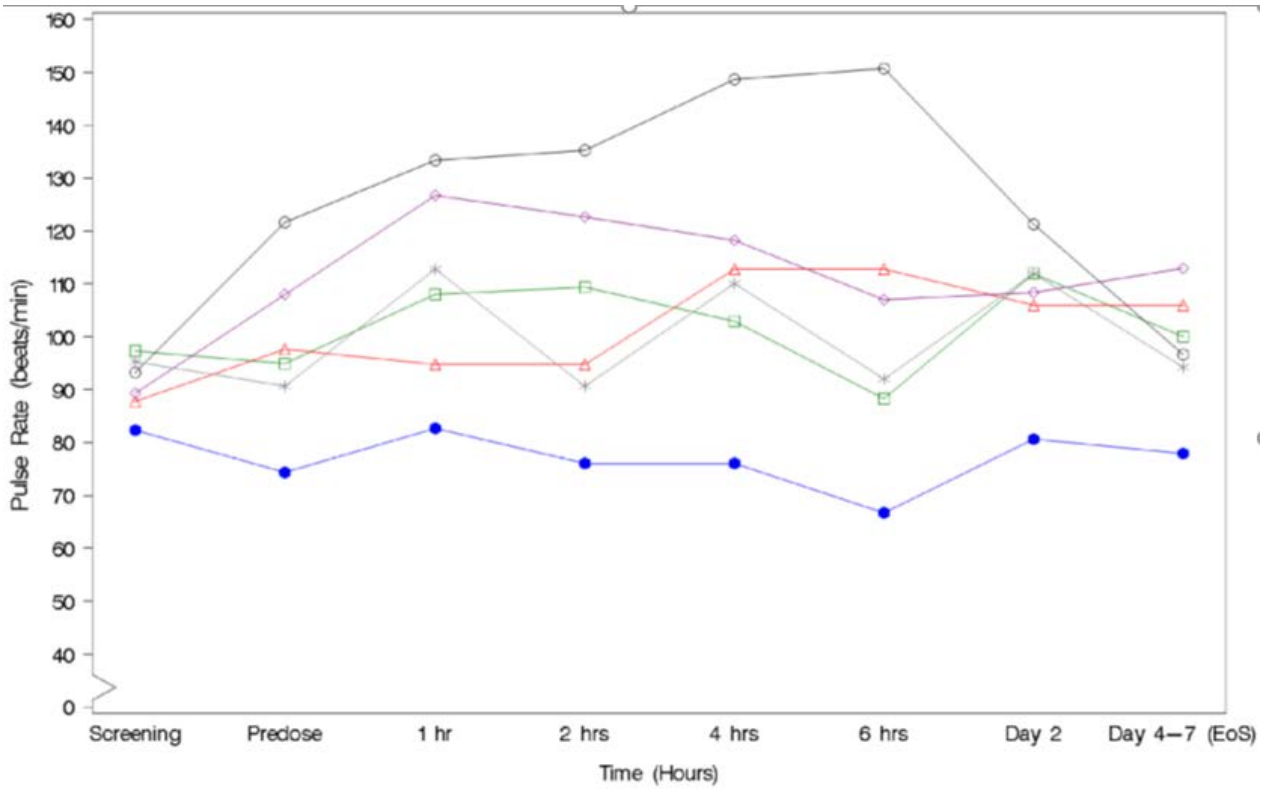
Figure 4 Hourly Holter Measurements (Heart Rate), for Reference and Dosing Day (Relative to Dosing Time) in the Total Population, SAF



Vital Signs in Subjects with NDO

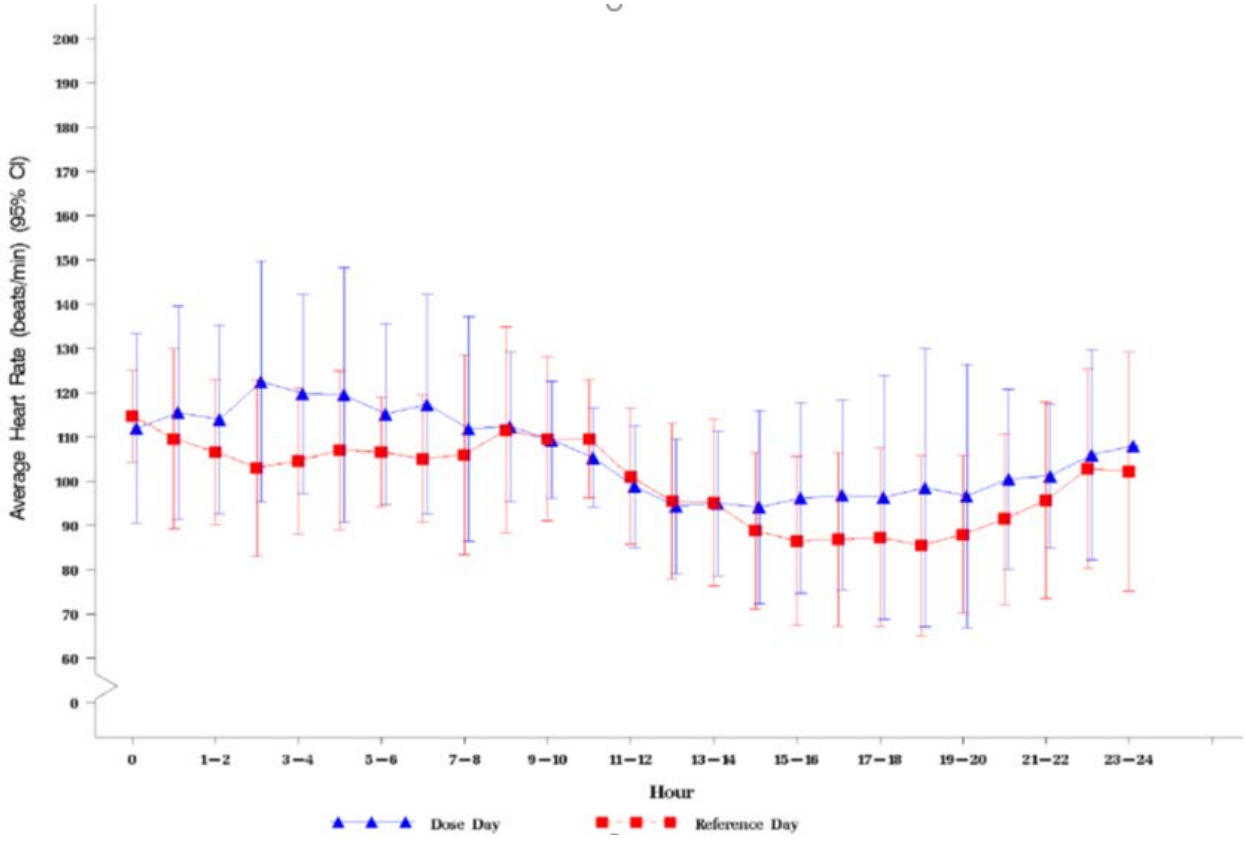
Increases in mean pulse rate after dosing were observed. The mean changes from predose were 11.8 bpm, 6.9 bpm, 13.6 bpm, 5.0 bpm, 8.8 bpm and 0.1 bpm at time points 1 h, 2 h, 4 h, 6 h, day 2 and day 4 to 7, respectively.

Figure 5 Individual Pulse Rate Values in Subjects with NDO, SAF



Hourly 24-h Holter measurements showed increased mean heart rates after dosing up to about 7 to 8 h postdose.

Figure 6 Hourly Holter Measurements (Heart Rate), for Reference and Dosing Day (Relative to Dosing Time) in Subjects with NDO, SAF



Electrocardiograms

There were no electrocardiogram abnormalities assessed as clinically significant by the investigator. Increases in corrected QT interval using Fridericia's method (QTcF) > 30 ms and QTcF intervals > 450 ms were not observed. One subject with NDO showed high corrected QT interval using Bazett's method values around 450 ms at predose, 1 h after dosing and at EoS.

A 5-year-old girl with NDO had abnormal ECGs at 2 h, 4 h and 6 h postdose, which were attributed to artifacts and rendered the ECG nonevaluable. For all other time points, evaluable ECG data were available for all subjects in the SAF (n = 9). Except in this subject, all mean QTcB values were normal. The 5-year-old girl with NDO showed mean QTcB intervals > 450 ms at predose (453 ms), 1 h postdose (450.67 ms), and at the EoS examination (453.33 ms). The QTcB triplicate values ranged from 445 ms (lowest value at 2 h) to 453 ms (predose and EoS), all below the 460 ms. No ECG data were available 4 h and 5 h postdose for this subject.

Other safety-related observations

Because all 6 NDO subjects were on clean intermittent catheterization, data for Postvoid residual (PVR) volume were available for the 3 subjects with OAB only. A bladder scan could not detect any PVR volume at 5 h postdose in any of these subjects (PVR volume = 0 mL)

Overall, the study medication was well tolerated.

Assessor´s comment

Overall, the study drug was well-tolerated. Pyrexia was reported in an eight years old girl that showed the highest exposure in the study. Observation was coincident with the time of maximal concentration however Cmax in this girl (23.1 ng/mL) was not higher than Cmax in other patients [Cmax mean (SD)

18.41 (11.72); min-max 2.56-42.4].
The absence of a placebo group, the low number of subjects and the high variability do not allow to draw meaningful conclusions about the safety.

2.3.3. Discussion on clinical aspects

This is the first study conducted with mirabegron prolonged-release granules for oral suspension in children.The aim was to explore the pharmacokinetics, safety profile and acceptability in pediatric subjects with neurogenic detrusor overactivity or overactive bladder, after single dose administrations.

Patients with an age within the range of 3 and 12, under light fed conditions, were considered for study 178-CL-203. Doses were adjusted by body weight and targeted to obtain exposure levels comparable to those of 50 mg prolonged-release tablets at steady state in adults. The pharmacokinetics, safety, tolerability, palatability and acceptability of the 2 mg/ml oral suspension were studied.

Four weight ranges were chosen based on modelling and simulation predictions from two other studies, i.e. a relative bioavailability study in healthy adults, and a phase I study using mirabegron prolonged release tablets in children ≥5 years and adolescents. Fifteen kilograms was selected as the lower cut-off weight, corresponding to an age of 3 years.

The dosing strategy in this study was appropriate to reach targeted exposures that remained within the ranges observed in adult studies for the 50 mg dose at steady-state. Nevertheless, direct comparisons are limited as steady state was not reached in the paediatric study.

Pharmacokinetic results are exploratory and interpretation should be treated with caution beyond defining median parameters derived from a limited number of patients.
The intersubject variability was as high as observed before.

It seems that joined results from 178-CL-202 and 178-CL-203 studies are to be used to determine the doses for phase II/III studies in the paediatric population. This approach is considered in principle adequate whenever a justification is provided for using one-dose versus multiple-dose concentrations for the comparison with steady-state levels in adults.

There were no deaths, serious TEAEs or AEs leading to withdrawal from the study.

One TEAE (pyrexia) was reported in a subject with NDO. The TEAE was mild in intensity and assessed as not related to study drug

Assessment of laboratory parameters and ECGs did not reveal any clinically important drug effects. Vital signs meeting PCS criteria were reported in 3 subjects with NDO. The subject with potentially clinically significant DBP and SBP values already had a DBP value > 99th percentile at screening. In the 2 subjects with increased heart rate no correlation between increased heart rate and mirabegron plasma concentration was apparent. The increase in mean heart rate in the 24-h Holter compared to the reference day may be explained at least in part by the stress due to the blood samplings and assessments done or to be done on that day and additionally the “white-coat phenomenon,” as the measurements for the dosing day were done at the clinic, while the reference day was performed at home.

The absence of a placebo group, the low number of subjects and the high variability do not allow to draw meaningful conclusions about the vital signs.

Overall, the study drug was well-tolerated.

3. Rapporteur's overall conclusion and recommendation

The presented information is consistent with the existing knowledge about the compound. There are no new or unexpected safety signals. The PK data is also in line with the expected profile.

Although the submitted data does not introduce any information requiring changes in the product information, additional clarification from the MAH is requested as stated below.

☒Not Fulfilled:

Based on the data submitted, the MAH should provide description of the additional clarifications requested per study 178-CL-202 and 178-CL-203 as part of this procedure. (see section 4"Additional clarification requested by the Rapporteur")

4. Additional clarification requested by the Rapporteur

Non clinical aspects

N/A

Clinical pharmacology aspects

None

Clinical efficacy aspects

Major Objections

None

Other concerns

1.-It seems that 178-CL-202 and 178-CL-203 studies are to be used to determine the doses for phase II/III studies in the paediatric population. This approach is considered in principle adequate whenever a justification is provided for using one-dose versus multiple-dose concentrations for the comparison with steady-state levels in adults. The MAH should clarify.

2.-Population pharmacokinetics was agreed with the PDCO to characterise the pharmacokinetic profile of mirabegron in children as well as the determination of AUC with individual prediction as a primary endpoint. This is not the case as only descriptive reporting of mirabegron pharmacokinetics is presented. The applicant states that population pharmacokinetic modelling is planned for future. The MAH is requested to provide clarifications in relation to the pharmacokinetic modelling planned for dose optimization and inform about phase 3 studies already initiated within the paediatric development plan, if it is the case, and the rational for the dosing in children and adolescents.

5. Assessment of the responses provided

Question 1

It seems that 178-CL-202 and 178-CL-203 studies are to be used to determine the doses for phase II/III studies in the paediatric population. This approach is considered in principle adequate whenever a justification is provided for using one-dose versus multiple-dose concentrations for the comparison with steady-state levels in adults. The MAH should clarify.

MAH Response

The area under the curve (AUC) was selected as the target exposure metric for dose estimation/prediction. A population pharmacokinetic model was developed on mirabegron pharmacokinetic data from adults, scaled to paediatric patients using allometric scaling, then externally validated with data from study 178-CL-202 (children and adolescents). The model described the pediatric data well, particularly the AUC. The AUC calculation is derived from the estimated model parameter, clearance, which is independent from the frequency of dosing.

Therefore, given the ability to well estimate AUC from the model, it was considered not necessary (and therefore unjustified) to have the concentrations after multiple dose confirmed in another P1-study in paediatric patients before conducting a study evaluating the multiple dose efficacy and safety in the paediatric population. The development and validation of the population pharmacokinetic model is described in detail in 178-PK-204.

A summary of study 178-PK-204 is included below by the assessor:

Study 178-PK-204 consisted in the development of a population pharmacokinetic model to describe the pharmacokinetics of mirabegron in adults after administration of prolonged-release tables and the 2mg/mL oral suspension under fasted and fed conditions (data from study 178-PK-201). The model that best describe the data was a 3-compartment model with a combination of first and zero-order absorption. Food, formulation, and dose were included in the model as covariates on the bioavailability (F1), and body weight was included through allometric scaling with fixed parameters on all clearance and volume terms. Final parameter estimates of the model are presented in table 7 bellow:

Table 7 Final Parameter Estimates (Run 34)

Parameter (units)	Estimate	SE	CV (%)	Shrinkage (%)
CL (L/h)	29.1	1.52	5.23	
V2 (L)	140	14.8	10.6	
Q3 (L/h)	13.5	1.89	14.0	
V3 (L)	3290	317	9.64	
Q4 (L/h)	128	8.44	6.59	
V4 (L)	1380	40.6	2.94	
ka (/h)	0.356	0.0231	6.49	
D1	3.64	FIXED		
SWF1 (food)	0.380	0.0302	7.95	
SWF2 (formulation)	0.462	0.00337	7.29	
FD50	0.228	FIXED		
COVD	0.459	FIXED		
Stochastic Model (IIV and Residual Error)				
IIV CL	0.0548 (23.7%)	0.0335	61.2	18.9
IIV CL, V2	0.0943 (50.1%)	0.0761	80.7	
IIV V2	0.648 (95.5%)	0.334	51.6	11.0
IIV F1	0.265 (55.1%)	0.0987	37.3	4.08
Proportional error	0.553	0.0168	3.04	1.69

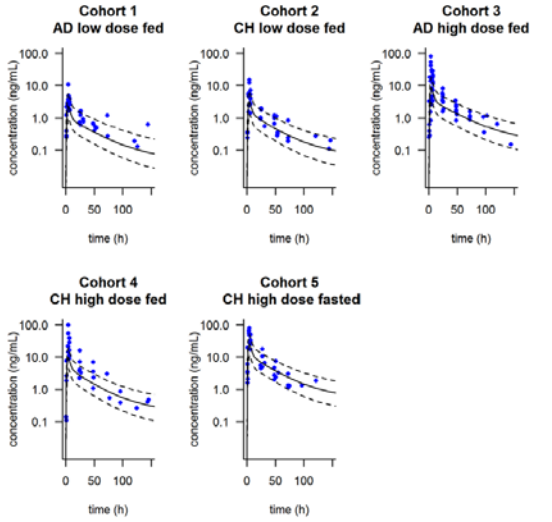
CL (clearance), V (volume of distribution), Q (intercompartmental clearance), ka (first order absorption rate constant), D1 (zero-order infusion duration), SWF1 (fasted/fed switch), SWF2 (tablet/suspension switch), FD50: absolute bioavailability for the dose of 50 mg of mirabegron; COVD: exponent for dose effect on bioavailability; IIV: interindividual variability

Source: ~ED178\YM178-Pediatrics\03_Phase 1 Studies\02_178CL201\PopPK\ 03_Formalanalysis\02_Final models\Model34

Internal validation of the model showed a good prediction of data when predicted v observed AUC were compared. The validation using visual predictive check showed bias in the absorption phase mostly for those patients receiving tablets.

Predictive capability of the model was evaluated by simulating the pharmacokinetic profiles of mirabegron in children following administration of tablets (Study 178-CL-202) under fasted and fed conditions and comparing the predictions with the observations from that study.

Figure 11 External Visual Predictive Check Results Using Interim Data From Study 178-CL-202



Blue symbols: observed data; solid black line: median simulated concentrations; dotted lines: 5th and 95th percentile of simulated data

Source: ED178\03_Phase 1 Studies\01b_178-CL-202\InterimPK\03_Formal analysis\03_Model evaluation\Eval_201_model

The model was further used to determine the single doses of the 2 mg/mL oral suspension under fed conditions in children that result in a similar exposure (AUC24h) to 50 mg tablets qd in adults at steady state (Study 178-CL-203).

The final dosing table for 178-CL-203 (2 mg/mL oral suspension) is shown below:

Weight Range (kg)	Suspension Volume, mL† (Dose, mg)
15-<20	40 (80)
20-<30	50 (100)
30-<40	55 (110)
≥40	65 (130)

† 2 mg/mL suspension

And finally the model was used to determine a weight cutoff after which 25 and 50 mg daily tablet doses under fed conditions in children at steady state results in a similar exposure (AUC24h) to adults at the same doses (Study 178-CL-206A). And based on the bioequivalent profiles of the 2 mg/mL and 8 mg/mL oral suspension, the dose of the last suspension that under fed conditions in children results in a similar exposure at steady state to the exposures (AUC24h) of 25 and 50 mg tablets qd in adults at steady state(Study 178-CL-206A) was predicted. Based on the simulations the following dosing table was proposed for 178-CL-206A (tablet and 8 mg/mL oral suspension).

PED	Weight Range (kg)	Tablet Dose (mg)	Suspension Volume, mL† (Dose, mg)
25	11 - < 22	--	3 (24)
	22 - < 35	--	4 (32)
	≥ 35	25	--‡
50	11 - < 22	--	6 (48)
	22 - < 35	--	8 (64)
	≥ 35	50	--‡

† 8 mg/mL suspension

‡ Patients ≥ 35 kg who cannot swallow tablets may take a suspension dose (6 mL for PED25 or 11 mL for PED50).

Assessor's comments:
A population pharmacokinetic model in adults has been presented. The model consists of a 3-compartment mamillary model with food, formulation, and dose as covariates on the bioavailability (F1) with an allometric scaling of disposition parameters on body weight. The internal validation of the model showed bias during the absorption phase. This bias was also seen when data for children were predicted. The model under predicted plasma concentrations of mirabegron in children and adolescents during the absorption phase when high doses were administered.
In spite of such bias the model was used to determine the dosing recommendations for studies 178-CL-203 (oral suspension) and 178-CL-206A (tablets and suspension) in children.

Conclusion
Issue solved

Question 2

Population pharmacokinetics was agreed with the PDCO to characterise the pharmacokinetic profile of mirabegron in children as well as the determination of AUC with individual prediction as a primary endpoint. This is not the case as only descriptive reporting of mirabegron pharmacokinetics is presented. The applicant states that population pharmacokinetic modelling is planned for future. The MAH is requested to provide clarifications in relation to the pharmacokinetic modelling planned for dose optimization and inform about phase 3 studies already initiated within the paediatric development plan, if it is the case, and the rational for the dosing in children and adolescents.

MAH Response

We confirm that the clinical study report for study 178-CL-203 does include the descriptive results of the non-compartmental analysis. However, the population pharmacokinetic model described in the above response (178-PK-204) was used to optimize dosing in subsequent paediatric studies. The model has been updated with data from studies 178-CL-202 and 178-CL-203 (178-PK-205). A key conclusion is that the individual estimates of exposure (AUCinf) based on the NCA assessment are similar to those derived from the population pharmacokinetic model. The population PK model will be further updated with the paediatric pharmacokinetic data from the currently ongoing study 178-CL-206, and will be used to increase the understanding of paediatric pharmacokinetics for mirabegron as well as further optimize paediatric dosing.

A summary of study 178-PK-205 is included below by the assessor:

The pharmacokinetic and demographic data from study 178-CL-201 was pooled with that from studies 178-CL-202 and 178-CL-203 in pediatric patients. In the final model including pediatric patients, D1 (the duration of the zero-order absorption model) was estimated rather than fixed. Interindividual variability terms for F1 and D1 were added to the OMEGA block; in the adult model, the variability on D1 had not been estimated. The final parameter estimates are presented in table 1 bellow:

Table 1 Population PK Parameters for the updated pediatric model

Fixed effects

Parameter (units)	Estimate	SE	RSE (%)
CL (L/h)	24.3	2.93	12.1
V2 (L)	181	116	64.1
Q3 (L/h)	10.4	4.72	45.4
V3 (L)	2240	1200	53.6
Q4 (L/h)	88.4	30.2	34.2
V4 (L)	970	138	14.2
ka (/h)	0.324	0.143	44.1
D1	3.47	0.174	5
SWF1 (food)	0.383	0.0299	7.8
SWF2 (formulation)	0.458	0.0318	6.9
FD50	0.228	FIXED	0
COVD	0.459	FIXED	0

Stochastic Model (IIV and Residual Error)

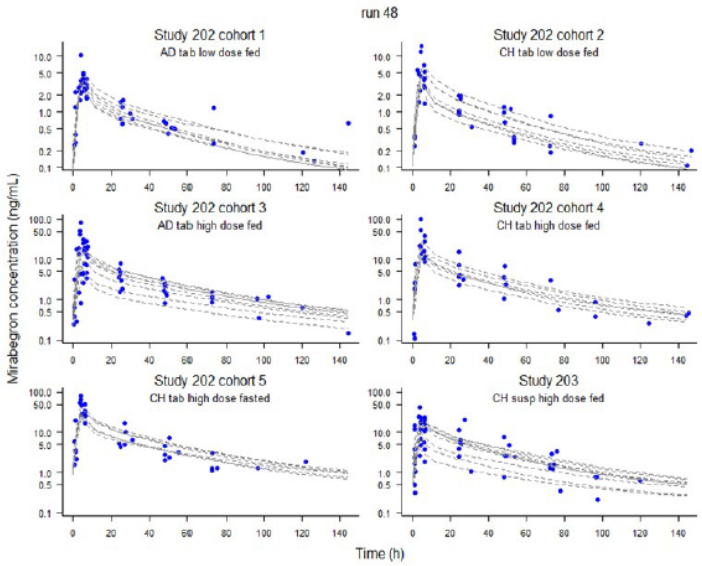
Parameter (units)	Estimate	SE	RSE (%)
SIGMA	0.552	0.0181	3.3

	1 CL	2 V2	3 F1	4 D1	Shrinkage
1 CL	0.125 (38.5%)				25.2%
2 V2	0.261 (50.6%)	0.867 (72.3%)			20.1%
3 F1	0.254 (32.4%)	0.631 (41.7%)	0.658 (23.9%)		13.7%
4 D1	0.0157 (130.6%)	0.0789 (71.5%)	0.0822 (57.7%)	0.0998 (26.4%)	33.9%

CL (clearance), V (volume of distribution), Q (intercompartmental clearance), ka (first order absorption rate constant), D1 (zero-order infusion duration), SWF1 (fasted/fed switch), SWF2 (tablet/suspension switch), FD50: absolute bioavailability for the dose of 50 mg of mirabegron; COVD: exponent for dose effect on bioavailability; IIV: interindividual variability

Individual predictions from the model for children a adolescents are depicted in figure 2 bellow:

Figure 2 Observed and individual predicted pediatric pharmacokinetic profiles by cohort

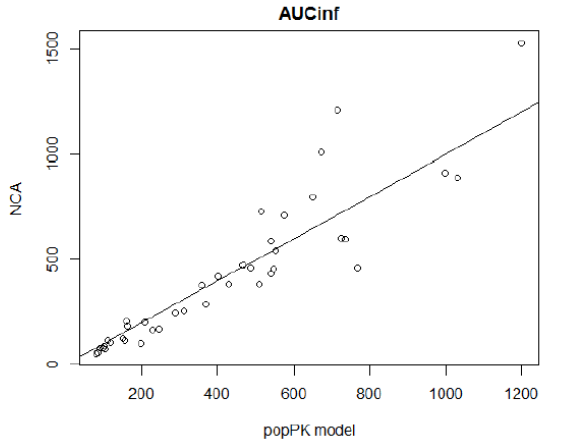


AD: adolescents, CH: children

Tab: OCAS tablet, susp: suspension (2 mg/mL)

A comparison of the AUCinf estimated from the population PK model and those calculated by noncompartmental model for studies 178-CL-202 and 178-CL-203 is represented in figure 3 bellow:

Figure 3 Comparison of AUC_{inf} estimates from the population PK model and NCA



Assessor's comments:
An update of the population pharmacokinetic model from study 178-CL-204 was presented. The new model pooled data from adults and children. The new model consisted of a 3-compartment mamillary model with food, formulation, and dose as covariates on the bioavailability (F1) with an allometric scaling of disposition parameters on body weight. In this model D1 (the duration of the zero-order absorption model) was estimated rather than fixed and interindividual variability terms for F1 and D1 were added to the OMEGA block. Although the model is claimed to predict the data with no bias, the assessor is concerned with this claim, since individual predictions in children does not seem to match with observations, especially for the cohorts receiving high doses. The values of AUCinf predicted with the model are lower than the values of AUC calculated directly from the observations by means of NCA. The applicant should consider how this under prediction of plasma concentrations and AUCinf would affect to the safety of any dosing schedules that are predicted based on the presented model.

Conclusion
Issue solved

6. Updated Rapporteur's overall conclusion and recommendation

With the responses submitted, all questions have now been resolved and this procedure could be considered finalized.

The presented information is consistent with the existing knowledge about the compound. There are no new or unexpected safety signals. The PK data is also in line with the expected profile. The limited available information regarding acceptability and palatability of the suspension prevent from reaching valid conclusions on this respect.

The approach of the MAH to optimized paediatric dosing using pharmacokinetic modelling and simulation is supported. Nevertheless, the MAH should keep in mind the limitations of the PK model for predicting individual parameters in children, in order to anticipate potential safety issues, especially for the cohorts receiving higher doses.

☒ Fulfilled:

No regulatory action required.