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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/P46/007

Note

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

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Abbreviation	Description
AUC_{24}	Area under the concentration-time curve at 24 h
AUC_{inf}	Area under the concentration-time curve to infinity
CL/F	Drug clearance
C_{max}	Maximum concentration of drug after administration
DBP	Diastolic blood pressure
NDO	Neurogenic detrusor overactivity
OAB	Overactive bladder
PCS	Potentially clinically significant
PIP	Paediatric Investigation Plan
popPK	Population-pharmacokinetic
SBP	Systolic blood pressure
t1/2	Half life
tmax	Time at which Cmax occurred
Vz/F	Volume of distribution

1. Introduction

On 15 March 2016, 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.

The MAH stated that Study 178-CL-202 is part of a clinical development program. The extension application consisting of the full relevant data package (i.e containing several studies) is expected to be submitted by 2024. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Mirabegron 25 and 50 mg prolonged-release tablets (authorized in adults) were used for Study 178-CL-202 in children and adolescents with a body weight of 20 kg or more. The doses administered in this study were predicted to result in exposure levels in the first 24 h after a single dose (AUC24) comparable to the steady-state exposure in adults following 25 mg for the low dose or 50 mg once daily for high dose; the target values were 69 ng•h/mL and 188 ng•h/mL, respectively. The study drug was administered as a single dose and assigned based on body weight.

Clinical aspects

2.2.1. Introduction

The MAH submitted a final report for Study 178-CL-202. This study is a part of paediatric clinical development program as detailed in agreed PIP's, as so-called Study 7, for the conditions "Treatment of idiopathic overactive bladder" (EMEA-000597-PIP02-10-M04), respectively "Treatment of neurogenic detrusor overactivity" (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.

2.2.2. Clinical study: Study 178-CL-202

A Multicentre, Open-label, Single Ascending Dose Phase 1 Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Mirabegron OCAS Tablets in Pediatric Subjects from 5 to Less than 18 Years of Age with Neurogenic Detrusor Overactivity (NDO) or Overactive Bladder (OAB) Single Ascending

Dose Study to Assess Pharmacokinetics of Mirabegron OCAS Tablets in Pediatric Subjects with NDO or OAB

Description

This study explored the pharmacokinetics, safety and tolerability of a low and a high dose of mirabegron prolonged-release tablets in children and adolescents.

Methods

Objectives

Primary: To evaluate the pharmacokinetics of mirabegron prolonged-release tablets after single-dose administration at different dose levels in children and adolescents with NDO or OAB.

Secondary: To evaluate the safety and tolerability of mirabegron prolonged-release tablets after single-dose administration at different dose levels in children and adolescents with NDO or OAB.

Study design

This was a multicenter, open-label, single-ascending-dose study in the pediatric NDO/OAB population. Centres from Belgium, Denmark, Norway and Poland participated in the study.

The following 5 cohorts of at least 6 subjects per cohort were planned and completed:

- Cohort 1: male and female adolescents (12 to less than 18 years); low dose (fed conditions)
- Cohort 2: male and female children (5 to less than 12 years); low dose (fed conditions)
- Cohort 3: male and female adolescents (12 to less than 18 years); high dose (fed conditions)
- Cohort 4: male and female children (5 to less than 12 years); high dose (fed conditions)
- Cohort 5: male and female children (5 to less than 12 years); high dose (fasted conditions)

Study population /Sample size

The study population consisted of male and female children (5 to less than 12 years of age) and adolescents (12 to less than 18 years of age) with NDO or OAB. The age of the subject upon signing the informed consent or assent form determined the age group.

Treatments

Mirabegron prolonged-release tablets, strengths 25 mg and 50 mg were administered orally with a glass of water. The doses tested were selected to be equivalent in exposure to efficacious doses in adults (25 and 50 mg once daily). The available adult exposure data were used to build a pharmacokinetic model; simulations were performed to predict the doses that result in the target exposures (69 and 188 ng·h/mL) following single doses in paediatric subjects.

Low: Cohort 1 (Adolescents) and Cohort 2 (Children)

- 20.0 to < 55.0 kg: 25 mg tablet
- ≥ 55.0 kg: 50 mg tablet

High: Cohort 3 (Adolescents), Cohorts 4 and 5 (Children)

- 20.0 to < 40.0 kg: 50 mg tablet
- ≥ 40.0 kg: 75 mg

The first 4 cohorts of this study were dosed under fed conditions (light breakfast and lunch). The fifth cohort (children) was dosed under fasted condition which was anticipated to result in about 2-fold higher exposure in these subjects.

Outcomes/endpoints

Pharmacokinetics

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

Safety

- AEs (nature, frequency, and severity)
- Clinical laboratory evaluations (hematology, biochemistry, and urinalysis)
- Vital signs (including 24-h Holter for heart rate)
- ECGs (including interval measurements)
- Physical examination
- Postvoid residual volume (PVR)

Statistical Methods

In general, all data were summarized with descriptive statistics for continuous endpoints, and frequency and percentage for categorical endpoints.

Population for Analysis

- 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.

The plasma concentration data were analyzed using a noncompartmental analysis. This analysis was used to derive the individual pharmacokinetic parameters.

A total of at least 30 subjects were expected to receive the study drug (5 treatment cohorts of 6 subjects each).

Results

Recruitment/ Number analysed

Subject Disposition

In total, 42 subjects signed the informed consent and 8 discontinued from the study before the first dose of study drug (7 subjects discontinued due to not fulfilling the inclusion/exclusion criteria and 1 subject decided not to continue in the study.

Thirty-four subjects (males and females) were allocated to treatment. All 34 subjects completed the study and were included in the SAF and PKAS.

Table 9 Demographics and Baseline Characteristics for Subjects, SAF

Parameter Category/ Statistic	Cohort 1 Adolescents Low Dose Fed (n = 7)	Cohort 2 Children Low Dose Fed (n = 7)	Cohort 3 Adolescents High Dose Fed (n = 8)	Cohort 4 Children High Dose Fed (n = 6)	Cohort 5 Children High Dose Fasted (n = 6)	Total (n = 34)
Sex, n (%)						
Male	2 (28.6)	2 (28.6)	2 (25.0)	2 (33.3)	3 (50.0)	11 (32.4)
Female	5 (71.4)	5 (71.4)	6 (75.0)	4 (66.7)	3 (50.0)	23 (67.6)
Race, n (%)						
White	7 (100.0)	7 (100.0)	8 (100.0)	6 (100.0)	6 (100.0)	34 (100.0)
Age, years						
n	7	7	8	6	6	34
Mean	14.9	8.1	14.1	8.2	9.3	11.1
(SD)	(1.6)	(0.9)	(1.6)	(0.8)	(0.8)	(3.2)
Median	15.0	8.0	14.5	8.0	9.5	10.0
Min-Max	13-17	7-9	12-16	7-9	8-10	7-17
Weight at Day 1 (Predose), kg						
n	7	7	8	6	6	34
Mean	50.99	31.19	55.34	26.65	31.30	40.16
(SD)	(7.49)	(5.43)	(14.00)	(4.79)	(5.32)	(14.50)
Median	50.20	31.70	53.25	25.35	30.30	36.30
Min-Max	43.0-66.6	21.0-37.8	36.9-80.0	22.0-35.7	25.1-41.0	21.0-80.0
Height at Screening, cm						
n	7	7	8	6	6	34
Mean	162.56	133.89	160.39	131.60	136.15	146.02
(SD)	(8.34)	(9.65)	(10.44)	(7.98)	(8.75)	(16.39)
Median	164.00	135.30	157.50	131.25	135.25	146.00
Min-Max	151.5-175.0	116.0-148.0	150.0-175.0	123.0-144.0	126.7-150.0	116.0-175.0
Diagnosis at Screening, n (%)						
NDO	2 (28.6)	2 (28.6)	3 (37.5)	2 (33.3)	2 (33.3)	11 (32.4)
OAB	5 (71.4)	5 (71.4)	5 (62.5)	4 (66.7)	4 (66.7)	23 (67.6)

For the indication OAB or NDO the majority of subjects received solifenacin and mirabegron at screening. Out of 4 subjects with OAB who received medication for this indication at screening, 3 subjects received solifenacin (1 adolescent in cohort 3 and 2 children [1 in cohort 4 and 1 in cohort 5]), and 1 child in cohort 2 received desmopressin and tolterodine.

Out of 10 subjects with NDO who received medication for this indication at screening, 9 received mirabegron (4 adolescents [2 in cohort 1 and 2 in cohort 3] and 5 children [2 in cohort 2, 2 in cohort 4 and 1 in cohort 5]), 2 children received solifenacin (1 in cohort 2 as addition to mirabegron and 1 in cohort 5 as monotherapy), and 1 adolescent received tamsulosin as addition to mirabegron in cohort 3.

Pharmacokinetic results

The pharmacokinetic data were analyzed using non-compartmental analysis.

Table 3 Summary of Plasma Pharmacokinetic Parameters of Mirabegron by Cohort, PKAS

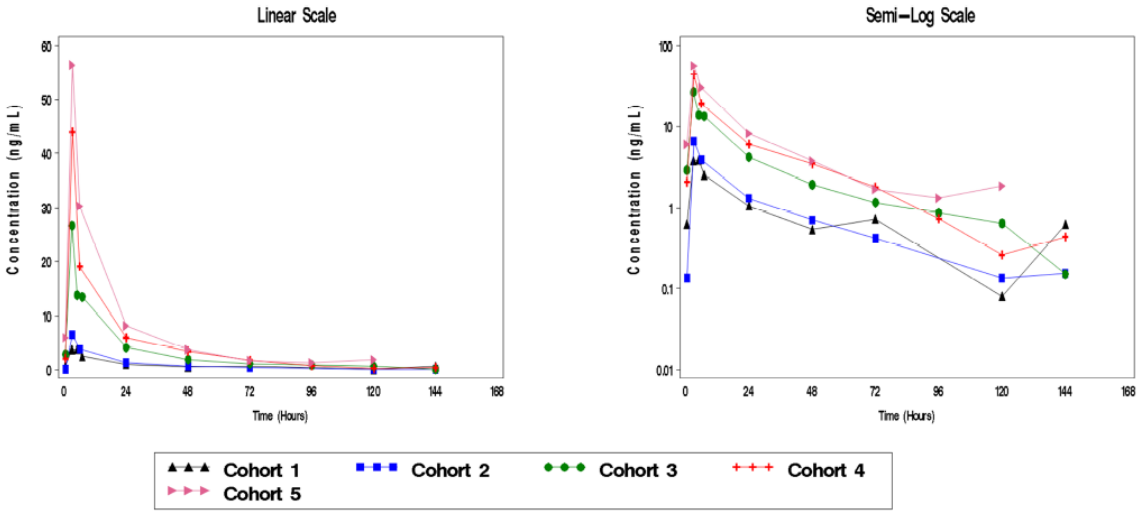
Parameter Statistics	Cohort 1 Adolescents Low Dose Fed (n = 7)	Cohort 2 Children Low Dose Fed (n = 7)	Cohort 3 Adolescents High Dose Fed (n = 8)	Cohort 4 Children High Dose Fed (n = 6)	Cohort 5 Children High Dose Fasted (n = 6)
AUC_{inf} (ng·h/mL)					
Mean (SD)	90.83 (25.56)	128.8 (65.48)	394.9 (205.5)	596.5 (385.5)	830.4 (384.8)
%CV	28.1	50.8	52.0	64.6	46.3
Median	89.44	103.7	420.1	417.9	745.2
Min-Max	56.4 - 116	53.1 - 204	124 - 713	245 - 1209	459 - 1526
N	5	7	8	5	6
C_{max} (ng/mL)					
Mean (SD)	4.730 (2.717)	6.909 (4.670)	31.98 (26.10)	43.99 (31.93)	56.42 (17.73)
%CV	57.4	67.6	81.6	72.6	31.4
Median	3.850	5.240	29.66	38.06	58.36
Min-Max	2.45 - 10.5	2.45 - 14.9	3.40 - 80.4	14.1 - 98.2	28.6 - 79.2
N	7	7	8	6	6
t_{max} (h)					
Mean (SD)	4.867 (0.6683)	4.534 (1.328)	4.995 (1.802)	4.227 (0.1909)	3.960 (0.2945)
%CV	13.7	29.3	36.1	4.5	7.4
Median	5.030	4.170	4.475	4.280	3.950
Min-Max	3.95 - 5.75	2.55 - 6.37	3.08 - 7.08	3.88 - 4.42	3.47 - 4.27
N	7	7	8	6	6
$t_{1/2}$ (h)					
Mean (SD)	27.16 (6.664)	30.76 (8.119)	29.20 (4.510)	28.97 (6.076)	26.16 (2.931)
%CV	24.5	26.4	15.4	21.0	11.2
Median	25.74	34.76	29.05	28.89	24.97
Min-Max	19.9 - 34.7	19.4 - 38.5	21.1 - 36.4	20.6 - 37.0	23.7 - 30.8
N	5	7	8	5	6
CL/F (L/h)					
Mean (SD)	339.1 (97.54)	248.7 (132.5)	230.1 (137.4)	113.0 (62.89)	79.08 (45.64)
%CV	28.8	53.3	59.7	55.7	57.7
Median	325.0	241.1	160.6	119.7	69.71
Min-Max	217 - 443	123 - 471	105 - 460	41.4 - 204	32.8 - 163
N	5	7	8	5	6
V_z/F (L)					
Mean (SD)	13063 (4569)	9959 (3639)	9918 (6702)	4895 (2921)	2866 (1438)
%CV	35.0	36.5	67.6	59.7	50.2
Median	12070	8705	6658	4603	2569
Min-Max	8894 - 20813	6156 - 15830	4401 - 21123	1227 - 8518	1455 - 5581
N	5	7	8	5	6
AUC_{24} (ng·h/mL)					
Mean (SD)	47.90 (14.24)	66.33 (31.66)	230.7 (132.5)	336.0 (225.4)	508.6 (190.2)
%CV	29.7	47.7	57.4	67.1	37.4
Median	49.03	53.63	254.0	247.1	474.2
Min-Max	31.8 - 66.3	26.8 - 116	50.0 - 423	159 - 743	272 - 831
N	7	7	8	6	6

The median AUCinf values in the low dose groups in children and adolescents (cohorts 1 and 2) were similar to each other; the same applies for the high dose groups (cohorts 3 and 4). Cmax was lower in adolescents than children. The median values of tmax and t1/2 appear to be relatively consistent across cohorts (4 to 5 h and 25 to 35 h, respectively). Compared to subjects in the fed high dose cohorts (3 and 4), subjects in cohort 5 had a higher exposure (AUC and Cmax) to mirabegron; however, this was expected as cohort 5 was under fasted conditions and the bioavailability of mirabegron is higher compared to fed.

The median values of CL/F and Vz/F were higher in adolescents than children within a dose group, which is expected due to the higher body weights in adolescents. The values of these 2 parameters were lower in the high dose compared to the low dose groups, and also lower in the fasted high dose cohort versus the fed, likely due to differences in bioavailability with dose and food.

The median AUC24 values in the fed low dose groups in both children and adolescents were similar and slightly lower than the exposure target of 69 ng·h/mL and for the fed high dose groups, the values were higher than the target of 188 ng·h/mL; however, the AUC24 values were within the range of the adult values at comparable doses.

Figure 1 Mean Plasma Concentrations of Mirabegron (Linear and Semi-log Scale Plot) by Cohort, PKAS



PKAS: pharmacokinetic analysis set
Cohort 1 = Adolescents low dose fed; Cohort 2 = Children low dose fed; Cohort 3 = Adolescents high dose fed; Cohort 4 = Children high dose fed; Cohort 5 = Children high dose fasted. Sampling times (Children, Cohorts 2, 4 and 5) for Mirabegron: 0.5-2h, 3-5h, 6-8h, 24-32h, and 2 of 48-56h, 72-80h, 96-104h, 120-128h, 144-152h. Sampling times (Adolescents, Cohorts 1 and 3) for Mirabegron: 0.5-2h, 3-4h, 5-6h, 7-8h, 24-32h, and 2 of 48-56h, 72-80h, 96-104h, 120-128h, 144-152h

Safety results

Four subjects developed a TEAE in 4 of 5 cohorts which was mild in intensity. Only 1 event, which was in a high-dose fed adolescent, was considered to be drug-related by the investigator. Across all cohorts, no SAEs were reported, no deaths occurred and none of the subjects discontinued the study due to an AE.

AEs of Special Interest

As per SAP, the following AEs were defined of special interest: increased blood pressure, increased heart rate (tachycardia), QT prolongation and hypersensitivity reactions. In addition, the following AEs were also considered of special interest: cardiac arrhythmia, cardiovascular AEs, urinary retention, hepatotoxicity, and nervous system (seizure, syncope).

Apart from QT prolongation, there were no other AEs of special interest reported. For 1 child in cohort 2 and 1 adolescent in cohort 3, ECG QT prolonged was reported as AE. The ECGs did not show clinically significant changes except for 1 of 2 reported AEs of QT prolongation with possible relationship with study drug.

Among 9 subjects with a mean QTcB > 450 ms, there was 1 single subject with OAB in cohort 2 receiving 25 mg dose for which the mean QTcB value was reported as a TEAE of ECG QT prolonged with no relationship with the study drug.

Analysis of QTc

- No QTcF increase > 60 ms compared to baseline was observed in any subject.
- A mean QTcF increase > 30 ms compared to baseline was observed in 1subject with OAB in cohort 5 receiving 50 mg. The ECG showed a mean increase of QTcF > 30 ms compared to baseline at 4 h postdose. This was accompanied of a mean increase of QTcB > 60 ms and a mean increase of pulse rate > 30 bpm. This was not considered by the Investigator as clinically significant and no TEAE was reported. No further information is available, supporting the Investigator's decision.
- Overall, no subjects had a mean QTcF > 480 ms.
- A mean QTcF > 450 ms was observed in 1 subject with OAB in cohort 4 receiving 50 mg who had 2 values of QTcF > 450 ms at screening and EoS. These abnormal values were not considered as clinically significant by the Investigator.

Overall there are no clinically relevant changes in ECG results.

Clinical Laboratory Evaluations

Overall, the collected values were within the reference ranges, across the cohorts for most subjects at all evaluated time points.

No clinically relevant changes were observed in the mean values per cohort of SBP or diastolic blood pressure (DBP) in cohorts 1 to 5. One patient in cohort 3 met the protocol-specified criteria for PCS for both SBP and DBP.

A numerical increase in mean heart rate per 24 h was seen in cohorts 4 and 5 (3.7 bpm and 7.1 bpm, respectively). There were no clinically relevant average heart rate changes relative to dosing time observed during the 24-h Holter measurements.

Table 15 PCS Vital Signs, SAF

Vital Sign	Criteria/n (%)	Cohort 1 Adolescents Low Dose Fed (n = 7)	Cohort 2 Children Low Dose Fed (n = 7)	Cohort 3 Adolescents High Dose Fed (n = 8)	Cohort 4 Children High Dose Fed (n = 6)	Cohort 5 Children High Dose Fasted (n = 6)
SBP (mmHg)	Above the 95th percentile† and ≥ 20 mmHg change from baseline‡	0	0	1 (12.5%)	0	0
DBP (mmHg)	Above the 95th percentile† and ≥ 15 mmHg change from baseline‡	0	0	1 (12.5%)	0	0
Pulse Rate (bpm)	Above the 95th percentile† and ≥ 15 bpm change from baseline‡	2 (28.6%)	1 (14.3%)	0	1 (16.7%)	3 (50%)

DBP: diastolic blood pressure; PCS: potentially clinically significant; SAF: safety analysis set; SBP: systolic blood pressure

† The method to compare values to 95% percentiles is described in the statistical analysis plan.

‡ Baseline is the last non-missing value prior to dosing.

Blood pressure and pulse were measured in triplicate at screening, day 1 predose and at 1 h, 2 h, 4 h, and 6 h after dosing just after electrocardiogram, on day 2 and at the end of study visit.

Subjects are presented in whom both of the above mentioned criteria per vital sign were met at any postdosing timepoint based on scheduled vital signs assessment.

No postdose post-voiding residual volumes exceeding the 20 mL threshold, as defined by the International Children's Continence Society, were noted.

Mirabegron tablets were accepted by the 14 children and 3 adolescents who completed the questionnaire; tablets were found easy to very easy to swallow and had neutral to really good taste.

2.2.3. Discussion on clinical aspects

The present PK study was conducted to update the pharmacokinetic model to predict the exposures in children and adolescents in order to select the doses for the paediatric studies. Exposure to mirabegron within the recommended dose range in adults was used as reference (steady state exposure following 25 mg dose and 50 mg dose were 69 ng•h/mL and 188 ng•h/mL, respectively).

Low and high single doses of mirabegron were administered to children and adolescents under fed or fasted conditions. The low dose provided similar PK exposure to that of reference in adults. Exposure achieved after receiving high level doses was higher than the targeted exposure, mainly when it was administered in fasted state. However, only one dose of the medicinal product has been given (the steady state was not reached) and without having a direct comparison between adults and children/adolescents exposure only limited conclusions can be reached.

There were no new or unexpected AEs reported with respect to the already known safety profile in adults. No relevant differences in AE rates were observed between doses or age subgroups. Among the AE of special interest followed during the study three cases of QT prolongation (1 of them with possible relationship with the study drug) were reported. A placebo arm would have provided additional data to properly qualify these findings. It is described in the SmPC and no clear dose relationship is observed. This adverse event will be monitored (AEs of special interest) in the paediatric clinical trials to be conducted.

3. CHMP'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. The submitted data does not introduce any information requiring change of the product information.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Active substance: mirabegron

Study title	Study number	Date of completion	Date of submission of final study report
A Preliminary 2-Week Oral Dose Toxicity Study of YM178 in Juvenile Rats	178-TX-054	10-05-2012	NA
A 13-Week Oral Dose Toxicity Study of YM178 in Juvenile Rats with a 4-Week Recovery Period	178-TX-055	28-02-2013	NA

Clinical studies

Product Name: Active substance: mirabegron

Study title	Study number	Date of completion	Date of submission of final study report
A Phase 1, Single Dose, 4-Period Crossover Study to Assess the Bioavailability of an Mirabegron Oral Suspension Relative to the Mirabegron Prolonged Release Tablet and to Assess the Effect of Food on the Pharmacokinetics of Mirabegron Oral uspension in Healthy Young Male and Female Subjects	178-CL-201	21-01-2015	NA
A multicentre, open-label, single ascending dose Phase 1 study to evaluate the pharmacokinetics, safety and tolerability of mirabegron OCAS tablets in pediatric subjects from 5 to less than 18 years of age with neurogenic detrusor overactivity (NDO) or overactive bladder (OAB	178-CL-202	21-09-2015	See enclosure
Double blind, randomised, multicentre, parallel group,placebo, active controlled (oxybutynin) sequential dose titration study to evaluate pharmacokinetics, safety and efficacy of mirabegron prolonged-release microgranula-based suspension in children from 5 to less than 18 years of age with overactive bladder	178-CL-204	NA	NA
Open label long-term safety study to evaluate safety and efficacy of mirabegron prolonged-release microgranula-based suspension in children from 5 to less than 18 years of age with overactive bladder.	178-CL-205	NA	NA
Open label, multicentre, baseline-controlled sequential dose titration study followed by a fixed dose observation period to evaluate harmacokinetics, efficacy and safety of mirabegron prolonged-release microgranula-based suspension in children from 6 months to less than 5 years of age with neurogenic detrusor overactivity.	178-CL-207	NA	NA

A Multicentre, Open-Label, Single Dose, Phase 1 Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Mirabegron Oral Suspension in Pediatric Subjects from 5 to Less than 12 Years of Age with Neurogenic Detrusor Overactivity (NDO) or Overactive Bladder (OAB)	178-CL-203	NA	NA
Open label, baseline controlled, multicentre, dose titration study followed by a fixed dose observation period to evaluate efficacy, safety and pharmacokinetics of mirabegron in children from 5 to less than 18 years of age with neurogenic detrusor overactivity on clean intermittent catheterization (CIC).	178-CL-206	NA	NA