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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/P46/011

Note

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



Status of this report and steps taken for the assessment				
Current step ¹	Description	Planned date	Actual Date	Need for discussion ²
<input type="checkbox"/>	Start of procedure	29 Apr 2024	29 Apr 2024	<input type="checkbox"/>
<input type="checkbox"/>	CHMP Rapporteur Assessment Report	03 Jun 2024	06 Jun 2024	<input type="checkbox"/>
<input type="checkbox"/>	CHMP members comments	17 Jun 2024	n/a	<input type="checkbox"/>
<input type="checkbox"/>	Updated CHMP Rapporteur Assessment Report	20 Jun 2024	n/a	<input type="checkbox"/>
<input checked="" type="checkbox"/>	CHMP adoption of conclusions:	27 Jun 2024	27 Jun 2024	<input type="checkbox"/>

Table of contents

1. Introduction	4
2. Scientific discussion	4
2.1. Information on the development program	4
2.2. Information on the pharmaceutical formulation used in the study.....	4
2.3. Clinical aspects	4
2.3.1. Introduction.....	4
2.3.2. Clinical study	4
2.3.3. Discussion on clinical aspects.....	13
3. CHMP's overall conclusion and recommendation.....	14
☒ Fulfilled:	14

1. Introduction

On 05/04/2024, the MAH submitted a completed paediatric study for Betmiga (mirabegron), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This study is part of paediatric clinical development program agreed with the EMA for the condition "Treatment of idiopathic overactive bladder" (OAB, EMEA-000597-PIP02-10-M10). A separate PIP has been agreed for the treatment of neurogenic detrusor overactivity.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the Study 178-CL-204 (*A Phase 3, Double blind, Randomized, Multicenter, Parallel Group, Placebo controlled Sequential Dose Titration Study to Evaluate Efficacy, Safety and Pharmacokinetics of Mirabegron in Pediatric Subjects from 5 to < 18 Years of Age with Overactive Bladder*) is part of a clinical development program.

Mirabegron is a selective human beta 3-AR agonist currently authorised for the Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

Mirabegron activation of beta 3-AR in the human bladder results in a relaxation of the detrusor smooth muscle during the fill-void cycle without interfering with the voiding contraction. Mirabegron is currently available as 25-mg and 50-mg tablets.

2.2. Information on the pharmaceutical formulation used in the study

The MAH has developed mirabegron granules (mirabegron for oral suspension) for the treatment of OAB and NDO as part of the pediatric development program. These granules form an oral suspension when reconstituted with water. Several formulations (A, B and C) have been developed. Formulation C was developed as the concentrated formulation, with a concentration of 8 mg/mL upon reconstitution with water.

The MAH supplied formulation C for the phase 3 efficacy, safety and pharmacokinetic study in pediatric participants with OAB (178-CL-204). Formulation C is the proposed formulation for commercialization. The 8 mg/mL mirabegron oral suspension of formulation C is intended for administration to pediatric patients with NDO or OAB weighing less than 35 kg and to patients weighing 35 kg or more who cannot swallow tablets.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for Study No. 178-CL-204.

2.3.2. Clinical study

Study No. 178-CL-204: A Phase 3, Double blind, Randomized, Multicenter, Parallel Group, Placebo controlled Sequential Dose Titration Study to Evaluate Efficacy, Safety and Pharmacokinetics of Mirabegron in Pediatric Subjects from 5 to < 18 Years of Age with Overactive Bladder.

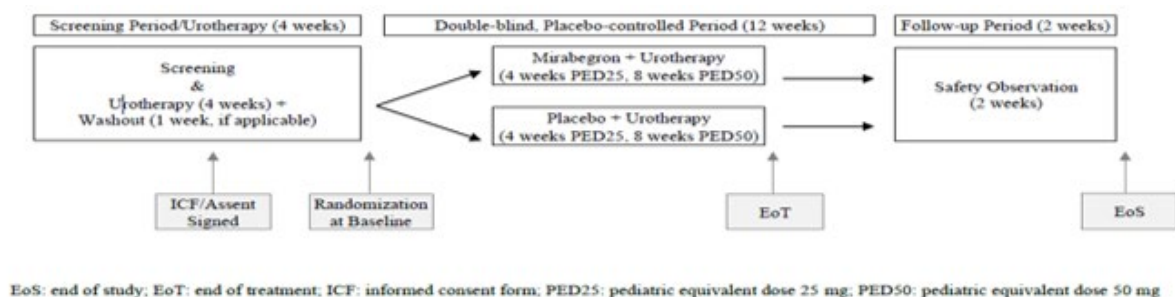
Description

This was a double-blind, randomized, multicenter, parallel group, placebo-controlled sequential dose titration study to evaluate efficacy, safety and PK of mirabegron in pediatric subjects with OAB.

The study consisted of 3 time periods with a total duration of 18 weeks:

- Screening period/urotherapy: for 4 weeks before baseline, and including screening, 4 weeks of urotherapy, washout (if applicable) and baseline. Subjects continuing urotherapy who still met the OAB entry criteria at baseline were randomized.
- Double-blind, placebo controlled period: beginning the day after baseline and continuing to week 12 (end of treatment).
- Follow-up period: safety observation beginning after week 12 and continuing to week 14 (end of study)

Figure 1 - Study Schema



Methods

Study participants

The key inclusion criteria were as follows:

- At visit 1/week -4 (Screening): Males or females between 5 to < 18 years of age with OAB defined according to the ICCS criteria
- At visit 3/week 0 (Baseline)
 - o Subject must have had a micturition frequency of at least 8 times (on average) per day, in the 7 days prior to visit 3/week 0 (baseline), as recorded in the bladder e-diary
 - o Subject must have had at least 1 daytime incontinence episode (on average) per day, during the 7-day period before visit 3/ week 0 (baseline), as recorded in the bladder e-diary

The key exclusion criteria were as follows:

- At visit 1/week -4 (Screening):
 - o Subject had extraordinary daytime only urinary frequency according to the ICCS definition
 - This applied to a toilet-trained child who had the frequent need to void that was associated with small micturition volumes solely during the day
 - The daytime voiding frequency was at least once per hour with an average voided volume of < 50% of EBC (typically 10% to 15%)
 - Incontinence was rare and nocturia was absent

- At visit 3/week 0 (Baseline):

- o Subject had extraordinary daytime only urinary frequency according to the ICCS definition based on the bladder e-diary
- o Subject had monosymptomatic enuresis confirmed by the bladder e-diary
- o Subject had a maximum voided volume (morning volume excluded) > EBC for age ($[\text{age} + 1] \times 30$) in mL, based on the bladder e-diary
- o Subject had polyuria defined as voided urine volumes of > 40 mL/kg baseline body weight during 24 hours or > 2.8 L urine for a child weighing ≥ 70 kg (ICCS definition) [Austin et al, 2014], based on bladder e-diary
- o Subject had PVR volume > 20 mL (lowest PVR volume result) as measured by ultrasonography

Treatments

Subjects were randomized to receive mirabegron in pediatric equivalent dose 25 mg (PED25) or placebo using a 1:1 ratio. Subjects with a body weight of ≥ 35 kg received the tablet unless unable to swallow tablets, in which case they received the oral suspension. Subjects with a body weight < 35 kg or those who could not be dosed with the tablet received an oral suspension.

At visit 5/week 4 (i.e., after 4 weeks on PED25), dose up-titration to PED50 was performed unless the investigator determined that the participant was adequately treated for OAB at the PED25 dose or if there were safety concerns identified and considered associated with the use of PED25.

Dose down titration from PED50 to PED25 could be performed at any time thereafter for safety reasons. Urotherapy was to continue throughout the study treatment period until visit 7/week 12 (EoT).

Participants who were receiving prohibited medication underwent a 1-week washout period while beginning 4 weeks of urotherapy.

Objective(s)

Primary

To evaluate the efficacy of mirabegron in children (5 to < 12 years of age) with OAB

Secondary

- To evaluate the efficacy of mirabegron in children (5 to < 12 years of age) with OAB
- To evaluate the safety and tolerability of mirabegron in pediatric subjects with OAB
- To evaluate the pharmacokinetics after multiple dose administration of mirabegron in pediatric subjects with OAB

Exploratory

To evaluate the efficacy of mirabegron in pediatric subjects (5 to < 18 years) with OAB

Outcomes/endpoints

Primary

Change from baseline at the end of the 12-week treatment period: Mean number of micturitions per 24 hours

Secondary

- Change from baseline at the end of the 12-week treatment period:
 - Mean volume voided per 24 hours
 - Maximum volume voided
 - Mean number of daytime incontinence episodes per 24 hours
 - Mean number of nighttime incontinence episodes per 24 hours
 - Mean number of daytime micturitions per 24 hours
- Number of dry (incontinence-free) days per 7 days at the end of the 12-week treatment period

Sample size

Approximately 368 children were planned to be enrolled in this study, to achieve 184 children (5 to < 12 years of age) randomized, including at least 92 children randomized to mirabegron; in addition, approximately 64 adolescents (12 to < 18 years of age) were planned to be enrolled to achieve at least 32 adolescents randomized, including at least 16 adolescents randomized to mirabegron.

Statistical Methods

Populations for Analysis

- All Screened Set consisted of all subjects for whom a valid informed consent/assent was available, as per applicable local law.
- All Randomized Set consisted of all randomized subjects, i.e., all those subjects with a randomization number.
- The FAS consisted of all subjects who were randomized and received at least 1 dose of IP and had at least 1 post baseline measurement for mean number of micturitions per 24 hours. The FAS was used for primary analyses of efficacy data, for sensitivity and subgroup analyses.
- The SAF consisted of all subjects who were randomized and who took at least 1 dose of IP. The SAF was used for summaries of demographic and baseline characteristics and all safety- and tolerability-related variables.
- The PKAS consisted of all subjects who took at least 1 dose of IP and contributed at least 1 pharmacokinetic sample in which the date and time of the sample and prior dose were known.

Primary Analysis

The primary estimator for the primary estimand was calculated according to the evaluation of the primary efficacy endpoint. The primary efficacy endpoint was analysed using an ANCOVA on the FAS. The ANCOVA model included treatment group, sex and geographical region as fixed effects and the mean number of micturitions per 24 hours at baseline as covariate. This analysis was performed with imputation of missing week 12 data using the LOCF method.

The ANCOVA model results were presented with LS means and 2-sided 90% CIs for mean changes from baseline within each treatment group. Differences in LS means between mirabegron versus placebo were derived and presented together with 2-sided 90% CIs. T-statistics corresponding to the Type III sums of squares for the differences in the LS means were used to obtain p-values for the comparisons. Model fitting was visually assessed. A scatter plot of residuals versus predicted values, along with histogram and normal probability plots, were produced.

As a general principle, no imputation of missing data for other variables was done. Exceptions were EoT values for certain safety variables (laboratory values, vital signs, ECGs and PVR volumes), the start and stop dates of AEs and concomitant treatments, and the diary time of the go to bed time on Sunday.

All statistical comparisons were conducted using 2-sided tests at the 10% significance level.

Results

Participant flow

This study was conducted at 25 centers that enrolled/randomized subjects in Europe, Latin America, South Africa, the Middle East, Asia-Pacific and North America.

The study ended early on 24 July 2023 (participants' last evaluation in the study) because of extremely low recruitment, partly due to the coronavirus disease 2019 pandemic, and study objectives were thus not achieved.

A total of 53 subjects aged 5 to < 18 years were screened and signed an informed consent form/assent, including 44 children and 9 adolescents. Of the screened children, 45.5% (20/44) were discontinued before randomization, and 52.3% (23/44) were randomized; screening disposition information was missing for one subject at the Ukraine site, and was not retrievable, due to the conflict in Ukraine. A total of 23 participants aged 5 to less than 12 years (children) received study drug and were included in the safety analysis set. Most of the randomized children completed the study treatment: 83.3% (10/12 participants) in the placebo group, and 81.8% (9/11 participants) in the mirabegron group and were included in the full analysis set.

Of the screened adolescents (aged 12 to less than 18 years), 66.7% (6/9) were discontinued before randomization and 33.3% (3/9) were randomized, including 1 adolescent who received placebo, and 2 who received mirabegron.

The quality management approach used in this study identified risks significant to subject safety and/or reliability of study results. A summary of important deviations from the QTLs and remedial actions taken is provided in Table 1.

Table 1 - Description of Important Quality Tolerance Limit Deviations and Remedial Actions

Quality Tolerance Limit	Observation Snapshot Date†	Deviation	Remedial Actions
Subject ePRO diary completion: Proportion (%) of randomized subjects who provide number of dry days and number of wet days for 7 days of ePRO diary data at week 4, week 8 and week 12 (QTL #3).	14 Feb 2023	<ul style="list-style-type: none"> Proportion observed: 30% Threshold: 25% 	PD forms were completed for subjects that met the compliance threshold related to ePRO diary entry for number of dry and number of wet days at weeks 4, 8 and 12. The team provided additional training for the study sites (slide deck) as well as including a cheat sheet for common eCOA issues/trends. Sites also received helpful tips/hints and reminders via study newsletters. The QTL decreased and no further action was needed.
	19 Jun 2023	<ul style="list-style-type: none"> Proportion observed: 27% Threshold: 25% 	No new observations made. The QTL decreased from 30% to 27% with remedial actions in place. No further action was needed.
Subject ePRO diary completion: Proportion (%) of randomized subjects with missing acceptability and palatability questionnaire at week 12 (QTL #4).	14 Feb 2023	<ul style="list-style-type: none"> Proportion observed: 29% Threshold: 25% 	PD forms were completed for subjects that did not complete the acceptability and palatability questionnaire at week 12. The team provided a cheat sheet for common eCOA issues/trends. Sites also received helpful tips/hints and reminders via study newsletters. The QTL decreased and no further action was needed.
	19 Jun 2023	<ul style="list-style-type: none"> Proportion observed: 26% Threshold: 25% 	No new observations made. The QTL decreased from 29% to 26% with remedial actions in place. No further action was needed.

Quality Tolerance Limit	Observation Snapshot Date†	Deviation	Remedial Actions
Pharmacokinetic sample results: Proportion (%) missing week 4 and week 12 PK sample results (QTL #5).	14 Feb 2023	<ul style="list-style-type: none"> Proportion observed: 17% Threshold: 12.5% 	The PK heparin sodium fluoride tubes were discontinued, and a replacement collection tube was identified. Ukraine sites received the discontinued collection tubes with short expiry date. This impacted multiple subjects who missed PK draws at weeks 4 and/or 12. A CAPA was implemented with the vendor and the issue did not occur thereafter.

CAPA: corrective action preventive action; eCOA: electronic clinical outcome assessment; PD: protocol deviation; PK: pharmacokinetic; QTL: quality tolerance limit.

† QTL with no observation on 19 June 2023 did not breach on that date

Baseline data

Among the children, the proportions of male and female subjects were rather balanced in the placebo group, with 41.7% (5/12) of male subjects and 58.3% (7/12) of female subjects, while most children were male in the mirabegron group: 81.8% (9/11) versus 18.2% (2/11) female subjects. There were no marked differences in the other baseline characteristics between both treatment groups, apart from the proportion of Asian children, which was higher in the placebo group (50.0% [6/12] of subjects) than in the mirabegron group (18.2% [2/11] of subjects).

Two of the three adolescents were female; one was White and the other one was Asian. The male participant was Asian.

Medical history at baseline was noted in 58.3% (7/12) of children on placebo and in 18.2% (2/11) of children on mirabegron. In the placebo group, 16.7% (2/12) of children had a UTI and/or vesicoureteric reflux; all other medical conditions were each noted in 8.3% (1/12) of children. In the mirabegron group, seasonal allergy and UTI were each reported in 9.1% (1/11) of children; there were no other medical conditions reported at baseline.

A total of 75.0% (9/12) of children on placebo, and 54.5% (6/11) of children on mirabegron had received at least 1 previous therapy. Apart from "analgesics", which were taken by 25.0% (3/12)

children on placebo (none for children on mirabegron) and “ascorbic acid (Vitamin C), plain” taken by 25.0% (3/12) children on placebo and 9.1% (1/11) children on mirabegron, all the other previous therapies were taken at low frequencies; of note, the frequency of drugs for urinary frequency and incontinence was reported in 16.7% (2/12) of children on placebo and 18.2% (2/11) of children on mirabegron.

A total of 66.7% (8/12) of children on placebo and 36.4% (4/11) of children on mirabegron received at least 1 concomitant therapy; frequency of each concomitant treatment was low, apart from ascorbic acid alone or combined with vitamins and/or zinc (33.3% [4/12] in children on placebo and 18.2% [2/11] in children on mirabegron).

The mean (SD) duration of exposure to study drug, from baseline to week 12, was 70.6 (30.9) days in the children receiving placebo and 70.8 (31.1) days in the children receiving mirabegron, irrespective of the formulation.

Three children in each treatment group received tablets, whereas 9 children in the placebo group and 8 children in the mirabegron group received an oral suspension. For the 2 adolescents who received mirabegron, the mean (SD) duration of exposure to study drug was 82.5 (0.7) days.

All participants started at PED25. The protocol-specified dose increase to PED50 by week 4 occurred in all but 4 children. There were no dose increases or decreases from week 4 onwards. The mean (SD) treatment compliance for tablets was 71.14% (37.89%) for the 3 children on placebo and 56.29% (39.10%) for the 3 children on mirabegron. The mean (SD) treatment compliance for oral suspension was 79.64% (36.60%) for the 9 children on placebo and 94.86% (8.84%) for the 8 children on mirabegron.

Efficacy results

Primary Efficacy Endpoint: Change from Baseline at the End of the 12-Week Treatment Period in Mean Number of Micturitions per 24 Hours

The primary efficacy endpoint was assessed in children only (male and female subjects with OAB, aged 5 to <12 years).

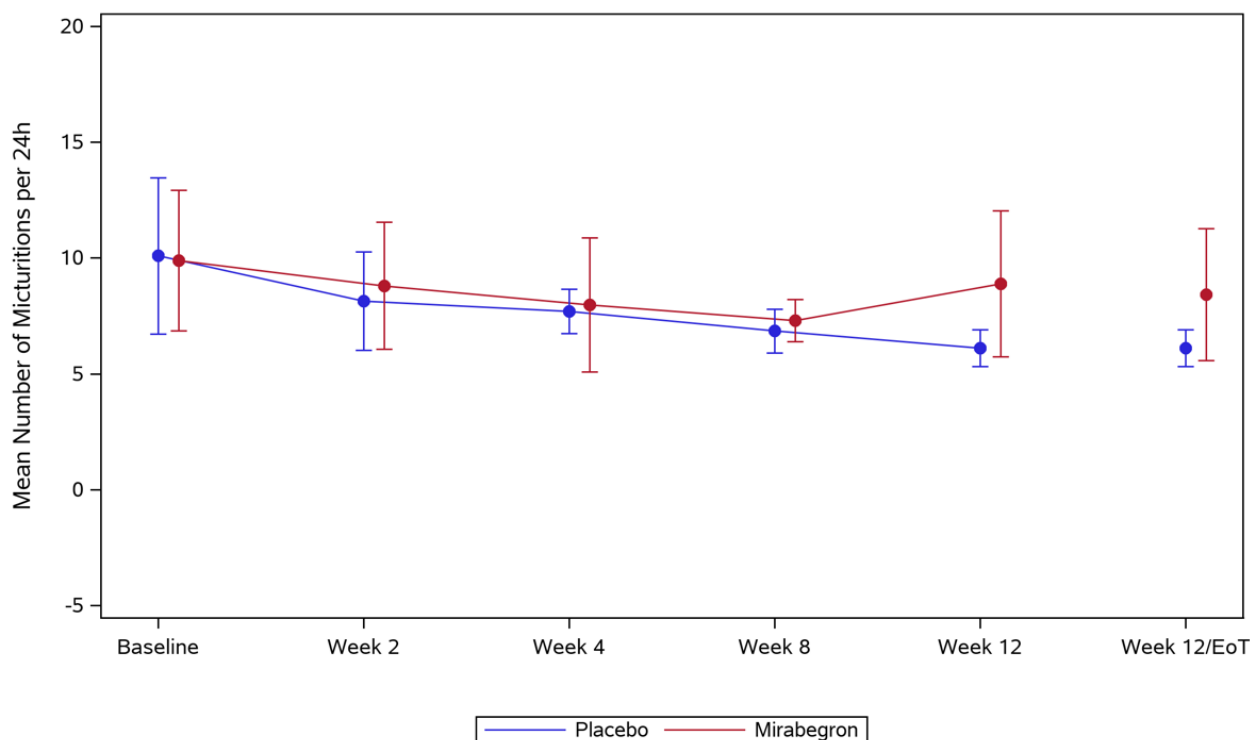
Table 2 - Change from Baseline to End of Treatment in Mean Number of Micturitions per 24 hours – Children Aged 5 to Less Than 12 Years (Full Analysis Set)

		Placebo (N=10)	Mirabegron (N=9)
Value at time point			
Baseline	n	9	9
	Mean (SD)	10.10 (5.45)	9.90 (4.90)
	Median (min, max)	8.57 (4.6, 23.0)	8.33 (5.3, 21.7)
Week 12	n	10	9
	Mean (SD)	6.11 (1.20)	8.42 (4.61)
	Median (min, max)	6.07 (4.5, 8.3)	6.57 (4.7, 19.6)
Change from baseline to week 12			
n		9	9
Mean (SD)		-3.98 (4.50)	-1.48 (2.78)
Median (min, max)		-2.29 (-14.7, 0.4)	-1.86 (-6.2, 2.7)
Adjusted change from baseline to week 12			
LS mean (SEM)		-3.84 (0.89)	-1.62 (0.89)
90% 2-sided CI		(-5.41, -2.26)	(-3.19, -0.05)
Difference in adjusted change from baseline to week 12			
LS mean (SEM)		2.22 (1.34)	
90% 2-sided CI		(-0.15, 4.59)	
2-sided p-value †		0.121	

Note: Statistics were based on participants in the FAS who had a non-missing result at baseline and at least one post-baseline time point during the treatment period for that endpoint. Analysis of Covariance was performed with change from baseline at week 12 LOCF as response, treatment group, sex and geographical region as fixed effects

and the mean number of micturitions per 24 hours at baseline as covariate.
CI: confidence interval; FAS: full analysis set; LOCF: last observation carried forward, LS: least squares; max: maximum, min: minimum; SEM: standard error of mean.
† p-value is for treatment comparison with placebo from the above-described model

Figure 2 - Mean ($\pm 90\%$ CI) Number of Micturitions per 24 hours by Study Week – Children Aged 5 to Less Than 12 Years (Full Analysis Set)



CI: confidence interval

Table 3 - Change from Baseline to End of Treatment in Secondary endpoints – Children Aged 5 to Less Than 12 Years (Full Analysis Set)

	Placebo (n=10)	Mirabegron (n=9)
Mean Volume Voided (mL)/ 24 h		
Baseline (mean [SD])	109.34 (48.18)	104.29 (60.22)
Wk 12 LOCF (Change from Baseline) (mean [SD])	24.55 (32.32)	18.38 (33.67)
Maximum Volume Voided (mL)		
Baseline (mean [SD])	199.38 (64.06)	162.63 (70.23)
Wk 12 LOCF (Change from Baseline) (mean [SD])	26.38(60.75)	26.00 (51.46)
Mean Number of Daytime Incontinence Episode/24 h		
Baseline (mean [SD])	2.75 (2.26)	2.04 (1.58)
Wk 12 LOCF (Change from Baseline) (mean [SD])	- 1.09 (1.74)	- 1.20 (1.02)
Mean Number of Daytime Micturitions/24h		
Baseline (mean [SD])	8.63 (7.18)	8.32 (3.55)
Wk 12 LOCF (Change from Baseline) (mean [SD])	- 3.21 (6.27)	- 0.85 (2.67)
Number of Dry (Incontinence Free) Days/7 Days		
Baseline (mean [SD])	0.49 (0.78)	0.44 (0.97)
Wk 12 LOCF (Change from Baseline) (mean [SD])	1.46 (2.18)	2.94 (3.47)
Mean Number of Nighttime Incontinence Episodes/24h		
Baseline (mean [SD])	2.24 (2.10)	1.27 (1.10)
Wk 12 LOCF (Change from Baseline) (mean [SD])	- 1.34 (1.51)	- 0.64 (0.55)

Pharmacokinetics

In children on mirabegron, the geometric mean of plasma trough concentrations increased from week 4 (3.03 ng/mL; n = 7) to week 12 (6.39 ng/mL; n = 8). In adolescents on mirabegron (n = 1), the plasma trough concentrations were below the lower limit of quantification and were excluded from summary statistics.

Safety results

In **children (participants aged 5 to less than 12 years)**, 19 TEAEs were reported in 58.3% (7/12) of children on placebo, and 8 TEAEs were reported in 45.5% (5/11) of children on mirabegron Table 4. TEAEs were considered by the investigator as related to study drug in 8.3% (1/12) of children on placebo (1 event) and in 9.1% (1/11) of children on mirabegron (2 events). There were no serious TEAEs, TEAEs leading to permanent study drug discontinuation or death during the entire study period.

Table 4 - Overview of Treatment-emergent Adverse Events and Deaths – Children Aged 5 to 12 Years (Safety Analysis Set)

	Placebo (N=12) n (%) #E	Mirabegron (N=11) n (%) #E
TEAE	7 (58.3) 19	5 (45.5) 8
Drug-Related † TEAE	1 (8.3) 1	1 (9.1) 2
Serious TEAE ‡	0 0	0 0
Drug-Related † Serious TEAE ‡	0 0	0 0
TEAE Leading to Permanent Discontinuation	0 0	0 0
Drug-Related † TEAE Leading to Permanent Discontinuation	0 0	0 0
Death §	0 0	0 0

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Number of participants (n), percentage of participants (%) and number of events (#E) are shown.

If a relationship was missing, then it was considered as drug-related.

TEAE: treatment emergent adverse event.

† A reasonable possibility that the event could have been caused by the study drug as assessed by the investigator.

‡ Included SAEs upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms or the important medical event process, if any upgrade was done.

§ All reported deaths after the first study drug administration.

The most commonly reported TEAEs (in more than 1 participant) were nasopharyngitis in 8.3% (1/12) of children on placebo and 18.2% (2/11) of children on mirabegron, and upper respiratory tract infection in 16.7% (2/12) of children on placebo and 9.1% (1/11) of children on mirabegron. All other TEAEs were reported in 1 participant only, including an event of ECG QT prolonged; this event was mild and not considered as related to study drug, and dose was not changed.

Study drug-related TEAEs included dry mouth in 1 child on placebo, and fatigue and mood swings in one child on mirabegron.

All TEAEs reported in children were of mild severity.

As regards TEAEs of special interest, a mild event of dermatitis considered by the investigator as not related to study drug was reported in a child on placebo; a mild event of ECG QT prolonged (18 ms increase from screening visit) considered by the investigator as not related to study drug and a mild event of headache considered as not related to study drug, were each reported in 1 child on mirabegron.

There were no clinically meaningful findings reported in children's clinical laboratory values, ECGs, and physical examinations in either treatment group. Regarding vital signs, 2 participants had single value measurements of slightly elevated blood pressure that were not confirmed by any subsequent measurements.

In **adolescents (participants aged 12 to less than 18 years [n = 3])**, 2 TEAEs were reported in the participant on placebo, and 3 TEAEs were reported in 1 of the 2 participants on mirabegron; no TEAEs were reported in more than 1 participant. TEAEs considered to be related to study drug by the investigator included only 1 serious event of ECG QT prolonged (an increase of 7 ms from screening visit), mild in severity, in the participant on placebo which led to permanent study drug discontinuation in that participant. A serious TEAE of severe diffuse axonal injury considered as not related to study drug and leading to permanent study drug discontinuation was reported in 1 of the 2 adolescents on mirabegron.

All TEAEs but one (severe diffuse axonal injury in 1 of the 2 participants on mirabegron) were mild in severity.

TEAEs of special interest were reported for the participant on placebo and included a mild headache considered by the investigator as not related to study drug and the event described above of mild ECG QT prolonged; an abnormal clinically significant ECG was also reported in that participant.

There were no clinically meaningful findings reported in the 3 adolescents' vital signs and physical examinations. Abnormal findings in clinical laboratory values were limited to a potentially clinically significant liver enzyme elevation (aspartate aminotransferase > 5 × upper limit of normal) in a participant on mirabegron; this liver enzyme elevation was not reported as an adverse event by the investigator and was only discovered upon statistical review after the study had ended.

2.3.3. Discussion on clinical aspects

Betmiga (mirabegron) is a beta 3-AR agonist authorised for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. It is currently available as 25-mg and 50-mg tablets. The MAH has developed mirabegron granules (mirabegron for oral suspension) for the pediatric development program.

The MAH is submitting a final report for Study 178-CL-204. This study is part of paediatric clinical development program agreed with the EMA for the condition "Treatment of idiopathic overactive bladder" (OAB, EMEA-000597-PIP02-10-M10). A separate PIP has been agreed for the treatment of neurogenic detrusor overactivity.

Study 178-CL-204 was a Phase 3 study aimed to evaluate the efficacy and safety of mirabegron in pediatric subjects from 5 to less than 18 years of age with overactive bladder. It followed a double blind, randomized, multicenter, parallel group, placebo controlled sequential dose titration design.

Patients received an initial dose of mirabegron based on the subject's body weight and predicted to achieve PED25 (pediatric equivalent dose to 25 mg in adults). After 4 weeks of treatment, dose up-titration to PED50 was performed. These doses are also administered in studies conducted in pediatric patients with NDO. In principle, children weighing less than 35 kg received oral suspension and patients weighing 35 kg or more received tablets (unless they cannot swallow).

Efficacy was based on the evaluation of main symptoms of the condition (number of micturitions per day, volume voided per 24 hours, number of incontinence episodes, number of dry days based on e-diary records) after 12 weeks of treatment.

The study was originally planned to enrol 184 children (5 to < 12 years of age) and 32 adolescents randomized. Due to extremely low recruitment, the study ended early on 24 July 2023 having included 23 children aged 5 to less than 12 years and 3 adolescents. Reasons given by the MAH refer to recruitment challenges (due to availability of other treatment options), concerns regarding inclusion in

the placebo arm and the coronavirus disease 2019 pandemic and the crisis in the Ukraine. Under these conditions study objectives were not achieved.

The majority of the children included were females (58.3%) and White (56.5%). The mean age was 8 years. The mean exposure to study drug was 70.6 (30.9) days in the children receiving placebo and 70.8 (31.1) days in the children receiving mirabegron. The compliance was lower for tablets (71.14% for placebo, 56.29% for mirabegron) than for oral suspension (79.64% for placebo, 94.86% for mirabegron).

At baseline children the mean number of daily micturitions was 10.10 in the placebo group and 9.90 in mirabegron group. After 12 weeks of treatment the adjusted LS mean (SEM) change from baseline in the frequency of micturition events per 24 hours was -3.84 (0.89) in children on placebo and -1.62 (0.89) in children on mirabegron. This difference between treatment groups was not statistically significant: 2.22 (1.34) (90% CI: -0.15, 4.59; P = 0.121). The fact that the result did not favour mirabegron was also observed in some secondary endpoints. Given the reduced number of studied subjects, the observed results are considered inconclusive.

PK parameters calculation was not possible due to the small number of samples collected due to the early termination of the study.

Regarding safety and taking into account the limited exposure, there were no new or unexpected AEs reported with respect to the already known safety profile in adults. Among the AE of special interest followed during the study two cases of QT prolongation (1 in a child on mirabegron and 1 in an adolescent with possible relationship with the study drug) and one case of diffuse axonal injury in one adolescent, and considered as not related to the study drug were reported..

As a consequence of the unsuccessful termination of this study and the unfeasibility of conducting a new study to provide the pharmacokinetic, efficacy and safety data of mirabegron in children with OAB the PDCO recommended to grant a product-specific waiver on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

3. CHMP's overall conclusion and recommendation

The MAH has submitted the final Study 178-CL-204. This study is part of paediatric clinical development program agreed with the EMA for the treatment of idiopathic overactive bladder. Due to early termination and low recruitment, the provided results are considered inconclusive. The safety profile of mirabegron in studied population does not show relevant differences with respect to that reported in adults.

According to paediatric legislation, a short description of the study as well as the safety results should be included in the SmPC in a further variation application. The MAH has committed to submitting a future variation application including an update of the Product Information Section 4.8 Undesirable effects and Section 5.1 Pharmacodynamic properties. Since a line extension for the granules for oral suspension and Type II variation affecting the Product Information are currently ongoing (EMA/H/C/2388/X/39), the MAH will submit the variation for Study 178-CL-204 within 6 months.

☒ **Fulfilled:**

No regulatory action required.