17 July 2025
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Betmiga

International non-proprietary name: Mirabegron

Procedure No. EMA/VR/0000249016

Note

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

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The CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion [2]**
☐	Submission deadline	21 March 2025	4 February 2025	☐
☐	Validation	6 April 2025	1 April 2025	☐
☐	Start date	7 April 2025	7 April 2025	☐
☐	CHMP Rapporteur AR	12 May 2025	12 May 2025	☐
☐	CHMP Comments	26 May 2025	n/a	☐
☐	Updated CHMP Rapporteur AR	28 May 2025	n/a	☐
☐	Start of CHMP written procedure	3 June 2025	3 June 2025	☐
☐	Request for supplementary information	5 June 2025	5 June 2025	☐
☐	Submission deadline	17 June 2025	17 June 2025	☐
☐	Start date	18 June 2025	18 June 2025	☐
☐	CHMP Rapporteur AR	02 July 2025	4 July 2025	☐
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☐	Start of CHMP written procedure	15 July 2026	15 July 2026	☐
☒	Opinion	17 July 2025	17 July 2025	☐

Procedure resources	
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Table of contents

1. Background information on the procedure 5

2. Overall conclusion and impact on the benefit/risk balance 5

3. Recommendations 6

4. EPAR changes 6

Annex: Rapporteur's assessment comments on the type II variation 7

5. Introduction 7

6. Non-clinical aspects 7

6.1. Introduction 7

6.2. Discussion on non-clinical aspects 8

6.3. Conclusion on non-clinical aspects 8

7. Clinical Pharmacology aspects 8

7.1. Methods – analysis of data submitted 8

7.2. Results 9

7.3. Discussion 9

8. Clinical Efficacy aspects 9

8.1. Methods – analysis of data submitted 9

8.2. Results 11

8.3. Discussion 13

9. Clinical Safety aspects 14

9.1. Methods – analysis of data submitted 14

9.2. Results 15

9.3. Discussion 16

10. PRAC advice 17

11. Changes to the Product Information 17

12. Request for supplementary information 17

12.1. Major objections 17

12.2. Other concerns 18

13. Assessment of the responses to the request for supplementary information 18

13.1. Major objections 18

13.2. Other concerns 19

14. Attachments 19

List of abbreviations

AE	adverse event
CI	confidence interval
COVID-19	coronavirus disease 2019
ECG	electrocardiogram
EoT	end of treatment
FAS	full analysis set
ICCS	International Children's Continence Society
LOCF	last observation carried forward
LS	least squares
NDO	neurogenic detrusor overactivity
OAB	overactive bladder
PED25	pediatric equivalent dose 25 mg
PED50	pediatric equivalent dose 50 mg
PIP	Pediatric Investigation Plan
PI	product information
PK	pharmacokinetics
PKAS	pharmacokinetics analysis set
PVR	post-void residual volume
SAE	serious adverse event
SAF	safety analysis set
SEM	standard error of the mean
TEAE	treatment-emergent adverse event

1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Astellas Pharma Europe B.V. submitted to the European Medicines Agency on 04 February 2025 an application for group of variations.

The following changes were proposed:

Variation(s) requested		Type
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

A grouped application consisting of: C.I.4: Update of sections 4.8, and 5.1 of the SmPC in order to update clinical information on Overactive bladder in the paediatric population based on final results from study 178-CL-204 listed as a category 3 study in the RMP; this is 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. In addition, the MAH took the opportunity to bring editorial changes to the PI. C.I.4: Update of section 5.3 of the SmPC in order to update non-clinical information based on results from previously submitted studies.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet

2. Overall conclusion and impact on the benefit/risk balance

On 04 February 2025, the MAH submitted to the European Medicines Agency (EMA) a group of variations consisting of updating sections 4.8 and 5.1 of the SmPC in order to include the clinical information on Overactive bladder in the paediatric population based on final results from study 178-CL-204, and updating section 5.3 of the SmPC to include non-clinical information based on results from previously submitted studies.

In addition, the MAH took the opportunity to bring editorial changes to the PI.

This Study (178-CL-204) was part of paediatric clinical development program agreed with the EMA for the treatment of idiopathic overactive bladder. According to paediatric legislation, a short description of the study as well as the safety results is proposed to be included in the SmPC in a current variation application.

Regarding efficacy results, given the reduced number of studies subjects due to early termination by low recruitment, the provided results are considered inconclusive.

With respect to safety profile of mirabegron in studied population does not show relevant differences with respect to that reported in adults.

A brief summary of the results is proposed to be inserted in the SmPC and considered acceptable. Please refer to the Attachment 1.

The benefit-risk balance of Betmiga remains positive

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		Type
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

A grouped application consisting of: C.I.4: Update of sections 4.8, and 5.1 of the SmPC in order to update clinical information on Overactive bladder in the paediatric population based on final results from study 178-CL-204 listed as a category 3 study in the RMP; this is 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. In addition, the MAH took the opportunity to bring editorial changes to the PI. C.I.4: Update of section 5.3 of the SmPC in order to update non-clinical information based on results from previously submitted studies.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion Betmiga EMA/VR/0000249016

For more information, please refer also to the Summary of Product Characteristics.

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

Betmiga is currently available as 25 mg and 50 mg prolonged-release tablets and also as 8 mg/mL granules for prolonged-release oral suspension.

Betmiga (mirabegron, 25 mg and 50 mg prolonged-release tablets) is currently approved in the EU for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with OAB syndrome (EMEA/H/C/002388, approved 20 Dec 2012) and for the treatment of NDO in pediatric patients aged 3 to less than 18 years (EMEA/H/C/002388/X/0039/G, approved 22 Aug 2024).

Betmiga (mirabegron 8 mg/mL granules for prolonged-release oral suspension) is currently approved in the EU for the treatment of NDO in pediatric patients aged 3 to less than 18 years (EMEA/H/C/002388/X/0039/G, approved 22 Aug 2024).

This addendum to the Clinical Overview is provided to include data from pediatric Study 178-CL-204 in the veractive bladder (OAB) condition, which terminated early due to extremely low recruitment.

The clinical development program of Betmiga includes studies in both NDO and OAB in the paediatric population. Study 178-CL-204 was planned according to a PIP (las modification EMEA-000597-PIP02-10-M10) but finally a full waiver was granted by the PDCO for the condition OAB based on lack of significant therapeutic benefit as clinical studies were not feasible. The study was designed as a placebo controlled trial with a targeted sample size of 196 patients but recruitment difficulties would made impossible to complete the recruitment in a reasonable period of time. Extrapolation of efficacy and safety from adults was also considered not possible for this indication by the PDCO and the CHMP SA. The decision was finally to prematurely close the study.

A short description of the study as well as the safety results is to be included in the SmPC. Therefore, the applicant, based on the efficacy and safety data of the Study 178-CL-204, proposes to update Sections 4.8, and Section 5.1 of the SmPC. Further minor correction were also performed in section 4.2.

In addition, the MAH took the opportunity to bring editorial changes to the PI and to update section 5.3 of the SmPC with non-clinical information based on results from previously submitted studies.

6. Non-clinical aspects

6.1. Introduction

The purpose of this application is to update the current SmPC non-clinical section (5.3 Preclinical safety data) to include data from previously submitted non-clinical studies.

All relevant nonclinical reports and summaries of nonclinical information for mirabegron (including nonclinical data generated to support paediatric development) have been previously reviewed as part of the initial BETMIGA MAA and subsequent variations. A summary of the findings in the juvenile toxicity studies (2-week DRF and 13-week pivotal) that support the proposed update to the SmPC section 5.3 is provided as an addendum to the Nonclinical Overview.

6.2. Discussion on non-clinical aspects

No new non-clinical studies have been submitted. Therefore, all the newly added information in section 5.3 of the SmPC within this procedure is taken from the previous non-clinical studies.

6.3. Conclusion on non-clinical aspects

SmPC section 5.3 should be updated as suggested (please refer to Attachment 1).

7. Clinical Pharmacology aspects

Betmiga (mirabegron) is a selective human beta-3 adrenoceptor agonist. Mirabegron activation of beta 3AR in the human bladder results in a relaxation of the detrusor smooth muscle during the fill-void cycle without interfering with the voiding contraction.

The clinical pharmacology of mirabegron, a beta-3 adrenoceptor agonist, is well characterized. Reference is made to the information on clinical pharmacology submitted as part of the existing marketing authorization application for 25 mg and 50 mg Betmiga prolonged-release tablets and granules for prolonged-release oral suspension, 8 mg/mL (EMEA/H/C/002388/X/0039/G).

A population pharmacokinetic model with food, formulation and dose as covariates on bioavailability, and body weight on clearance and volume terms, was constructed on adult data (Study 178-CL-201) and validated on pediatric data (Study 178-CL-202 in NDO or OAB paediatric patients). Weight-based dosing in the clinical studies was based on simulations from the model to result in target exposure levels comparable to the steady-state exposure in adults following the approved doses of 25 and 50 mg mirabegron prolonged-release tablets once daily, i.e., 69 ng·h/mL and 188 ng·h/mL, respectively. The selected doses accounted for the difference in bioavailability between the oral suspension and prolonged-release tablets and were based upon administration in the fed state.

7.1. Methods – analysis of data submitted

Study 178-CL-204 is a phase 3, 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 (defined according to the International Children's Continence Society criteria). Subjects were to receive 4 weeks of urotherapy prior to randomization.

One of the secondary objectives in the Study 178-CL-204 included the evaluation of the PK of mirabegron in children with OABThe secondary objective endpoint was to evaluate the PK after multiple dose administration of mirabegron in pediatric subjects with OAB measures as the steady-state C_{max}, AUC_{tau}, C_{trough}, T_{max}, CL/F and Vz/F. Additional parameters may be calculated based on the population pharmacokinetic model used.

Target exposures (AUC) at steady-state of 69 and 188 ng·h/mL in the pediatric population after daily dosing of 25 mg and 50 mg mirabegron respectively, were obtained from a population PK model developed with pooled data from adult studies.

The starting dose was PED25 starting administration the day after visit 3/week 0 (baseline). At visit 5/week 4, dose up-titration to PED50 was performed unless the investigator determined that the subject 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 have been done at any time thereafter for safety reasons.

7.2. Results

A total of 44 children and 9 adolescents were screened. Of these, 23 children and 3 adolescents were randomized. Two of the 11 children on mirabegron and 1 of the 2 adolescents on mirabegron were discontinued early and did not fulfill the criteria for inclusion in the Pharmacokinetic analysis set (PKAS). Data of nine paediatric patients with OAB (8 children and 1 adolescent) were collected for the PK analysis.

The PKAS consisted of all subjects who took at least 1 dose of treatment and contributed at least 1 pharmacokinetic sample in which the date and time of the sample and prior dose were known. Additional subjects could be excluded from the PKAS at the discretion of the pharmacokineticist.

All children included in the PK analysis up-titrated to the PED50 dose at week 4 (range: day 25 to 31). The geometric mean plasma trough concentration increased from week 4 (3.03 ng/mL; n = 7) to week 12 (6.39 ng/mL; n = 8).

Of the 3 adolescents enrolled, only 1 adolescent on mirabegron provided PK results, but the plasma trough concentrations were below the lower limit of quantification and were excluded from summary statistics. This adolescent received PED25 and up-titration at week 4 was not done.

Calculation of all PK parameters, except for trough concentration, was not possible due to the low number of samples collected (n=9), since the study was terminated early.

7.3. Discussion

Among the secondary objectives in the Study 178-CL-204 included the evaluation of the PK of mirabegron in children with OAB.

The agreed early termination of the Study due to operational futility based on the low recrutiment lead to the lack of calculation of all PK parameter. Only the trough concentration was determined and no further PK parameters could be calculated. Therefore, no additional PK data can contribute to the description of the PK profile of mirabegron in the paediatric population with OAB.

8. Clinical Efficacy aspects

8.1. Methods – analysis of data submitted

Description

The Study Design was a phase 3, 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 (defined according to the International Children's Continence Society criteria).

The study consisted of 3 time periods with a total duration of 18 weeks: (a) screening period/urotherapy: for 4 weeks before baseline, and including screening, 4 weeks of urotherapy, washout (if applicable) and baseline (b) double-blind, placebo-controlled period: beginning the day after baseline and continuing to week 12/end of treatment (EoT) and, (c) a follow-up period: safety observation beginning after week 12 and continuing to week 14 (end of study)

Participants

The key inclusion criteria were as follows; (a) Subject with OAB defined according to the ICCS criteria, (b) Subject was a male or female between 5 to < 18 years of age, (c) Subject must have 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, (d) Subject must have 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; (a) Subject had extraordinary daytime only urinary frequency according to the ICCS definition: 1. 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, 2. the daytime voiding frequency was at least once per hour with an average voided volume of < 50% of expected bladder capacity (EBC) (typically 10% to 15%), 3. the incontinence was rare and nocturia was absent; (b) Subject had extraordinary daytime only urinary frequency according to the ICCS definition based on the bladder e-diary; (c) Subject had monosymptomatic enuresis confirmed by the bladder e-diary; (d) Subject had a maximum voided volume (morning volume excluded) > EBC for age ([age +1] × 30) in mL, based on the bladder e-diary; (e) 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), based on bladder e-diary; (f) Subject had post-void residual (PVR) volume > 20 mL (lowest PVR volume result) as measured by ultrasonography.

The Study Population were male and female children aged 5 to less than 12 years and adolescents aged 12 years to less than 18 years with OAB. Among the children, the proportions of male and female subjects were relatively balanced in the placebo group, while most subjects 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 treatment groups, apart from the proportion of Asian subjects, which was higher in the placebo group (50.0% [6/12] of subjects) than in the mirabegron group (18.2% [2/11] of subjects).

Treatments

Subjects were randomized to receive mirabegron or placebo using a 1:1 ratio.

Depending upon body weight, subjects were administered either mirabegron oral suspension 8 mg/mL (subjects with a body weight < 35 kg) or mirabegron tablets (subjects with a body weight ≥ 35 kg; subjects unable or unwilling to take tablets could take the suspension). Treatment was to be administered orally, once daily in the morning around the same time of day and around time of food intake (i.e., within 1 hour before or after breakfast).

The starting dose of mirabegron was based on the subject's body weight and was predicted to achieve PED25. The starting administration was the day after visit 3/week 0 (baseline). At visit 5/week 4 (after 4 weeks on PED25), dose up-titration to PED50 was performed unless the investigator determined that the subject 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 have been done at any time thereafter for safety reasons.

Objective(s)

The primary study objective was to evaluate the efficacy of mirabegron in children (aged 5 to less than 12 years) with OAB. The secondary objectives were to evaluate: the efficacy of mirabegron in children (5 to < 12 years of age) with OAB; the safety and tolerability of mirabegron in pediatric subjects with OAB and the pharmacokinetics after multiple dose administration of mirabegron in pediatric subjects with OAB. The exploratory objective was to evaluate the efficacy of mirabegron in pediatric subjects (5 to less than 18 years) with OAB.

Outcomes/endpoints

The primary efficacy endpoint was assessed in children (aged 5 to less than 12 years) as the change from baseline in the mean number of micturitions per 24 hours at week 12 as the adjusted LS mean (SEM). The safety evaluation continued for 2 weeks after the end of treatment.

The secondary efficacy endpoints were assessed in children (aged 5 to less than 12 years) as the change from baseline at the end of the 12-weeks treatment period in the (a) mean volume voided per 24 hours, (b) maximum volume voided, (c) mean number of daytime incontinence, (d) episodes per 24 hours, and (d) mean number of daytime micturitions per 24 hours, as well as the number of dry (incontinence-free) days per 7 days at the end of the 12-week treatment period.

The exploratoy objective endpoint to evaluate the efficacy of mirabegron in pediatric subjects (5 to less than 18 years) with OAB was assessed as percentage of subjects with a reduction in daytime incontinence episodes; improvement from baseline in worst incontinence grading; mean number of micturitions, volume voided and incontinence episodes per 24 hours; number of dry (incontinence-free) days; mean number of daytime grade 3 or 4 urgency episodes per 24 hours, and mean volume voided per micturition.

Statistical Methods

Populations for Analysis

The full analysis set (FAS) consisted of all subjects who were randomized and received at least 1 dose of treatment 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 treatment. The FAS 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 treatment 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 analysis of the primary efficacy endpoint of change from baseline in mean number of micturitions per 24 hours after 12 weeks of treatment in children (aged 5 to <12 years) was analyzed using an analysis of covariance (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 primary analysis was performed with imputation of missing week 12 data using the last observation carried forward (LOCF) method.

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

8.2. Results

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.

From 15 March 2021 (first subject's first evaluation in the study) to 24 July 2023 (last subject's last evaluation in the study), 53 subjects aged 5 to less than 18 years were screened and signed an informed consent form/assent (44 children and 9 adolescents).

Of the screened children, the 52.3% (23/44) were randomized. A total of 23 children (aged 5 to less than 12 years) received study drug: 12 of them received placebo and 11 subject received mirabegron. Most of them completed the study treatment: 83.3% (10/12 subjects) in the placebo group, and 81.8% (9/11

subjects) in the mirabegron group. 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.

Of the screened adolescents (aged 12 to less than 18 years), the 33.3% (3/9) were randomized to treatment: 1 adolescent received placebo and 2 adolescents received mirabegron.

Per protocol, all subjects 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.

The primary efficacy endpoint was the change from baseline at the end of the 12 week treatment period in mean number of micturitions per 24 hour. The primary efficacy endpoint was assessed only in children (aged 5 to less than 12 years).

The adjusted LS mean (SEM) change from baseline to week 12/EoT 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, and the LS mean (SEM) difference between treatment groups (placebo minus mirabegron) was not statistically significant: 2.22 (1.34) (90% CI: -0.15, 4.59; p = 0.121) (Table 1).

Table 1. 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	

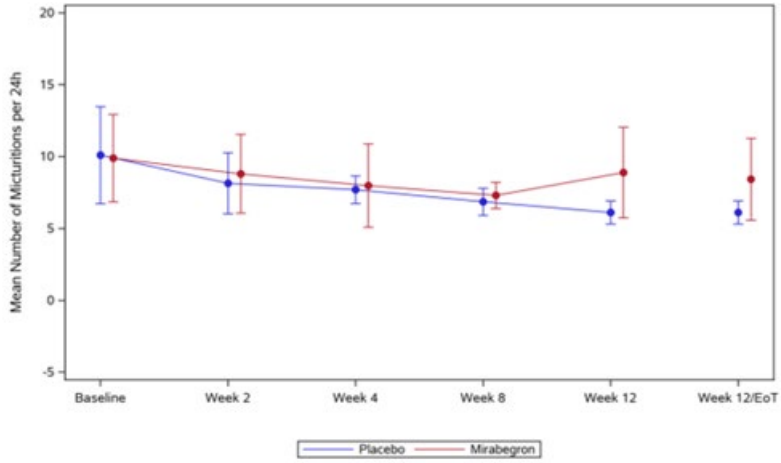
Note: Statistics were based on subjects in the FAS who had a non-missing result at baseline and at least one post-baseline time point during the treatment period for that endpoint. Analysis of Covariance was performed with change from baseline at week 12 LOCF as response, treatment group, sex and geographical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

† p-value is for treatment comparison with placebo from the above-described model

Graphically, the mean number of micturition per 24 hours in children is plotted by study week in (Figure 1).

Figure 1. Mean (±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 2 shows results from secondary endpoints, as follows

Table 2. 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)

8.3. Discussion

The study 178-CL-204 ended early on 24 July 2023 (subjects' last evaluation in the study) because of extremely low recruitment, partly due to the coronavirus disease 2019 pandemic. Study objectives were thus not achieved.

Due to the small number of subjects in Study 178-CL-204, a proper assessment of the efficacy endpoints was not possible and the observed results are considered inconclusive.

The changes in mean number of micturitions per 24 hours tended to be more favourable to placebo treatment, however, no statistically significant difference between placebo and the active treatment (mirabegron) was observed for the primary analysis of the primary endpoint at the end of the 12-week treatment period. The fact that the result did not favour mirabegron was also observed in some secondary endpoints.

Although limited, data from this inconclusive study are proposed to be included in the Product Information (Section 5.1). This is supported in order to provide healthcare professionals with the most updated information. No further measures are considered necessary to address issues related to efficacy, (please refer to separate Attachment 1).

9. Clinical Safety aspects

9.1. Methods – analysis of data submitted

The safety data presented focus on the 26 pediatric subjects (23 children and 3 adolescents) with OAB in Study 178-CL-204.

Per protocol, all subjects 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 secondary objectives of the study were to evaluate the safety, tolerability and PK of mirabegron in children with OAB. To evaluate the safety and tolerability of mirabegron in pediatric subjects with OAB, following endpoints were measured (a) nature, frequency and severity of AEs, (b) clinical laboratory tests (hematology, biochemistry and urinalysis), (c) vital signs (blood pressure and pulse), (d) routine 12-lead ECG, (e), PVR volume and (f) acceptability and palatability questionnaire.

Treatment-emergent adverse event (TEAEs) were assessed as events of interest based on risks associated with the drug class and data available to date in studies of mirabegron; TEAEs of special interest were identified using all preferred terms from standardized MedDRA queries or sponsor-defined list of search terms: Abnormal cardiac electrophysiology (including QTc prolongation); Cardiac arrhythmia, and other cardiovascular Aes; Increased BP as assessed through vital signs monitoring; Hypersensitivity reactions; Urinary retention; Abnormal nervous system events (seizure, syncope, headache, dizziness).

Treatment-emergent Adverse events (TEAEs) were coded using MedDRA v25.0 and summarized by frequency, severity (i.e., mild, moderate, severe), seriousness and by relationship to study drug according to the investigator (i.e., yes, no). Number and percentage of subjects with TEAEs, serious TEAEs, TEAEs leading to permanent discontinuation, also including drug-relatedness, were summarized by age group and overall, system organ class, preferred term and treatment group.

Systolic and diastolic blood pressure (SBP and DBP) were converted to percentiles specific to the age, sex and height of the subject. SBP and DBP categories (normal, elevated, stage 1 hypertension (HTN) and stage 2 HTN were obtained from the 2017 American Academy of Pediatric Clinical Practice Guidelines. Pulse rate was compared to age-related norms. The safety variables: laboratory results, vital signs, electrocardiograms (ECGs); height, weight, and body mass index, post-void residual volume, and acceptability and palatability questionnaire outcome were summarized descriptively by age group and overall, treatment group and visit.

The Safety Analysis Set (SAF) consisted of all subjects who were randomized and who took at least 1 dose of mirabegron prolonged-release tablets or mirabegron granules for prolonged-release oral suspension. This set was analysed by treatment arm as treated (i.e., based on the treatment the subject

actually received rather than the treatment to which the subject was randomized). The SAF was used for summaries of demographic and baseline characteristics and all safety- and tolerability-related variables.

Among the 23 randomized children, 12 children received placebo and 11 children were treated with mirabegron, for up to 12 weeks. Three children in each treatment group received tablets, whereas 9 children in the placebo group and 8 children in the mirabegron group received oral suspension.

Of the 3 adolescents, 1 adolescent received placebo and the other 2 adolescents received mirabegron.

9.2. Results

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. For the 2 adolescents who received mirabegron, the mean (SD) duration of exposure to study drug was 82.5 (0.7) days.

Treatment-Emergent Adverse Events (TEAEs)

In **children** (subjects aged 5 to less than 12 years, n=23), 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 3).

Table 3. Overview of Treatment-emergent Adverse Events and Deaths – Children Aged 5 to 12 Years (Safety Analysis Set)

Parameter	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
Drug-related serious TEAE†‡	0	0
TEAE leading to permanent discontinuation	0	0
Drug-related TEAE leading to permanent discontinuation†	0	0
Death§	0	0

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

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

SAE: serious adverse event; 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.

TEAEs were considered by the investigator as related to study drug in 8.3% (1/12) of children on placebo (dry mouth, 1 event) and in 9.1% (1/11) of children on mirabegron (2 events, fatigue and mood swing). All TEAEs reported in children were of mild severity.

In **adolescents** (subjects aged 12 to less than 18 years, n = 3), 2 TEAEs were reported in the subject on placebo, and 3 TEAEs were reported in 1 of the 2 subjects on mirabegron; no TEAEs were reported in more than 1 subject. TEAEs considered to be related to study drug by the investigator included 1 serious event of ECG QT prolonged (placebo arm). All TEAEs but 1 (severe diffuse axonal injury in 1 of the 2 subjects on mirabegron) were mild in severity. The severe diffuse axonal injury ocurred in the active treatment arm and led to permanent discontinuation. It was classified by the investigator as no related to study drug.

- Common TEAEs

In **children,** the most commonly reported TEAEs (in more than 1 subject) 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 subject only, including an event of ECG QT prolonged; this event was mild and not considered as related to study drug.

In **adolescents**, no TEAEs were reported in more than 1 subject

- Serious TEAEs

In **children**, no serious TEAEs occurred during the entire study period.

In **adolescents**, 2 serious TEAEs were reported (a) ECG QT prolonged (placebo arm) which was mild in severity (increase of 7 ms from screening), and considered as related to study drug and, (b) Diffuse Axonal Injury (mirabegron arm) which was severe, and considered as no related to study-drug.

There were no deaths during the entire study period.

- TEAEs Leading to discontinuation

No TEAEs leading to discontinuation of study drug were reported in **children** and 2 TEAEs led to permanent discontinuation of study drug were reported in **adolescents** (ECG QT prolonged and diffuse axonal injury in 1 subject.

- TEAEs of Special Interest

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

In **adolescents**, a mild headache was reported in the placebo arm and a mild ECG QT prolonged (abnormal clinically significant ECG) was also reported in the same subject.

In **children**, 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**, there were no clinically meaningful findings reported for 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.

9.3. Discussion

Mirabegron, administered as tablets and an oral suspension in Study 178-CL-204, was well tolerated by pediatric subjects with OAB aged 5 years to less than 18 years under the condition of this clinical study.

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) and one case of diffuse axonal injury in one adolescent, and they were considered as not related to the study drug by the investigator.

Overall, mirabegron, administered as tablets and an oral suspension was well tolerated the paediatric population. No new relevant safety findings were identified in the pediatric population studied and no

further impact on the subject's safety occurred. No further measures are considered necessary to address issues related to safety (please refer to separate Attachment 1).

Quality

The Applicant has updated the CE Certificates of medical devices in Module 3.2.R according to Regulation (EU) 2017/745:

the management system was assessed and certified as meeting the requirements of MDR EU Quality Assurance certificate (Annex XI Part A) for Class 1m device non-active, non-implantable, non-sterile plastic oral and vaginal dosing applicators for administration of medication.

Measuring cup:

- Certificate UE d'assurance qualite de la production.
- EC Declaration of conformity for dosing cups.
- Certificate of registration. It is certified that the quality management system developed complies with the requirements of the international standards NF EN ISO 13485:2016.
- was assessed and certified as meeting the requirements of ISO 15378:2017 Primary packaging materials for medicinal products – Particular requirements for the application of ISO 9001:2015 with reference to Good Manufacturing Practices (GMP).

10. PRAC advice

N/a

11. Changes to the Product Information

As a result of this variation, modifications to Section 4.2, Section 4.8, Section 5.1 and Section 5.3 of the Summary of Product Characteristics were proposed by the applicant.

PI changes only affect to the Summary of Product Characteristics. The Package Leaflet remains unchanged, except for a correction if a missed dose occurs. Pending MAH response is expected.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

12. Request for supplementary information

12.1. Major objections

Non-clinical aspects

None

Clinical aspects

None

12.2. Other concerns

Non-clinical aspects

SmPC section 5.3 should be updated as suggested.

Clinical aspects

None

13. Assessment of the responses to the request for supplementary information

13.1. Major objections

Non-clinical aspects

Question X

Summary of the MAH's response

Assessment of the MAH's response

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Clinical aspects

Question X

Summary of the MAH's response

Assessment of the MAH's response

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

13.2. Other concerns

Non-clinical aspects

Question

SmPC section 5.3 should be updated as suggested.

Summary of the MAH's response

Section 5.3 of the SmPC has been updated to incorporate the requested edits. Astellas has modified the proposed edit by adding the word 'gain' in the preclinical section 5.3 to accurately reflect the data in Study Report 178-TX-055: 'Mirabegron administration increased lipolysis and food consumption and decreased body weight gain in juvenile rats'.

Assessment of the MAH's response

SmPC section 5.3 has been updated as suggested with minor corrections.

Conclusion

Issue solved.

Clinical aspects

Question X

Summary of the MAH's response

Assessment of the MAH's response

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

14. Attachments

1. Betmiga Product Information (trackchanges and clean version) are enclosed.