Clinical trial results:
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

Summary

EudraCT number	2016-001767-37
Trial protocol	DE NL BE NO FR DK PL IT ES
Global end of trial date	24 July 2023

Results information

Result version number	v1 (current)
This version publication date	28 December 2023
First version publication date	28 December 2023

Trial information

Trial identification

Sponsor protocol code	178-CL-204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04641975
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc. (APGD)
Sponsor organisation address	1 Astellas Way, Northbrook, IL, United States, 60062
Public contact	Clinical Transparency, Astellas Pharma Global Development, Inc. (APGD), 60062 8008887704, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Transparency, Astellas Pharma Global Development, Inc. (APGD), 60062 8008887704, astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000597-PIP02-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 July 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Main objective of the trial was to evaluate the efficacy of mirabegron in children (5 to < 12 years of age) with overactive bladder (OAB).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Philippines: 7
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Türkiye: 1
Country: Number of subjects enrolled	Ukraine: 3
Worldwide total number of subjects	26
EEA total number of subjects	8

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	23
Adolescents (12-17 years)	3
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants who had received 4 weeks of urotherapy prior to randomization were enrolled in the study. Specific interventions included various forms of pelvic floor training, behavioral modification, electrical stimulation, catherization and biofeedback and elements of cognitive behavioral therapy.

Pre-assignment

Screening details:

Standard urotherapy included information on demystification of voiding function and dysfunction, instruction on voiding habits, lifestyle advice regarding fluid intake, prevention of constipation, recording of symptoms and voiding habits in bladder diaries and support via regular follow-up.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Monitor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Mirabegron (5 to<12 years)

Arm description:

Participants aged 5 to < 12 years received placebo matched to mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Arm type	Experimental
Investigational medicinal product name	Mirabegron
Investigational medicinal product code	YM178
Other name	Betanis Betmiga Myrbetriq
Pharmaceutical forms	Coated tablet, Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants aged 5 to < 12 years received initial dose of 25 milligram (mg) of mirabegron orally once daily based on weight (pediatric equivalent dose of 25 mg [PED25]) on day 1. Participants with a body weight ≥ 35 kilogram (kg) received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the pediatric equivalent dose of 50 mg [PED50] based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Arm title	Placebo (5 to < 12 years)

Arm description:

Participants aged 12 to < 18 years received placebo matched to mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet, Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants aged 5 to < 12 years received placebo matched to mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Arm title	Mirabegron(12 to<18 years)

Arm description:

Participants aged 5 to < 12 years received initial dose of 25 mg of mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Arm type	Experimental
Investigational medicinal product name	Mirabegron
Investigational medicinal product code	YM178
Other name	Betanis Betmiga Myrbetriq
Pharmaceutical forms	Concentrate for oral suspension, Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants aged 12 to < 18 years received initial dose of 25 mg of mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Arm title	Placebo (12 to < 18 years)

Arm description:

Participants aged 12 to < 18 years received initial dose of 25 mg of mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet, Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants aged 12 to < 18 years received placebo matched to mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Number of subjects in period 1	Mirabegron (5 to<12 years)	Placebo (5 to < 12 years)	Mirabegron(12 to<18 years)
Started	11	12	2
Completed	9	10	1
Not completed	2	2	1
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	-	1

Protocol deviation	1	2	-

Number of subjects in period 1	Placebo (12 to < 18 years)
Started	1
Completed	0
Not completed	1
Consent withdrawn by subject	-
Adverse event, non-fatal	1
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Mirabegron (5 to<12 years)
Reporting group description:	
Participants aged 5 to < 12 years received placebo matched to mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.	
Reporting group title	Placebo (5 to < 12 years)
Reporting group description:	
Participants aged 12 to < 18 years received placebo matched to mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.	
Reporting group title	Mirabegron(12 to<18 years)
Reporting group description:	
Participants aged 5 to < 12 years received initial dose of 25 mg of mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.	
Reporting group title	Placebo (12 to < 18 years)
Reporting group description:	
Participants aged 12 to < 18 years received initial dose of 25 mg of mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.	

Reporting group values	Mirabegron (5 to<12 years)	Placebo (5 to < 12 years)	Mirabegron(12 to<18 years)
Number of subjects	11	12	2
Age categorical Units: Subjects			

Age			
Here "99999"denotes that data was not analyzed since there was only 1 evaluable participant.			
Units: years			
arithmetic mean	8.4	7.7	16
standard deviation	± 1.9	± 1.7	± 1.4
Sex Units: Subjects			
Female	2	7	2
Male	9	5	0
Analysis Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	6	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0

White	7	6	1
More than one race	0	0	0
Unknown or Not Reported	2	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	0
Unknown or Not Reported	2	0	0
Not Hispanic or Latino	9	11	2
Mean Number of Micturitions per 24 hours			
A micturition was defined as any voluntary act of passing urine (excluding incontinence only episodes). The mean number of micturitions per 24 hours was calculated as the average number of times a participant urinated per day during the 7-day micturition diary period. Participants in the SAF with available data were analyzed. Here "99999"denotes that data was not analyzed since there was only 1 evaluable participant.			
Units: Micturitions per 24 hours			
arithmetic mean	9.48	9.72	19.43
standard deviation	± 4.53	± 4.95	± 3.16

Reporting group values	Placebo (12 to < 18 years)	Total	
Number of subjects	1	26	
Age categorical Units: Subjects			

Age			
Here "99999"denotes that data was not analyzed since there was only 1 evaluable participant.			
Units: years			
arithmetic mean	12		
standard deviation	± 99999	-	
Sex Units: Subjects			
Female	0	11	
Male	1	15	
Analysis Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	10	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	0	14	
More than one race	0	0	
Unknown or Not Reported	0	2	
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	
Unknown or Not Reported	0	2	
Not Hispanic or Latino	1	23	
Mean Number of Micturitions per 24 hours			
A micturition was defined as any voluntary act of passing urine (excluding incontinence only episodes). The mean number of micturitions per 24 hours was calculated as the average number of times a participant urinated per day during the 7-day micturition diary period. Participants in the SAF with available data were analyzed. Here "99999"denotes that data was not analyzed since there was only 1			

evaluable participant.			
Units: Micturitions per 24 hours			
arithmetic mean	9.29		
standard deviation	± 99999	-	

End points

End points reporting groups

Reporting group title	Mirabegron (5 to<12 years)

Reporting group description:

Participants aged 5 to < 12 years received placebo matched to mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Reporting group title	Placebo (5 to < 12 years)

Reporting group description:

Participants aged 12 to < 18 years received placebo matched to mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Reporting group title	Mirabegron(12 to<18 years)

Reporting group description:

Participants aged 5 to < 12 years received initial dose of 25 mg of mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Reporting group title	Placebo (12 to < 18 years)

Reporting group description:

Participants aged 12 to < 18 years received initial dose of 25 mg of mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Primary: Change from baseline to week 12/EoT in mean number of micturitions per 24 hours for age group 5 to <12 years

End point title	Change from baseline to week 12/EoT in mean number of micturitions per 24 hours for age group 5 to <12 years[1]

End point description:

A micturition was defined as any voluntary act of passing urine (excluding incontinence only episodes). The mean number of micturitions per 24 hours was calculated as the average number of times a participant urinated per day during the 7-day micturition diary period. The analysis was performed with imputation of missing visit 7/week 12 data using the last observation carried forward (LOCF) method. Full Analysis set: All participants who were randomized and received at least 1 dose of study drug and had at least 1 post baseline measurement for mean number of micturitions per 24 hours.

End point type	Primary

End point timeframe:

Baseline, week 12

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: It was intended to report data for 5 to <12 years of age only.

End point values	Mirabegron (5 to<12 years)	Placebo (5 to < 12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: Micturitions per 24 hours				
least squares mean (standard error)	-1.62 (± 0.89)	-3.84 (± 0.89)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis of Covariance (ANCOVA) was performed with change from baseline at week 12 Last Observation Carried Forward (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.

Comparison groups	Mirabegron (5 to<12 years) v Placebo (5 to < 12 years)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.121
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	2.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.15
upper limit	4.59
Variability estimate	Standard error of the mean
Dispersion value	1.34

Secondary: Change from baseline to week 12/EoT in mean volume voided per 24 hours for age group 5 to <12 years

End point title	Change from baseline to week 12/EoT in mean volume voided per 24 hours for age group 5 to <12 years[2]

End point description:

Mean volume voided was derived from "Pee Volume" of the 2-day Weekend Episodic Diary. Mean volume voided per day was calculated as the sum of the volumes voided on that (valid diary) day divided by the number of times a volume was recorded on that day in the 2-day Weekend Episodic Diary. The analysis was performed with LOCF and without LOCF method. Full Analysis Set with available data was analyzed.

End point type	Secondary

End point timeframe:

Baseline, week 12

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was intended to report data for 5 to <12 years of age only.

End point values	Mirabegron (5 to<12 years)	Placebo (5 to < 12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: milliliter (mL)/24 hours				
arithmetic mean (standard deviation)				
Week 12 (without LOCF)	18.38 (± 33.67)	24.55 (± 32.32)		
Week 12 (with LOCF)	18.38 (± 33.67)	24.55 (± 32.32)		

Statistical analyses

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Week 12 LOCF	
Comparison groups	Mirabegron (5 to<12 years) v Placebo (5 to < 12 years)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.43
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-15.51
Confidence interval	
level	90 %
sides	2-sided
lower limit	-49.47
upper limit	18.46
Variability estimate	Standard error of the mean
Dispersion value	18.91

Notes:

[3] - ANCOVA was performed with change from baseline at week 12 with LOCF as response, treatment group, sex and geographical region as fixed effects and the mean volume voided per 24 hours at baseline as covariate. Statistically significant treatment difference at 0.10 level for mirabegron vs placebo.

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Week 12 without LOCF	
Comparison groups	Mirabegron (5 to<12 years) v Placebo (5 to < 12 years)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.43
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-15.51

Confidence interval	
level	90 %
sides	2-sided
lower limit	-49.47
upper limit	18.46
Variability estimate	Standard error of the mean
Dispersion value	18.91

Notes:

[4] - ANCOVA was performed with change from baseline at week 12 without LOCF as response, treatment group, sex and geographical region as fixed effects and the mean volume voided per 24 hours at baseline as covariate. Statistically significant treatment difference at 0.10 level for mirabegron vs placebo.

Secondary: Change from baseline to week 12/EoT in maximum volume voided (MVV) for age group 5 to <12 years

End point title	Change from baseline to week 12/EoT in maximum volume voided (MVV) for age group 5 to <12 years[5]

End point description:

MVV data was derived from "Pee Volume" of the 2-day Weekend Episodic Diary. The MVV was the largest (non-zero) volume recorded over both of the 2 (valid) measuring days in the diary. The analysis was performed with LOCF and without LOCF method. Full Analysis Set with available data was analyzed.

End point type	Secondary

End point timeframe:

Baseline, week 12

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: It was intended to report data for 5 to <12 years of age only.

End point values	Mirabegron (5 to<12 years)	Placebo (5 to < 12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mL				
arithmetic mean (standard deviation)				
Week 12 (without LOCF)	26.00 (± 51.46)	26.38 (± 60.75)		
Week 12 (With LOCF)	26.00 (± 51.46)	26.38 (± 60.75)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week 12 without LOCF

Comparison groups	Mirabegron (5 to<12 years) v Placebo (5 to < 12 years)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.935
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.58

Confidence interval	
level	90 %
sides	2-sided
lower limit	-53.23
upper limit	58.38
Variability estimate	Standard error of the mean
Dispersion value	31.08

Notes:

[6] - ANCOVA was performed with change from baseline at week 12 without LOCF as response, treatment group, sex and geographical region as fixed effects and the max volume voided at baseline as covariate. Statistically significant treatment difference at 0.10 level for mirabegron vs placebo.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Week 12 LOCF

Comparison groups	Mirabegron (5 to<12 years) v Placebo (5 to < 12 years)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.935
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.58
Confidence interval	
level	90 %
sides	2-sided
lower limit	-53.23
upper limit	58.38
Variability estimate	Standard error of the mean
Dispersion value	31.08

Notes:

[7] - ANCOVA was performed with change from baseline at week 12 with LOCF as response, treatment group, sex and geographical region as fixed effects and the max volume voided at baseline as covariate. Statistically significant treatment difference at 0.10 level for mirabegron vs placebo.

Secondary: Change from baseline to week 12/EoT in mean number of daytime incontinence episodes per 24 hours for age group 5 to <12 years

End point title	Change from baseline to week 12/EoT in mean number of daytime incontinence episodes per 24 hours for age group 5 to <12 years[8]

End point description:

A daytime incontinence episode was defined as the complaint of any involuntary leakage of urine during daytime hours. Daytime was defined as time between waking up in the morning and going to sleep later the same day or next day. The mean number of daytime incontinence episodes per 24 hours was calculated by taking the sum of all daytime urinary incontinence episodes recorded in the participant diary, divided by the number of valid diary days. The analysis was performed with LOCF and without LOCF method. Full Analysis Set with available data was analyzed.

End point type	Secondary

End point timeframe:

Baseline, week 12

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was intended to report data for 5 to <12 years of age only.

End point values	Mirabegron (5 to<12 years)	Placebo (5 to < 12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: incontinence episodes per 24 hours				
arithmetic mean (standard deviation)				
Week 12 (without LOCF)	-1.29 (± 1.04)	-1.28 (± 1.73)		
Week 12 (with LOCF)	-1.20 (± 1.02)	1.09 (± 1.74)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Week 12 without LOCF	
Comparison groups	Mirabegron (5 to<12 years) v Placebo (5 to < 12 years)
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.073
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.99
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.53

Notes:

[9] - ANCOVA as performed with change from baseline at week 12 without LOCF as response, treatment group, sex and geographical region as fixed effects and the mean number of daytime incontinence episodes per 24 hours at baseline as covariate. Statistically significant treatment difference at 0.10 level for mirabegron vs placebo.

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Week 12 LOCF	
Comparison groups	Mirabegron (5 to<12 years) v Placebo (5 to < 12 years)
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.044
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1

Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.8
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.45

Notes:

[10] - ANCOVA as performed with change from baseline at week 12 with LOCF as response, treatment group, sex and geographical region as fixed effects and the mean number of daytime incontinence episodes per 24 hours at baseline as covariate. Statistically significant treatment difference at 0.10 level for mirabegron vs placebo.

Secondary: Change from baseline to week 12/EoT in mean number of nighttime incontinence episodes per 24 hours for age group 5 to <12 years

End point title	Change from baseline to week 12/EoT in mean number of nighttime incontinence episodes per 24 hours for age group 5 to <12 years[11]

End point description:

A nighttime incontinence episode was defined as the complaint of any involuntary leakage of urine during nighttime hours. Nighttime was defined as time between between going to sleep on a day and waking up on the same or next day. The mean number of nighttime incontinence episodes per 24 hours was calculated by taking the sum of all nighttime urinary incontinence episodes recorded in the participant diary, divided by the number of valid diary days. The analysis was performed with LOCF and without LOCF method. Full Analysis Set.

End point type	Secondary

End point timeframe:

Baseline, week 12

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was intended to report data for 5 to <12 years of age only.

End point values	Mirabegron (5 to<12 years)	Placebo (5 to < 12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: incontinence episodes per 24 hours				
arithmetic mean (standard deviation)				
Week 12 (without LOCF)	-0.64 (± 0.55)	-1.34 (± 1.51)		
Week 12 (with LOCF)	-0.64 (± 0.55)	-1.34 (± 1.51)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 12 without LOCF

Comparison groups	Mirabegron (5 to<12 years) v Placebo (5 to < 12 years)

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.91
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.74
upper limit	0.64
Variability estimate	Standard error of the mean
Dispersion value	0.39

Notes:

[12] - ANCOVA as performed with change from baseline at week 12 without LOCF as response, treatment group, sex and geographical region as fixed effects and the mean number of daytime incontinence episodes per 24 hours at baseline as covariate. Statistically significant treatment difference at 0.10 level for mirabegron vs placebo.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Week 12 with LOCF

Comparison groups	Mirabegron (5 to<12 years) v Placebo (5 to < 12 years)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.91
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.74
upper limit	0.64
Variability estimate	Standard error of the mean
Dispersion value	0.39

Notes:

[13] - ANCOVA as performed with change from baseline at week 12 with LOCF as response, treatment group, sex and geographical region as fixed effects and the mean number of daytime incontinence episodes per 24 hours at baseline as covariate. Statistically significant treatment difference at 0.10 level for mirabegron vs placebo.

Secondary: Change from baseline to week 12/EoT in mean number of daytime micturitions per 24 hours for age group 5 to <12 years

End point title	Change from baseline to week 12/EoT in mean number of daytime micturitions per 24 hours for age group 5 to <12 years[14]

End point description:

For a week day the daytime micturitions was derived from "Number of Times using the Toilet During the Day" was entered into the 5-day Week Diary. For a weekend day the daytime micturitions was derived from the number of times a "Pee in Toilet" or a "Pee in Toilet and Leakage" was entered into the 2-day Weekend Episodic Diary between the time the participant woke-up (exclusive). The total number of micturitions per weekend day was equal to the total number of times, in the diary, an amount of pee was recorded during daytime for that day. For each participant, the mean number of daytime

micturitions was calculated as:Sum of the Number of Daytime Micturitions (per day) over the Valid Diary Days prior to Visit/Number of Valid Diary Days"
The analysis was performed with LOCF and without LOCF method. Full Analysis Set.

End point type	Secondary

End point timeframe:

Baseline, week 12

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was intended to report data for 5 to <12 years of age only.

End point values	Mirabegron (5 to<12 years)	Placebo (5 to < 12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: micturitions per 24 hours				
arithmetic mean (standard deviation)				
Week 12 (without LOCF)	-0.85 (± 2.67)	-3.21 (± 6.65)		
Week 12 (with LOCF)	-0.85 (± 2.67)	-3.21 (± 6.27)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week 12 without LOCF

Comparison groups	Mirabegron (5 to<12 years) v Placebo (5 to < 12 years)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.012
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.48
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.97
upper limit	3.99
Variability estimate	Standard error of the mean
Dispersion value	0.85

Notes:

[15] - ANCOVA was performed with change from baseline at week 12 without LOCF as response, treatment group, sex and geographical region as fixed effects and the mean number of daytime micturitions per 24 hours at baseline as covariate. Statistically significant treatment difference at 0.10 level for mirabegron vs placebo.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Week 12 LOCF

Comparison groups	Mirabegron (5 to<12 years) v Placebo (5 to < 12 years)

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.007
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.46
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.1
upper limit	3.82
Variability estimate	Standard error of the mean
Dispersion value	0.77

Notes:

[16] - ANCOVA was performed with change from baseline at week 12 with LOCF as response, treatment group, sex and geographical region as fixed effects and the mean number of daytime micturitions per 24 hours at baseline as covariate. Statistically significant treatment difference at 0.10 level for mirabegron vs placebo.

Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Serious TEAEs

End point description:

An AE was any untoward medical occurrence in a participant administered a study drug and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug whether or not considered related to the study drug. A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, resulted a congenital anomaly/birth defect or other medically important event. A TEAE was defined as an AE observed after starting administration of the study drug until 30 days after last dose. SAF.

End point type	Secondary

End point timeframe:

From first dose up to week 14

End point values	Mirabegron (5 to<12 years)	Placebo (5 to < 12 years)	Mirabegron(12 to<18 years)	Placebo (12 to < 18 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	12	2	1
Units: Participants				
number (not applicable)				
Treatment emergent adverse events	5	7	1	1
Serious treatment emergent adverse events	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to week 12/EoT in Number of dry (incontinence-free) days per 7 days for age group 5 to <12 years

End point title	Change From Baseline to week 12/EoT in Number of dry (incontinence-free) days per 7 days for age group 5 to <12 years[17]

End point description:

A dry (incontinence free) day was defined as a day where the response is "Dry" to the question "How was your Day" and to "How was your Night". For a weekend day a "Dry (incontinence free) Day" was defined a day where no "New pee or leakage" was reported. Let Ddry be the number of valid diary days where the response to both questions was "Dry". Let Dwet be the number of valid diary days where the response to one of the two questions or to both questions was "Wet". If (Ddry + Dwet) > 3, the number of dry days per 7 days was calculated as Ddry/(Ddry + Dwet)* 7, otherwise the value was missing. The analysis was performed with LOCF and without LOCF method. Full Analysis Set with available data was analyzed.

End point type	Secondary

End point timeframe:

Baseline, week 12

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was intended to report data for 5 to <12 years of age only.

End point values	Mirabegron (5 to<12 years)	Placebo (5 to < 12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: incontinence-free days				
arithmetic mean (standard deviation)				
Week 12 (without LOCF) (n= 8, 7)	3.12 (± 3.36)	1.45 (± 2.33)		
Week 12 (with LOCF) (n= 9, 9)	2.94 (± 3.47)	1.46 (± 2.18)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Week 12 with LOCF

Comparison groups	Mirabegron (5 to<12 years) v Placebo (5 to < 12 years)
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111 [18]
Method	Binomial regression
Parameter estimate	Rate ratio
Point estimate	0.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.05
upper limit	1.05

Notes:

[18] - From a negative binomial regression model including treatment group, sex and region as factors and the log baseline rate of number of dry days (the log of the ratio of dry days at baseline and number of diary days at baseline) as covariate.

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Week 12 Without LOCF	
Comparison groups	Mirabegron (5 to<12 years) v Placebo (5 to < 12 years)
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 105 [19]
Method	Binomial regression
Parameter estimate	Rate ratio
Point estimate	0.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.04
upper limit	1.02

Notes:

[19] - From a negative binomial regression model including treatment group, sex and region as factors and the log baseline rate of number of dry days (the log of the ratio of dry days at baseline and number of diary days at baseline) as covariate.

Secondary: Change from baseline in post void residual (PVR) volume

End point title	Change from baseline in post void residual (PVR) volume
End point description:	
PVR was assessed by ultrasonography. Here "99999"denotes that data is not available as there were no participants or only 1 participant was analyzed. SAF with available data was analyzed	
End point type	Secondary
End point timeframe:	
Baseline, weeks 4, 12, 14	

End point values	Mirabegron (5 to<12 years)	Placebo (5 to < 12 years)	Mirabegron(12 to<18 years)	Placebo (12 to < 18 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	2	1
Units: mL				
arithmetic mean (standard deviation)				
Week 4 (n=2, 9, 0, 10)	-0.56 (± 11.59)	8.80 (± 29.90)	-3.00 (± 9.90)	99999 (± 99999)
Week 12 (n=1, 8, 1, 7)	1.63 (± 4.27)	5.43 (± 12.79)	5.00 (± 99999)	0.00 (± 99999)
Week 14 (n=2,10, 1, 10)	2.20 (± 8.44)	11.00 (± 33.60)	4.50 (± 0.71)	0.00 (± 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Study Drug Acceptability and Palatability for Tablets

End point title	Number of Participants With Study Drug Acceptability and Palatability for Tablets

End point description:

Participants evaluated the taste of the study drug/tablets by ticking 1 of the following categories: "Really Bad" (0), "Bad" (1), "Not Bad, Not Good" (2), "Good" (3) & "Really Good" (4). Participants evaluated the swallow of the study drug/tablets by ticking one of the following categories: "Really Difficult" (0), "Difficult" (1), "Not Difficult, Not Easy" (2), "Easy" (3) and "Really Easy" (4). SAF with available data was analyzed.

End point type	Secondary

End point timeframe:

Week 12

End point values	Mirabegron (5 to<12 years)	Placebo (5 to < 12 years)	Mirabegron(12 to<18 years)	Placebo (12 to < 18 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	1	2	0[20]
Units: Participants				
number (not applicable)				
Taste: Really bad	0	0	0	
Taste: Bad	1	0	0	
Taste: Not Bad, Not Good	1	1	2	
Taste: Good	1	0	0	
Taste: Really Good	0	0	0	
Swallow: Really Difficult	0	0	0	
Swallow: Difficult	0	0	0	
Swallow: Not Difficult, Not Easy	0	0	1	
Swallow: Easy	2	0	0	
Swallow: Really Easy	1	1	1	

Notes:

[20] - No participants was analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Study Drug Acceptability and Palatability for Oral Suspension

End point title	Number of Participants With Study Drug Acceptability and Palatability for Oral Suspension

End point description:

Participants evaluated the taste of the study drug/oral suspension by ticking 1 of the following categories: "Really Bad" (0), "Bad" (1), "Not Bad, Not Good" (2), "Good" (3) & "Really Good" (4). Participants evaluated the smell of the study drug/oral suspension by ticking 1 of the following categories: "Really Bad" (0), "Bad" (1),"Not Bad, Not Good" (2), "Good" (3) & "Really Good" (4). Participants evaluated the consumption of the study drug/oral suspension by ticking 1 of the following categories: "Really Difficult" (0),"Difficult" (1), "Not Difficult, Not Easy" (2), "Easy" (3) & "Really Easy" (4). Participants evaluated the preparation of the study drug/oral suspension by ticking 1 of the following categories: “Really Difficult” (0), “Difficult” (1), “Not Difficult, Not Easy” (2), “Easy” (3) &

"Really Easy" (4). SAF with available data was analyzed.

End point type	Secondary

End point timeframe:

Week 12

End point values	Mirabegron (5 to<12 years)	Placebo (5 to < 12 years)	Mirabegron(12 to<18 years)	Placebo (12 to < 18 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	7	0[21]	0[22]
Units: Participants				
number (not applicable)				
Taste: Really Bad	0	0		
Taste: Bad	0	0		
Taste: Not Bad, Not Good	4	6		
Taste: Good	1	1		
Taste: Really Good	1	0		
Smell: Really Bad	0	0		
Smell: Bad	0	0		
Smell: Not Bad, Not Good	3	4		
Smell: Good	0	2		
Smell: Really Good	3	1		
Taking: Really Difficult	0	0		
Taking: Difficult	0	0		
Taking: Not Difficult, Not Easy	0	1		
Taking: Easy	4	5		
Taking: Really Easy	2	1		
Preparing: Really Difficult	0	0		
Preparing: Difficult	0	0		
Preparing: Not Difficult, Not Easy	0	2		
Preparing: Easy	4	5		
Preparing: Really Easy	2	0		

Notes:

[21] - No participants was analyzed.

[22] - No participants was analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) of mirabegron in plasma: Maximum concentration (Cmax)

End point title	Pharmacokinetic (PK) of mirabegron in plasma: Maximum concentration (Cmax)[23]

End point description:

Maximum observed plasma concentration (Cmax). PK parameter calculation was not possible due to low number of samples collected.

End point type	Secondary

End point timeframe:

Predose (1 hour prior) at weeks 4 and 12

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was intended to report data for mirabegron arms (5 to <12 years and 12<18 years).

End point values	Mirabegron (5 to<12 years)	Mirabegron(12 to<18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[24]	0[25]		
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)	()	()		

Notes:

[24] - No participant was analyzed.

[25] - No participant was analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: PK of mirabegron in plasma: Apparent total clearance (CL/F)

End point title	PK of mirabegron in plasma: Apparent total clearance (CL/F)[26]

End point description:

Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. Clearance obtained after oral dose (apparent oral clearance) is influenced by the fraction of the dose absorbed. Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. PK parameter calculation was not possible due to low number of samples collected.

End point type	Secondary

End point timeframe:

Predose (1 hour prior) at weeks 4 and 12

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was intended to report data for mirabegron arms (5 to <12 years and 12<18 years).

End point values	Mirabegron (5 to<12 years)	Mirabegron(12 to<18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[27]	0[28]		
Units: Liter/hour				
arithmetic mean (standard deviation)	()	()		

Notes:

[27] - No participant was analyzed.

[28] - No participant was analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: PK of mirabegron in plasma: Concentration immediately prior to dosing (Ctrough)

End point title	PK of mirabegron in plasma: Concentration immediately prior to dosing (Ctrough)[29]

End point description:

Trough level or trough concentration (Ctrough) in the concentration reached by the drug immediately before the next dose is administered. Here "99999"denotes that data is not available as there were no participants were analyzed

End point type	Secondary

End point timeframe:

Predose (1 hour prior) at weeks 4 and 12

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was intended to report data for mirabegron arms (5 to <12 years and 12<18 years).

End point values	Mirabegron (5 to<12 years)	Mirabegron(12 to<18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	1		
Units: nanograms/mL (ng/mL)				
arithmetic mean (standard deviation)				
Week 4 (n= 1, 7) Week 12 (n= 0, 8)	3.18 (± 1.01) 12.68 (± 21.33)	0.00 (± 99999) 99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time of the maximum concentration (Tmax)

End point title	Time of the maximum concentration (Tmax)[30]

End point description:

Time taken to reach Cmax (Tmax). PK parameter calculation was not possible due to low number of samples collected.

End point type	Secondary

End point timeframe:

Predose (1 hour prior) at weeks 4 and 12

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was intended to report data for mirabegron arms (5 to <12 years and 12<18 years).

End point values	Mirabegron (5 to<12 years)	Mirabegron(12 to<18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[31]	0[32]		
Units: hours				
median (full range (min-max))	(to)	(to)		

Notes:

[31] - No participant was analyzed.

[32] - No participant was analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: PK of mirabegron in plasma: PK of mirabegron in plasma: Area under concentration-time curve over dosing interval (AUCtau)

End point title	PK of mirabegron in plasma: PK of mirabegron in plasma: Area under concentration-time curve over dosing interval (AUCtau)[33]

End point description:

AUCtau is the measure of the plasma drug concentration from time zero to end of dosing interval. It is used to characterize drug absorption. PK parameter calculation was not possible due to low number of samples collected.

End point type	Secondary

End point timeframe:

Predose (1 hour prior) at weeks 4 and 12

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was intended to report data for mirabegron arms (5 to <12 years and 12<18 years).

End point values	Mirabegron (5 to<12 years)	Mirabegron(12 to<18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[34]	0[35]		
Units: ng*h/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[34] - No participant was analyzed.

[35] - No participant was analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: PK of mirabegron in plasma: Apparent volume of distribution (Vz/F)

End point title	PK of mirabegron in plasma: Apparent volume of distribution (Vz/F)[36]

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Vz/F is influenced by the fraction absorbed. PK parameter calculation was not possible due to low number of samples collected.

End point type	Secondary

End point timeframe:

Predose (1 hour prior) at weeks 4 and 12

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: It was intended to report data for mirabegron arms (5 to <12 years and 12<18 years).

End point values	Mirabegron (5 to<12 years)	Mirabegron(12 to<18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[37]	0[38]		
Units: Liters				
arithmetic mean (standard deviation)	()	()		

Notes:

[37] - No participant was analyzed.

[38] - No participant was analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose up to week 14

Adverse event reporting additional description:

SAF

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v25.0

Reporting groups

Reporting group title	Mirabegron(5 to<12 years)

Reporting group description:

Participants aged 5 to < 12 years received initial dose of 25 mg of mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Reporting group title	Placebo (5 to < 12 years)

Reporting group description:

Participants aged 5 to < 12 years received placebo matched to mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Reporting group title	Mirabegron (12 to<18 years)

Reporting group description:

Participants aged 12 to < 18 years received initial dose of 25 mg of mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Reporting group title	Placebo (12 to < 18 years)

Reporting group description:

Participants aged 12 to < 18 years received placebo matched to mirabegron orally once daily based on weight PED25 on day 1. Participants with a body weight ≥ 35 kg received tablet and participants with a body weight< 35 kg or those who could not be dosed with the tablet received an oral suspension. At week 4, participants were up-titrated to the PED50 based on the given dose titration criteria up to week 12. Urotherapy continued throughout the study treatment period until week 12.

Serious adverse events	Mirabegron(5 to<12 years)	Placebo (5 to < 12 years)	Mirabegron (12 to<18 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 12 (0.00%)	1 / 2 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 11 (0.00%)	0 / 12 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Diffuse axonal injury			
subjects affected / exposed	0 / 11 (0.00%)	0 / 12 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo (12 to < 18 years)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Diffuse axonal injury			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Mirabegron(5 to<12 years)	Placebo (5 to < 12 years)	Mirabegron (12 to<18 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 11 (45.45%)	7 / 12 (58.33%)	1 / 2 (50.00%)
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			

Head injury			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Eyelid abrasion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 12 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Medical device pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Dry mouth			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0

Reproductive system and breast disorders			
Genital erythema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Mood swings			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Viral infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 12 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	2 / 12 (16.67%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Respiratory tract infection viral			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
COVID-19			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	2 / 11 (18.18%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	2	2	0

Non-serious adverse events	Placebo (12 to < 18 years)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Investigations			

Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Injury, poisoning and procedural complications Head injury subjects affected / exposed occurrences (all) Eyelid abrasion subjects affected / exposed occurrences (all) Skin abrasion subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 1 / 1 (100.00%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Medical device pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Dry mouth	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 		

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Reproductive system and breast disorders Genital erythema subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Skin and subcutaneous tissue disorders Dermatitis subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Psychiatric disorders Mood swings subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Infections and infestations Viral infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Respiratory tract infection viral subjects affected / exposed occurrences (all) COVID-19 subjects affected / exposed occurrences (all) Gastroenteritis viral subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2021	The schedule of assessments is updated with the following changes: • Physical examination is added to visit 5 (week 4). • Height and body weight measurement is added to visit 7 (week 12). • Clinical Laboratory Tests (Hematology and Biochemistry) footnote is removed from visit 5 (week 4) • Self-blood pressure measurement (SBPM) is added visit 2 (week -2) and removed from visit 8 (week 14). • Pregnancy tests are added to visit 3 (week 0), visit 5 (week 4) and visit 7 (week 12). • Additional text is added to footnote h to explain that the SBPM should be done during the weekend preceding the study visit. • Footnote i is revised to remove visit 5 (week 4). Footnote j is revised to clarify that urine pregnancy tests will be performed for females of childbearing potential at all on-site visits. • The minimum weight of subjects is changed from 11 kg to 13 kg. This is updated in the dose rationale and Inclusion Criterion #4. • A criterion (#11) that subjects must have a pulse of > 99th percentile for age at Screening is deleted • Text is added to allow the option that the subject is currently taking medication known to prolong the QT interval. • The criterion is updated to exclude subjects who use moderate or strong cytochrome CYP3A4/5 or P-gp inhibitors or inducers.
01 February 2023	• The following secondary endpoint is removed: "mean number of nighttime incontinence episodes per 24 hours" • The following inclusion criterion is removed: "16 Subject must have at least 1 daytime incontinence episode (on average) per day, during the 7 day period before visit 3/baseline, as recorded in the bladder e diary." • The following exclusion criteria are removed: "1. Subject has extraordinary daytime only urinary frequency according to the ICCS definition. o This applies to a toilet-trained child who has the frequent need to void that is associated with small micturition volumes solely during the day. o The daytime voiding frequency is at least once per hour with an average voided volume of < 50% of expected bladder capacity (EBC) (typically 10% to 15%). o Incontinence is rare and nocturia is absent." "26. Subject has extraordinary daytime only urinary frequency according to the ICCS definition based on the bladder e diary." • The following exclusion criteria are removed: "3. Subject has monosymptomatic enuresis." "27. Subject has monosymptomatic enuresis confirmed by the bladder e-diary." • Exclusion criterion no. 2 is updated to: "flow indices as a predictor" of pathology other than OAB • The following text is added to exclusion criteria nos. 7 and 32: "Note: subjects with microhematuria without gross proteinuria are eligible." • The following new exclusion criteria at 'Visit 1/Week -4 (Screening)' are added after exclusion criterion no. 25: "36. Subject has a current or previous history of epilepsy. 37. Subject with neuropsychiatric diagnoses (e.g., ADHD, anxiety, severe depression, autism, bipolar disorder)" • Exclusion criterion no. 30 and footnote m in Table 1 is updated to: "> 30 mL (average of 2 lowest PVR volume results) as measured by a bladder ultrasound device that gives images in 3 planes." • Text in Sections 1.3 (Table 1, Footnote m) and 7.2.5 is updated to: "a bladder ultrasound device that gives images in 3 planes."

01 February 2023	• The following text is updated from: "Subject with (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mmHg." To: "Blood pressure at or above the stage II HTN threshold (≥ 95th percentile + 12 mmHg, or ≥ 140/90 mmHg [whichever is lower]) [Flynn et al, 2017]" • The interim analysis is updated from: "blinded" To: "comparative" • The uroflow assessment is removed from the screening visit and added to visit 3 (baseline). • The following text is added: • "Subjects with previously normal or pre HTN BPs will have a timely in-clinic visit, either scheduled or unscheduled, within 2 weeks of any home SBPM measurements that are at, or above, the stage l HTN threshold to measure, document and confirm BP increases. At this timely in person visit, BP measurements intended to confirm home SBPM measurements will be taken by trained healthcare personnel. • Subjects will have an expedited in-clinic visit, either scheduled or unscheduled, within 1 week of any home SBPM measurement that are at, or above, the stage II HTN threshold, and/or a pulse rate above the 99th percentile compared to age-related pulse rate norms and ≥ 15 bpm change from baseline, to measure, document and confirm BP and/or pulse rate increases. At this expedited in clinic visit, BP measurements will be taken by trained healthcare personnel." • The statistical methodology is updated From: In general, all data will be summarized with descriptive statistics frequency and percentage for categorical data. Data will be summarized by age group, treatment group and visit unless otherwise stated. To: In general, continuous data will be summarized descriptively including the number of subjects (n), mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized by frequencies and percentages.
01 February 2023	• The following bolded text is added to the age group details for the analysis of vital signs: "Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and within treatment group and across age group. In addition to the presentation by age groups for 5 to < 12 years of age and 12 to < 18 years of age and overall, vital signs will also be presented for age groups 5 to < 8 years of age and 8 to < 12 years of age."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 July 2023	Termination due to operational futility.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the small number of subjects, a proper assessment of the efficacy endpoints was not possible, and observed results were inconclusive and efficacy could not be determined due to early termination of the study.

Notes: