Clinical trial results:
An Open-label, Baseline-controlled, Multicenter, Phase 3 Dose-titration Study Followed by a Fixed-dose Observation Period to Evaluate Efficacy, Safety and Pharmacokinetics of Mirabegron in Children and Adolescents From 3 to Less Than 18 Years of Age with Neurogenic Detrusor Overactivity (NDO) on Clean Intermittent Catheterization

Summary

EudraCT number	2015-002876-25
Trial protocol	DK LT NO BE SK RO LV HR
Global end of trial date	06 May 2019

Results information

Result version number	v1
This version publication date	14 November 2019
First version publication date	14 November 2019

Trial information

Trial identification

Sponsor protocol code	178-CL-206A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02751931
WHO universal trial number (UTN)	-
Other trial identifiers	Acronym: Crocodile Study

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe B.V.
Sponsor organisation address	Sylviusweg 62, Leiden, Netherlands, 2333 BE
Public contact	Clinical Trial Disclosure, Astellas Pharma Europe B.V., astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Europe B.V., 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-PIP03-15
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
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	06 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of mirabegron after multiple-dose administration in the pediatric population.

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	17 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Jordan: 3
Country: Number of subjects enrolled	Latvia: 2
Country: Number of subjects enrolled	Lithuania: 7
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Philippines: 10
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Serbia: 4

Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Turkey: 6
Worldwide total number of subjects	91
EEA total number of subjects	52

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)	56
Adolescents (12-17 years)	35
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Pediatric participants consisting of male and female children from 3 to <12 and adolescents from 12 to <18 years of age, with a body weight of ≥11 kg, with NDO on clean intermittent catheterization (CIC) were enrolled in this study.

Pre-assignment

Screening details:

Eligible participants who met inclusion and none of the exclusion criteria were enrolled. Participants who received oral drug to manage their NDO completed a 2 week washout period. A total of 113 pediatric patients were screened, 22 of whom were screening failures.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Children (3 to < 12 Years)

Arm description:

Children age 3 to < 12 received an initial dose of 25 mg of mirabegron (pediatric equivalent dose [PED25]), orally once daily. Initial dose was up-titrated at weeks 2, 4 or 8 up to 50 mg of mirabegron (pediatric equivalent dose [PED50]). After week 24, participants stayed on their individual dose level until week 52 end-of-study (EOS) or end-of-treatment (EOT).

Arm type	Experimental
Investigational medicinal product name	Mirabegron Tablets
Investigational medicinal product code	YM178
Other name	Myrbetriq, Betmiga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received initial dose of 25 mg of mirabegron PED25 orally once daily. At weeks 2, 4 or 8, participants were up-titrated to PED50 based on the given dose titration criteria. Following week 24, participants stayed on their individual dose level until week 52 EOS or EOT. Participants with a body weight ≥35 kg received mirabegron tablets. At week 24, participants on mirabegron oral suspension could switch to tablets if the body weight became ≥35 kg. Participants who received mirabegron oral suspension could switch to mirabegron tablets for acceptability reasons after sponsor’s prior approval and on a case-by-case basis.

Investigational medicinal product name	Mirabegron Oral Suspension
Investigational medicinal product code	YM178
Other name	Myrbetriq, Betmiga
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants received initial dose of 25 mg of mirabegron PED25 orally once daily. At weeks 2, 4 or 8, participants were up-titrated to PED50 based on the given dose titration criteria. Following week 24, participants stayed on their individual dose level until week 52 EOS or EOT. Participants with a body weight <35 kg received mirabegron oral suspension. For participants with a body weight ≥35 kg who did not want to or were unable to take tablets, the oral suspension could have been supplied. Participants who received mirabegron tablets could switch to mirabegron oral suspension for acceptability reasons after sponsor’s prior approval and on a case-by-case basis. Mirabegron extended-release granules were reconstituted with water to prepare a mirabegron oral suspension of 8 mg/mL. Administration was via an oral syringe with a sip of water afterwards.

Arm title	Adolescents (12 to < 18 Years)

Arm description:

Adolescents age 12 to < 18 received an initial dose of 25 mg of mirabegron (PED25), orally once daily. Initial dose was up-titrated at weeks 2, 4 or 8 up to 50 mg of mirabegron (PED50). After week 24, participants stayed on their individual dose level until week 52 end-of-study (EOS) or end-of-treatment (EOT).

Arm type	Experimental
Investigational medicinal product name	Mirabegron Tablets
Investigational medicinal product code	YM178
Other name	Myrbetriq, Betmiga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received initial dose of 25 mg of mirabegron PED25 orally once daily. At weeks 2, 4 or 8, participants were up-titrated to PED50 based on the given dose titration criteria. Following week 24, participants stayed on their individual dose level until week 52 EOS or EOT. Participants with a body weight ≥35 kg received mirabegron tablets. At week 24, participants on mirabegron oral suspension could switch to tablets if the body weight became ≥35 kg. Participants who received mirabegron oral suspension could switch to mirabegron tablets for acceptability reasons after sponsor’s prior approval and on a case-by-case basis.

Investigational medicinal product name	Mirabegron Oral Suspension
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Other name	Myrbetriq, Betmiga
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants received initial dose of 25 mg of mirabegron PED25 orally once daily. At weeks 2, 4 or 8, participants were up-titrated to PED50 based on the given dose titration criteria. Following week 24, participants stayed on their individual dose level until week 52 EOS or EOT. Participants with a body weight <35 kg received mirabegron oral suspension. For participants with a body weight ≥35 kg who did not want to or were unable to take tablets, the oral suspension could have been supplied. Participants who received mirabegron tablets could switch to mirabegron oral suspension for acceptability reasons after sponsor’s prior approval and on a case-by-case basis. Mirabegron extended-release granules were reconstituted with water to prepare a mirabegron oral suspension of 8 mg/mL. Administration was via an oral syringe with a sip of water afterwards.

Number of subjects in period 1	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)
Started	56	35
Received Study Drug	55	31
Completed	43	27
Not completed	13	8
Adverse Event	3	-
Miscellaneous	10	8

Baseline characteristics

Reporting groups	
Reporting group title	Children (3 to < 12 Years)
Reporting group description:	
Children age 3 to < 12 received an initial dose of 25 mg of mirabegron (pediatric equivalent dose [PED25]), orally once daily. Initial dose was up-titrated at weeks 2, 4 or 8 up to 50 mg of mirabegron (pediatric equivalent dose [PED50]). After week 24, participants stayed on their individual dose level until week 52 end-of-study (EOS) or end-of-treatment (EOT).	
Reporting group title	Adolescents (12 to < 18 Years)
Reporting group description:	
Adolescents age 12 to < 18 received an initial dose of 25 mg of mirabegron (PED25), orally once daily. Initial dose was up-titrated at weeks 2, 4 or 8 up to 50 mg of mirabegron (PED50). After week 24, participants stayed on their individual dose level until week 52 end-of-study (EOS) or end-of-treatment (EOT).	

Reporting group values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)	Total
Number of subjects	56	35	91
Age categorical			
Units: Subjects			
Age continuous			
The baseline characteristics analysis population consisted of the all enrolled/all allocated set (total of 91 participants).			
Units: years			
arithmetic mean	7.9	13.9	
standard deviation	± 2.5	± 1.6	-
Gender categorical			
The baseline characteristics analysis population consisted of the all enrolled/all allocated set (total of 91 participants).			
Units: Subjects			
M	23	20	43
F	33	15	48
Analysis Race			
The baseline characteristics analysis population consisted of the all enrolled/all allocated set (total of 91 participants).			
Units: Subjects			
White	41	25	66
Asian	13	8	21
American Indian/Alaska Native	0	1	1
Other	2	1	3
Ethnicity			
The baseline characteristics analysis population consisted of the all enrolled/all allocated set (total of 91 participants).			
Units: Subjects			
NOT HISPANIC OR LATINO	55	33	88
HISPANIC OR LATINO	1	2	3
Maximum Cystometric Capacity (MCC) (mL)			
The study specific baseline characteristics analysis population consisted of the all enrolled/all allocated set with MCC baseline data collected (total of 86 participants).			
Units: Year			

arithmetic mean	167.35	242.42	
standard deviation	± 100	± 100.64	-

End points

End points reporting groups

Reporting group title	Children (3 to < 12 Years)

Reporting group description:

Children age 3 to < 12 received an initial dose of 25 mg of mirabegron (pediatric equivalent dose [PED25]), orally once daily. Initial dose was up-titrated at weeks 2, 4 or 8 up to 50 mg of mirabegron (pediatric equivalent dose [PED50]). After week 24, participants stayed on their individual dose level until week 52 end-of-study (EOS) or end-of-treatment (EOT).

Reporting group title	Adolescents (12 to < 18 Years)

Reporting group description:

Adolescents age 12 to < 18 received an initial dose of 25 mg of mirabegron (PED25), orally once daily. Initial dose was up-titrated at weeks 2, 4 or 8 up to 50 mg of mirabegron (PED50). After week 24, participants stayed on their individual dose level until week 52 end-of-study (EOS) or end-of-treatment (EOT).

Subject analysis set title	Children PED25
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants aged 3 to < 12 years who received pediatric equivalent dose of 25 mg at the time of PK sampling.

Subject analysis set title	Adolescents PED25
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants aged 12 to < 18 years who received pediatric equivalent dose of 25 mg at the time of PK sampling.

Subject analysis set title	Children PED50
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants aged 3 to < 12 years who received pediatric equivalent dose of 50 mg at the time of PK sampling.

Subject analysis set title	Adolescents PED50
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants aged 12 to < 18 years who received pediatric equivalent dose of 50 mg at the time of PK sampling.

Primary: Change From Baseline in Maximum Cystometric Capacity (MCC) at Week 24

End point title	Change From Baseline in Maximum Cystometric Capacity (MCC) at Week 24

End point description:

Change from baseline in MCC was based on filling urodynamics, volume at the end of filling. During urodynamic assessments, the bladder was filled until voiding/leakage began, or until the participant experienced pain or discomfort, or because dangerous high detrusor pressure, or 135% of maximum catheterized volume for age had been reached. A valid urodynamic assessment was confirmed valid by the central reviewers. The analysis population consisted of the full analysis set (FAS) which consisted of all participants who took ≥ 1 dose of study drug and provided both valid (as by the central reviewer's assessment) nonmissing MCC measurements at baseline and at a postbaseline visit for the primary efficacy endpoint. Missing MCC observations at week 24 were imputed using last observation carried forward (LOCF).

End point type	Primary

End point timeframe:

Baseline and week 24

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: mL				
arithmetic mean (standard deviation)	72.09 (± 87.09)	113.21 (± 82.99)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 24 - Children

Statistical analysis description:

Change from baseline in MCC in children at week 24. The number of participants included in this analysis was 43.

Comparison groups	Adolescents (12 to < 18 Years) v Children (3 to < 12 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [1]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	45.28
upper limit	98.89

Notes:

[1] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Adolescents

Statistical analysis description:

Change from baseline in MCC in adolescents at week 24. The number of participants included in this analysis was 25.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [2]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	78.95
upper limit	147.47

Notes:

[2] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Secondary: Change From Baseline in MCC at Week 4

End point title	Change From Baseline in MCC at Week 4

End point description:

Change from baseline in MCC was based on filling urodynamics (volume at the end of filling). During urodynamic assessments, the bladder was filled until voiding/leakage began, or until the participant experienced pain or discomfort, or because dangerous high detrusor pressure, or 135% of maximum catheterized volume for age had been reached. A valid urodynamic assessment was confirmed valid by the central reviewers. The analysis population consisted of the FAS.

End point type	Secondary

End point timeframe:

Baseline and week 4

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	25		
Units: mL				
arithmetic mean (standard deviation)	41.36 (± 71.64)	80.78 (± 96.15)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 4 - Children

Statistical analysis description:

Change from baseline in MCC in children at week 4. The number of participants included in this analysis was 41.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [3]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.75
upper limit	63.97

Notes:

[3] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Adolescents

Statistical analysis description:

Change from baseline in MCC in adolescents at week 4. The number of participants included in this analysis was 25.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [4]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	39.2
upper limit	122.36

Notes:

[4] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Secondary: Change From Baseline in Bladder Compliance (ΔV/ΔP)

End point title	Change From Baseline in Bladder Compliance (ΔV/ΔP)

End point description:

Change from baseline in bladder compliance (change in volume/change in pressure) was assessed by the independent central reviewers and reported as annotations on the urodynamic trace and in an external database. During urodynamic assessments, the bladder was filled until voiding/leakage began, or until the participant experienced pain or discomfort, or because dangerous high detrusor pressure, or 135% of maximum catheterized volume for age had been reached. A valid urodynamic assessment was confirmed valid by the central reviewers. The analysis population consisted of the FAS. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 4 and 24

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: mL/cm H2O				
arithmetic mean (standard deviation)				
Week 4 (N=39, 22)	-4.09 (± 50.78)	15.16 (± 22.69)		
Week 24 (N=33, 21)	14.62 (± 42.09)	13.59 (± 15.02)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 4 - Children

Statistical analysis description:

Change from baseline in ΔV/ΔP in children at week 4. The number of participants included in this analysis was 39.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.618 [5]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.55
upper limit	12.38

Notes:

[5] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Adolescents

Statistical analysis description:

Change from baseline in ΔV/ΔP in adolescents at week 4. The number of participants included in this analysis was 22.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.005 [6]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.1
upper limit	25.22

Notes:

[6] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Children

Statistical analysis description:

Change from baseline in ΔV/ΔP in children at week 24. The number of participants included in this analysis was 33.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.055 [7]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	29.54

Notes:

[7] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Adolescents

Statistical analysis description:

Change from baseline in ΔV/ΔP in adolescents at week 24. The number of participants included in this analysis was 21.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [8]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.75
upper limit	20.42

Notes:

[8] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Secondary: Change From Baseline in Number of Overactive Detrusor Contractions (> 15 cm H20) Until End of Filling

End point title	Change From Baseline in Number of Overactive Detrusor Contractions (> 15 cm H20) Until End of Filling

End point description:

Detrusor overactivity is the occurrence of involuntary detrusor contractions during filling cystometry. During urodynamic assessments, the bladder was filled until voiding/leakage began, or until the participant experienced pain or discomfort, or because dangerous high detrusor pressure, or 135% of maximum catheterized volume for age had been reached. A valid urodynamic assessment was confirmed valid by the central reviewers. The analysis population consisted of the FAS. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 4 and 24

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: overactive detrusor contractions				
arithmetic mean (standard deviation)				
Week 4 (N=41, 22)	0.44 (± 5.82)	-0.64 (± 2.94)		
Week 24 (N=36, 22)	-1.86 (± 4.16)	-0.77 (± 3.87)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 4 - Children

Statistical analysis description:

Change from baseline in number of overactive detrusor contractions in children at week 4. The number of participants included in this analysis was 41.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.632 [9]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	2.28

Notes:

[9] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Adolescents

Statistical analysis description:

Change from baseline in number of overactive detrusor contractionsin adolescents at week 4. The number of participants included in this analysis was 22.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.321 [10]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.94
upper limit	0.67

Notes:

[10] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Children

Statistical analysis description:

Change from baseline in number of overactive detrusor contractions in children at week 24. The number of participants included in this analysis was 36.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.011 [11]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.27
upper limit	-0.45

Notes:

[11] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Adolescents

Statistical analysis description:

Change from baseline in number of overactive detrusor contractions in adolescents at week 24. The number of participants included in this analysis was 22.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.359 [12]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.49
upper limit	0.94

Notes:

[12] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Secondary: Change From Baseline in Detrusor Pressure at End of Filling

End point title	Change From Baseline in Detrusor Pressure at End of Filling

End point description:

Filling was stopped (end of filling) when the detrusor pressure exceeded 100 cm H2O or was considered dangerously high by the investigator or urodynamicist (for instance, a prolonged passive detrusor pressure > 40 cm H2O). During urodynamic assessments, the bladder was filled until voiding/leakage began, or until the participant experienced pain or discomfort, or because dangerous high detrusor pressure, or 135% of maximum catheterized volume for age had been reached. A valid urodynamic assessment was confirmed valid by the central reviewers. The analysis population consisted of the FAS. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 4 and 24

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: cm H2O				
arithmetic mean (standard deviation)				
Week 4 (N=41, 22)	-12.38 (± 19.56)	-6.48 (± 30.70)		
Week 24 (N=36, 22)	-18.11 (± 19.97)	-13.19 (± 19.91)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 4 - Children

Statistical analysis description:

Change from baseline in detrusor pressure in children at week 4. The number of participants included in this analysis was 41.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [13]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.56
upper limit	-6.21

Notes:

[13] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Adolescents

Statistical analysis description:

Change from baseline in detrusor pressure in adolescents at week 4. The number of participants included in this analysis was 22.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.334 [14]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.09
upper limit	7.13

Notes:

[14] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Children

Statistical analysis description:

Change from baseline in detrusor pressure in children at week 24. The number of participants included in this analysis was 36.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [15]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.87
upper limit	-11.35

Notes:

[15] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Adolescents

Statistical analysis description:

Change from baseline in detrusor pressure in adolescents at week 24. The number of participants included in this analysis was 22.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.005 [16]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.02
upper limit	-4.36

Notes:

[16] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Secondary: Change From Baseline in Filling Bladder Volume Until First Overactive Detrusor Contraction (> 15 cm H20)

End point title	Change From Baseline in Filling Bladder Volume Until First Overactive Detrusor Contraction (> 15 cm H20)

End point description:

Detrusor overactivity is the occurrence of involuntary detrusor contractions during filling cystometry. During urodynamic assessments, the bladder was filled until voiding/leakage began, or until the participant experienced pain or discomfort, or because dangerous high detrusor pressure, or 135% of maximum catheterized volume for age had been reached. A valid urodynamic assessment was confirmed valid by the central reviewers. The analysis population consisted of the FAS. N is the number of participants with available data at each time point. If no detrusor contraction of > 15 cm H2O occurred, the bladder volume was imputed with maximum cystometric capacity.

End point type	Secondary

End point timeframe:

Baseline and weeks 4 and 24

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: mL				
median (inter-quartile range (Q1-Q3))				
Week 4 (N=21, 8)	54.00 (13.00 to 105.30)	41.15 (3.00 to 62.50)		
Week 24 (N=13, 8)	68.00 (32.00 to 110.0)	62.00 (4.00 to 95.15)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 4 - Children

Statistical analysis description:

Change from baseline in filling bladder volume until first overactive detrusor contraction in children at week 4. The number of participants included in this analysis was 21.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [17]
Method	Wilcoxon signed-rank test

Notes:

[17] - From a Wilcoxon signed-rank test, testing the null hypothesis that week 24 median is equal to baseline median.

Statistical analysis title	Change From Baseline at Week 4 - Adolescents

Statistical analysis description:

Change from baseline in filling bladder volume until first overactive detrusor contraction in adolescents at week 4. The number of participants included in this analysis was 8.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.148 [18]
Method	Wilcoxon signed-rank test

Notes:

[18] - From a Wilcoxon signed-rank test, testing the null hypothesis that week 24 median is equal to baseline median.

Statistical analysis title	Change From Baseline at Week 24 - Children

Statistical analysis description:

Change from baseline in filling bladder volume until first overactive detrusor contraction in children at week 24. The number of participants included in this analysis was 13.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 [19]
Method	Wilcoxon signed-rank test

Notes:

[19] - From a Wilcoxon signed-rank test, testing the null hypothesis that week 24 median is equal to baseline median.

Statistical analysis title	Change From Baseline at Week 24 - Adolescents

Statistical analysis description:

Change from baseline in filling bladder volume until first overactive detrusor contraction in adolescents at week 24. The number of participants included in this analysis was 8.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.039 [20]
Method	Wilcoxon signed-rank test

Notes:

[20] - From a Wilcoxon signed-rank test, testing the null hypothesis that week 24 median is equal to baseline median.

Secondary: Change From Baseline in Average Catheterized Volume Per Catheterization

End point title	Change From Baseline in Average Catheterized Volume Per Catheterization

End point description:

For each participant, the average catheterized volume per catheterization was calculated as the sum of all available/non-missing catheterized volumes recorded over 2 measuring days in the weekend diary, whether or not the 2 days were consecutive divided by the number of catheterizations with non-missing volumes. If volumes were recorded on 1 single day of the weekend diary, the average catheterized volume per catheterization was calculated using all available/non-missing catheterized volumes recorded that day. If no volumes were recorded on any day of the weekend diary, the average catheterized volume per catheterization was missing. A valid bladder diary day in the weekend diary was any e-diary day for which ≥1 catheterized volume >0 mL was recorded with complete date and time. Analysis population consisted of the FAS. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: mL				
arithmetic mean (standard deviation)				
Week 2 (N=43, 24)	14.58 (± 43.98)	35.99 (± 54.19)		
Week 4 (N=42, 24)	30.08 (± 49.50)	51.96 (± 64.71)		
Week 8 (N=43, 22)	36.90 (± 46.05)	45.10 (± 53.77)		
Week 12 (N=43, 24)	32.25 (± 45.51)	43.94 (± 58.49)		
Week 24 (N=41, 23)	41.63 (± 58.03)	59.31 (± 82.22)		
Week 36 (N=40, 24)	53.87 (± 91.74)	52.14 (± 74.90)		
Week 52 (N=40, 23)	42.84 (± 65.31)	42.40 (± 69.25)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 2 - Children

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in children at week 2. The number of participants included in this analysis was 43.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.035 [21]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	28.1

Notes:

[21] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 2 - Adolescents

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in adolescents at week 2. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003 [22]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.1
upper limit	58.9

Notes:

[22] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Children

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in children at week 4. The number of participants included in this analysis was 42.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [23]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.7
upper limit	45.5

Notes:

[23] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Adolescents

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in adolescents at week 4. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [24]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.6
upper limit	79.3

Notes:

[24] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 8 - Children

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in children at week 8. The number of participants included in this analysis was 43.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [25]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.7
upper limit	51.1

Notes:

[25] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 8 - Adolescents

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in adolescents at week 8. The number of participants included in this analysis was 2.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [26]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.3
upper limit	68.9

Notes:

[26] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 12 - Children

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in children at week 12. The number of participants included in this analysis was 43.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [27]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.2
upper limit	46.3

Notes:

[27] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 12 - Adolescents

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in adolescents at week 12. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001 [28]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.2
upper limit	68.6

Notes:

[28] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Children

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in children at week 24. The number of participants included in this analysis was 41.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [29]
Method	Paired t-test

Confidence interval	
level	95 %
sides	2-sided
lower limit	23.3
upper limit	60

Notes:

[29] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Adolescents

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in adolescents at week 24. The number of participants included in this analysis was 23.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 [30]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.8
upper limit	94.9

Notes:

[30] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 36 - Children

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in children at week 36. The number of participants included in this analysis was 40.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [31]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.5
upper limit	83.2

Notes:

[31] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 36 - Adolescents

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in adolescents at week 36. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 [32]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.5
upper limit	83.8

Notes:

[32] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Children

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in children at week 52. The number of participants included in this analysis was 40.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [33]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	22
upper limit	63.7

Notes:

[33] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Adolescents

Statistical analysis description:

Change from baseline in average catheterized volume per catheterization in adolescents at week 52. The number of participants included in this analysis was 23.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.008 [34]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.5
upper limit	72.3

Notes:

[34] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Secondary: Change From Baseline in Maximum Catheterized Volume

End point title	Change From Baseline in Maximum Catheterized Volume

End point description:

For each participant, the maximum catheterized volume per day was calculated using all available/non-missing catheterized volumes recorded for the 2 measuring days in the weekend e-diary, whether or not these 2 days were consecutive. Maximum value was calculated separately for each measuring day & the mean of the two values was used. If volumes recorded on 1 single day of the weekend e-diary, the maximum catheterized volume per day was calculated using all available/non-zero catheterized volumes recorded that day. If no volumes were recorded on any day of the weekend e-diary, the maximum catheterized volume per day was missing. A valid bladder diary day in the weekend diary was any e-diary day for which ≥1 catheterized volume >0 mL was recorded with complete date and time. Analysis population consisted of the FAS. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: mL				
arithmetic mean (standard deviation)				
Week 2 (N=43, 24)	17.50 (± 73.58)	42.38 (± 78.23)		
Week 4 (N=42, 24)	46.69 (± 80.29)	73.25 (± 103.98)		
Week 8 (N=43, 22)	45.27 (± 75.22)	42.86 (± 79.97)		
Week 12 (N=43, 24)	33.23 (± 68.31)	47.29 (± 69.83)		
Week 24 (N=41, 23)	49.88 (± 103.70)	84.39 (± 121.98)		
Week 36 (N=40, 24)	60.09 (± 121.66)	54.78 (± 104.54)		
Week 52 (N=40, 23)	53.51 (± 96.72)	54.30 (± 104.74)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 2 - Children

Statistical analysis description:

Change from baseline in maximum catheterized volume in children at week 2. The number of participants included in this analysis was 43.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.126 [35]
Method	Paired t-test

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	40.1

Notes:

[35] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 2 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized volume in adolescents at week 2. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.014 [36]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.3
upper limit	75.4

Notes:

[36] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Children

Statistical analysis description:

Change from baseline in maximum catheterized volume in children at week 4. The number of participants included in this analysis was 42.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [37]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.7
upper limit	71.7

Notes:

[37] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized volume in adolescents at week 4. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 [38]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.3
upper limit	117.2

Notes:

[38] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 8 - Children

Statistical analysis description:

Change from baseline in maximum catheterized volume in children at week 8. The number of participants included in this analysis was 43.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [39]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.1
upper limit	68.4

Notes:

[39] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 8 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized volume in adolescents at week 8. The number of participants included in this analysis was 22.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.4
upper limit	78.3

Statistical analysis title	Change From Baseline at Week 12 - Children

Statistical analysis description:

Change from baseline in maximum catheterized volume in children at week 12. The number of participants included in this analysis was 43.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003 [40]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.2
upper limit	54.3

Notes:

[40] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 12 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized volume in adolescents at week 12. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003 [41]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.8
upper limit	76.8

Notes:

[41] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Children

Statistical analysis description:

Change from baseline in maximum catheterized volume in children at week 24. The number of participants included in this analysis was 41.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004 [42]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.1
upper limit	82.6

Notes:

[42] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized volume in adolescents at week 24. The number of participants included in this analysis was 23.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003 [43]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.6
upper limit	137.1

Notes:

[43] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 36 - Children

Statistical analysis description:

Change from baseline in maximum catheterized volume in children at week 36. The number of participants included in this analysis was 40.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003 [44]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.2
upper limit	99

Notes:

[44] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 36 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized volume in adolescents at week 36. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.017 [45]
Method	Paired t-test

Confidence interval	
level	95 %
sides	2-sided
lower limit	10.6
upper limit	98.9

Notes:

[45] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Children

Statistical analysis description:

Change from baseline in maximum catheterized volume in children at week 52. The number of participants included in this analysis was 40.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001 [46]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.6
upper limit	84.4

Notes:

[46] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized volume in adolescents at week 52. The number of participants included in this analysis was 23.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.021 [47]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	9
upper limit	99.6

Notes:

[47] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Secondary: Change From Baseline in Maximum Catheterized Daytime Volume (MCDV)

End point title	Change From Baseline in Maximum Catheterized Daytime Volume (MCDV)

End point description:

For each participant, the MCDV was calculated using all available/non-missing catheterized daytime volumes for the 2 measuring days in the weekend e-diary, whether or not the 2 days were consecutive.

Maximum value was calculated separately for each measuring day & the mean of the 2 values was used. If volumes were recorded on 1 single day of the weekend e-diary, the MCDV was calculated using all available/non-zero catheterized daytime volumes recorded that day. If no volumes were recorded on any day of the weekend e-diary, the MCDV was missing. Daytime was defined as the time between wake-up time (minus 30 min) & time to sleep (plus 29 min) recorded in the e-diary. A valid bladder diary day in the weekend diary was any e-diary day for which ≥1 catheterized volume >0 mL was recorded with complete date and time. Analysis population consisted of the FAS. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: mL				
arithmetic mean (standard deviation)				
Week 2 (N=43, 24)	18.13 (± 73.38)	35.58 (± 86.78)		
Week 4 (N=42, 24)	37.71 (± 83.33)	70.35 (± 113.98)		
Week 8 (N=43, 22)	43.91 (± 74.44)	38.11 (± 90.88)		
Week 12 (N=43, 24)	29.05 (± 67.86)	43.04 (± 73.82)		
Week 24 (N=41, 23)	44.20 (± 98.31)	81.37 (± 117.77)		
Week 36 (N=40, 24)	58.49 (± 121.12)	50.90 (± 114.05)		
Week 52 (N=40, 23)	53.76 (± 100.24)	49.13 (± 117.23)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 2 - Children

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in children at week 2. The number of participants included in this analysis was 43.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.113 [48]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	40.7

Notes:

[48] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 2 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in adolescents at week 2. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.056 [49]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	72.2

Notes:

[49] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Children

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in children at week 4. The number of participants included in this analysis was 42.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.005 [50]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.7
upper limit	63.7

Notes:

[50] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in adolescents at week 4. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006 [51]
Method	Paired t-test

Confidence interval	
level	95 %
sides	2-sided
lower limit	22.2
upper limit	118.5

Notes:

[51] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 8 - Children

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in children at week 8. The number of participants included in this analysis was 43.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [52]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	21
upper limit	66.8

Notes:

[52] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 8 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in adolescents at week 8. The number of participants included in this analysis was 22.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.063 [53]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	78.4

Notes:

[53] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 12 - Children

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in children at week 12. The number of participants included in this analysis was 43.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.008 [54]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.2
upper limit	49.9

Notes:

[54] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 12 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in adolescents at week 12. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009 [55]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.9
upper limit	74.2

Notes:

[55] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Children

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in children at week 24. The number of participants included in this analysis was 41.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006 [56]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.2
upper limit	75.2

Notes:

[56] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in adolescents at week 24. The number of participants included in this analysis was 23.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003 [57]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	30.4
upper limit	132.3

Notes:

[57] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 36 - Children

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in children at week 36. The number of participants included in this analysis was 40.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004 [58]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.8
upper limit	97.2

Notes:

[58] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 36 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in adolescents at week 36. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.039 [59]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.7
upper limit	99.1

Notes:

[59] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Children

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in children at week 52. The number of participants included in this analysis was 40.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 [60]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.7
upper limit	85.8

Notes:

[60] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Adolescents

Statistical analysis description:

Change from baseline in maximum catheterized daytime volume in adolescents at week 52. The number of participants included in this analysis was 23.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.057 [61]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	99.8

Notes:

[61] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Secondary: Change From Baseline in Average Morning Catheterized Volume

End point title	Change From Baseline in Average Morning Catheterized Volume

End point description:

The first morning catheterized volume was the first recorded non-zero volume within or after the hour of the wake-up time on a volume-measuring day in the e-diary. The average first morning catheterized volume was calculated as the average of the available first morning catheterized volumes recorded for the 2 measuring days in the weekend e-diary, whether or not these 2 days were consecutive. If the first morning catheterized volume was recorded on 1 single day of the weekend e-diary, the average morning catheterized is the first morning catheterized that day. If no first morning catheterized volumes are recorded on any day of the weekend e-diary, the average first morning catheterized volume was missing. A valid bladder diary day in the weekend diary was any e-diary day for which ≥1 catheterized volume >0 mL was recorded with complete date and time. Analysis population consisted of the FAS. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: mL				
arithmetic mean (standard deviation)				
Week 2 (N=41, 21)	7.98 (± 101.36)	39.52 (± 80.24)		
Week 4 (N=40, 20)	19.81 (± 89.04)	75.25 (± 105.72)		
Week 8 (N=41, 21)	34.01 (± 89.53)	44.43 (± 89.01)		
Week 12 (N=39, 21)	8.68 (± 80.16)	38.23 (± 66.80)		
Week 24 (N=36, 20)	40.76 (± 116.41)	86.66 (± 96.55)		
Week 36 (N=37, 21)	31.08 (± 145.63)	68.47 (± 122.43)		
Week 52 (N=39, 21)	31.83 (± 94.25)	38.14 (± 108.06)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 2 - Children

Statistical analysis description:

Change from baseline in average morning catheterized volume in children at week 2. The number of participants included in this analysis was 41.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.617 [62]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24
upper limit	40

Notes:

[62] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 2 - Adolescents

Statistical analysis description:

Change from baseline in average morning catheterized volume in adolescents at week 2. The number of participants included in this analysis was 21.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.035 [63]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	3
upper limit	76

Notes:

[63] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Children

Statistical analysis description:

Change from baseline in average morning catheterized volume in children at week 4. The number of participants included in this analysis was 40.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.167 [64]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	48.3

Notes:

[64] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Adolescents

Statistical analysis description:

Change from baseline in average morning catheterized volume in adolescents at week 4. The number of participants included in this analysis was 20.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.005 [65]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.8
upper limit	124.7

Notes:

[65] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 8 - Children

Statistical analysis description:

Change from baseline in average morning catheterized volume in children at week 8. The number of participants included in this analysis was 41.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02 [66]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.7
upper limit	62.3

Notes:

[66] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 8 - Adolescents

Statistical analysis description:

Change from baseline in average morning catheterized volume in adolescents at week 8. The number of participants included in this analysis was 21.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.033 [67]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.9
upper limit	84.9

Notes:

[67] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 12 - Children

Statistical analysis description:

Change from baseline in average morning catheterized volume in children at week 12. The number of participants included in this analysis was 39.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.503 [68]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.3
upper limit	34.7

Notes:

[68] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 12 - Adolescents

Statistical analysis description:

Change from baseline in average morning catheterized volume in adolescents at week 12. The number of participants included in this analysis was 21.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.016 [69]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.8
upper limit	68.6

Notes:

[69] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Children

Statistical analysis description:

Change from baseline in average morning catheterized volume in children at week 24. The number of participants included in this analysis was 36.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.043 [70]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	80.2

Notes:

[70] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Adolescents

Statistical analysis description:

Change from baseline in average morning catheterized volume in adolescents at week 24. The number of participants included in this analysis was 20.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [71]
Method	Paired t-test

Confidence interval	
level	95 %
sides	2-sided
lower limit	41.5
upper limit	131.8

Notes:

[71] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 36 - Children

Statistical analysis description:

Change from baseline in average morning catheterized volume in children at week 36. The number of participants included in this analysis was 37.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.203 [72]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.5
upper limit	79.6

Notes:

[72] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 36 - Adolescents

Statistical analysis description:

Change from baseline in average morning catheterized volume in adolescents at week 36. The number of participants included in this analysis was 21.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.019 [73]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.7
upper limit	124.2

Notes:

[73] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Children

Statistical analysis description:

Change from baseline in average morning catheterized volume in children at week 52. The number of participants included in this analysis was 39.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.042 [74]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	62.4

Notes:

[74] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Adolescents

Statistical analysis description:

Change from baseline in average morning catheterized volume in adolescents at week 52. The number of participants included in this analysis was 21.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.121 [75]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	87.3

Notes:

[75] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Secondary: Change From Baseline in Mean Number of Leakage Episodes per Day

End point title	Change From Baseline in Mean Number of Leakage Episodes per Day

End point description:

For each participant, the mean number of leakage episodes per day (during day & night time) was calculated using all available/non-missing number of leakage episodes for the 2 measuring days in the weekend diary during day & night time. If the number of leakage episodes was recorded on 1 single day in the 7-day diary during day & night time, the mean number of leakage episodes per day during day & night time is equal to the total number of leakage episodes recorded that day during day & night time. If no leakage episodes were recorded on any day of the weekend diary during day & night time, the mean number of leakage episodes per day was zero. If nothing was recorded/diary not completed the result was missing. A valid bladder diary day in the weekend diary was any e-diary day for which ≥1 catheterized volume >0 mL was recorded with complete date and time. Analysis population consisted of the FAS. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: leakage episodes per day				
arithmetic mean (standard deviation)				
Week 2 (N=38, 15)	0.33 (± 9.47)	-0.73 (± 1.25)		
Week 4 (N=35, 13)	-1.23 (± 3.40)	-1.19 (± 1.56)		
Week 8 (N=34, 9)	1.16 (± 16.36)	-0.94 (± 1.61)		
Week 12 (N=32, 12)	0.35 (± 13.24)	-0.79 (± 1.53)		
Week 24 (N=31, 13)	0.18 (± 10.05)	-0.88 (± 1.23)		
Week 36 (N=28, 12)	-2.20 (± 4.41)	-0.96 (± 1.42)		
Week 52 (N=27, 13)	-1.52 (± 2.78)	-1.12 (± 1.97)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 2 - Children
Statistical analysis description:	
Change from baseline in mean number of leakage episodes per day in children at week 2. The number of participants included in this analysis was 38.	
Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.832 [76]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	3.4

Notes:

[76] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 2 - Adolescents
Statistical analysis description:	
Change from baseline in mean number of leakage episodes per day in adolescents at week 2. The number of participants included in this analysis was 15.	
Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04 [77]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0

Notes:

[77] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Children

Statistical analysis description:

Change from baseline in mean number of leakage episodes per day in children at week 4. The number of participants included in this analysis was 35.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04 [78]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	-0.1

Notes:

[78] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Adolescents

Statistical analysis description:

Change from baseline in mean number of leakage episodes per day in adolescents at week 4. The number of participants included in this analysis was 13.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.018 [79]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	-0.2

Notes:

[79] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 8 - Children

Statistical analysis description:

Change from baseline in mean number of leakage episodes per day in children at week 8. The number of participants included in this analysis was 34.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.681 [80]
Method	Paired t-test

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	6.9

Notes:

[80] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 8 - Adolescents

Statistical analysis description:

Change from baseline in mean number of leakage episodes per day in adolescents at week 8. The number of participants included in this analysis was 9.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.116 [81]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	0.3

Notes:

[81] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 12 - Children

Statistical analysis description:

Change from baseline in mean number of leakage episodes per day in children at week 12. The number of participants included in this analysis was 32.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.882 [82]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	5.1

Notes:

[82] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 12 - Adolescents

Statistical analysis description:

Change from baseline in mean number of leakage episodes per day in adolescents at week 12. The number of participants included in this analysis was 12.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1 [83]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0.2

Notes:

[83] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Children

Statistical analysis description:

Change from baseline in mean number of leakage episodes per day in children at week 24. The number of participants included in this analysis was 31.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.922 [84]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	3.9

Notes:

[84] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Adolescents

Statistical analysis description:

Change from baseline in mean number of leakage episodes per day in adolescents at week 24. The number of participants included in this analysis was 13.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.023 [85]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-0.1

Notes:

[85] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 36 - Children

Statistical analysis description:

Change from baseline in mean number of leakage episodes per day in children at week 36. The number of participants included in this analysis was 28.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.014 [86]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	-0.5

Notes:

[86] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 36 - Adolescents

Statistical analysis description:

Change from baseline in mean number of leakage episodes per day in adolescents at week 36. The number of participants included in this analysis was 12.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.039 [87]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	-0.1

Notes:

[87] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Children

Statistical analysis description:

Change from baseline in mean number of leakage episodes per day in children at week 52. The number of participants included in this analysis was 27.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009 [88]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	-0.4

Notes:

[88] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Adolescents

Statistical analysis description:

Change from baseline in mean number of leakage episodes per day in adolescents at week 52. The number of participants included in this analysis was 13.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.064 [89]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	0.1

Notes:

[89] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Secondary: Change From Baseline in Number of Dry Days per 7 Days (Day and Night Time)

End point title	Change From Baseline in Number of Dry Days per 7 Days (Day and Night Time)

End point description:

Dry days were defined as leakage-free days, this included day and night time. Participants recorded dry days in the 7-day diary. Dry days were calculated as follows: Ddry was the number of valid diary days where the response to the question 'Did you leak between this catheterization and the last one' was 'No' each time a new catheterization was entered in the e-diary during the day & night time period. Dwet was the number of valid diary days where the response to the question 'Did you leak between this catheterization and the last one' was 'Yes' for at least one catheterization entered during the day & night time period. If (Ddry + Dwet) > 3, the number of dry days per 7 days was calculated as Ddry/(Ddry + Dwet) x 7, otherwise the value was missing. Analysis population consisted of the FAS. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 2, 4, 8, 12, 24, 36, and 52

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: number of dry days per 7 days				
arithmetic mean (standard deviation)				
Week 2 (N=43, 24)	0.34 (± 0.91)	0.82 (± 1.90)		
Week 4 (N=42, 24)	0.68 (± 1.69)	1.36 (± 1.91)		
Week 8 (N=43, 23)	1.14 (± 2.15)	2.26 (± 2.48)		
Week 12 (N=43, 24)	1.31 (± 2.50)	1.93 (± 2.46)		
Week 24 (N=41, 24)	1.34 (± 2.18)	2.17 (± 2.38)		

Week 36 (N=39, 24)	1.33 (± 2.43)	1.88 (± 2.13)		
Week 52 (N=40, 24)	1.38 (± 2.65)	2.14 (± 2.51)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 2 - Children
Statistical analysis description:	
Change from baseline in number of dry days per 7 days (day and night time) in children at week 2. The number of participants included in this analysis was 43.	
Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.018 [90]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.6

Notes:

[90] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 2 - Adolescents
Statistical analysis description:	
Change from baseline in number of dry days per 7 days (day and night time) in adolescents at week 2. The number of participants included in this analysis was 24.	
Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.045 [91]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1.6

Notes:

[91] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Children
Statistical analysis description:	
Change from baseline in number of dry days per 7 days (day and night time) in children at week 4. The number of participants included in this analysis was 42.	
Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.013 [92]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.2

Notes:

[92] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 4 - Adolescents

Statistical analysis description:

Change from baseline in number of dry days per 7 days (day and night time) in adolescents at week 4. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 [93]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	2.2

Notes:

[93] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 8 - Children

Statistical analysis description:

Change from baseline in number of dry days per 7 days (day and night time) in children at week 8. The number of participants included in this analysis was 43.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001 [94]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.8

Notes:

[94] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 8 - Adolescents

Statistical analysis description:

Change from baseline in number of dry days per 7 days (day and night time) in adolescents at week 8. The number of participants included in this analysis was 23.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [95]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	3.3

Notes:

[95] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 12 - Children

Statistical analysis description:

Change from baseline in number of dry days per 7 days (day and night time) in children at week 12. The number of participants included in this analysis was 43.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001 [96]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	2.1

Notes:

[96] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 12 - Adolescents

Statistical analysis description:

Change from baseline in number of dry days per 7 days (day and night time) in adolescents at week 12. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [97]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	3

Notes:

[97] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Children

Statistical analysis description:

Change from baseline in number of dry days per 7 days (day and night time) in children at week 24. The number of participants included in this analysis was 41.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [98]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2

Notes:

[98] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Adolescents

Statistical analysis description:

Change from baseline in number of dry days per 7 days (day and night time) in adolescents at week 24. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [99]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	3.2

Notes:

[99] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 36 - Children

Statistical analysis description:

Change from baseline in number of dry days per 7 days (day and night time) in children at week 36. The number of participants included in this analysis was 39.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 [100]
Method	Paired t-test

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	2.1

Notes:

[100] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 36 - Adolescents

Statistical analysis description:

Change from baseline in number of dry days per 7 days (day and night time) in adolescents at week 36. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [101]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.8

Notes:

[101] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Children

Statistical analysis description:

Change from baseline in number of dry days per 7 days (day and night time) in children at week 52. The number of participants included in this analysis was 40.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 [102]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	2.2

Notes:

[102] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Adolescents

Statistical analysis description:

Change from baseline in number of dry days per 7 days (day and night time) in adolescents at week 52. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [103]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	3.2

Notes:

[103] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Secondary: Change From Baseline in Pediatric Incontinence Questionnaire (PIN-Q) Score

End point title	Change From Baseline in Pediatric Incontinence Questionnaire (PIN-Q) Score

End point description:

PIN-Q measured quality of life via an e-diary. Total score ranged from 0/no effect to 80/worst effect; decrease in score indicated improvement. Total score was 20x average of individual PinQ items, the 20 Likert scales were converted to a score: Items 6 & 17; 0: "No" to 4: "Definitely" was used; & For the other 18 items; 0: "No" to 4: "All the time" was used. Expectation that questionnaires had limited missing values; if answers >2 questions were missing, total score was not calculated & was missing. Individual item scores were directly imputed. Change from baseline to each post-baseline visit in the total score was post-baseline visit value minus baseline value. If either baseline or post-baseline visit value was missing, change from baseline was missing. If change was: <0, improvement between 2 time-points; =0, no change between 2 time points; >0, worsening between 2 time points. FAS population. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 24 and 52

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 24 (N=24, 21)	2.04 (± 10.53)	-4.90 (± 14.13)		
Week 52 (N=23, 19)	1.30 (± 12.17)	-6.79 (± 14.50)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 24 - Children

Statistical analysis description:

Change from baseline in PIN-Q score in children at week 24. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.352 [104]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	6.49

Notes:

[104] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Adolescents

Statistical analysis description:

Change from baseline in PIN-Q score in adolescents at week 24. The number of participants included in this analysis was 21.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.127 [105]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.34
upper limit	1.53

Notes:

[105] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Children

Statistical analysis description:

Change from baseline in PIN-Q score in children at week 52. The number of participants included in this analysis was 23.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.613 [106]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.96
upper limit	6.57

Notes:

[106] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Adolescents

Statistical analysis description:

Change from baseline in PIN-Q score in adolescents at week 52. The number of participants included in this analysis was 19.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.056 [107]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.78
upper limit	0.2

Notes:

[107] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Secondary: Change From Baseline in Patient Global Impression of Severity Scale (PGI-S)

End point title	Change From Baseline in Patient Global Impression of Severity Scale (PGI-S)

End point description:

The PGI-S is an answer to the question: "How did you feel about your bladder condition during the past 3 days?" Participants evaluated their recent condition as "Really Bad"(0), "Bad" (1), "Not Bad, Not Good" (2), "Good" (3) & "Really Good" (4). An increase indicated improvement. The change from baseline to each postbaseline visit in the PGI-S score is the value at the post-baseline visit minus the value at the baseline visit. If either the baseline or the post-baseline visit value is missing, the change from baseline was missing. A positive change indicated an improvement while a negative change indicated a worsening. Analysis population consisted of the FAS. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 24 and 52

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 24 (N=25, 22)	0.36 (± 1.22)	0.64 (± 1.00)		
Week 52 (N=24, 19)	0.42 (± 1.21)	0.95 (± 1.18)		

Statistical analyses

Statistical analysis title	Change From Baseline at Week 24 - Children

Statistical analysis description:

Change from baseline in PGI-S in children at week 24. The number of participants included in this analysis was 25.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.153 [108]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.86

Notes:

[108] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 24 - Adolescents

Statistical analysis description:

Change from baseline in PGI-S in adolescents at week 24. The number of participants included in this analysis was 22.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007 [109]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	1.08

Notes:

[109] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Children

Statistical analysis description:

Change from baseline in PGI-S in children at week 52. The number of participants included in this analysis was 24.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.106 [110]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.93

Notes:

[110] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Statistical analysis title	Change From Baseline at Week 52 - Adolescents

Statistical analysis description:

Change from baseline in PGI-S in adolescents at week 52. The number of participants included in this analysis was 19.

Comparison groups	Children (3 to < 12 Years) v Adolescents (12 to < 18 Years)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003 [111]
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.51

Notes:

[111] - From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.

Secondary: Clinician Global Impression of Change (CGI-C)

End point title	Clinician Global Impression of Change (CGI-C)

End point description:

The Clinician Global Impression of Change (CGI-C) is a 7 point scale that requires the clinician to assess how much the participant's overall bladder symptoms since the start of the study on day 1 has improved or worsened and rated as: very much improved (1); much improved (2); minimally improved (3); no change (4); minimally worse (5); much worse (6); or very much worse (7). Analysis population consisted of the FAS. N is the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Weeks 24 and 52

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	25		
Units: participants				
Week 24 - Very Much Improved (N=41, 24)	6	10		
Week 24 - Much Improved (N=41, 24)	24	7		
Week 24 - Minimally Improved (N=41, 24)	6	5		
Week 24 - No Change (N=41, 24)	4	1		
Week 24 - Minimally Worse (N=41, 24)	1	1		
Week 24 - Much Worse (N=41, 24)	0	0		
Week 24 - Very Much Worse (N=41, 24)	0	0		
Week 52 - Very Much Improved (N=38, 23)	8	9		
Week 52 - Much Improved (N=38, 23)	23	12		

Week 52 - Minimally Improved (N=38, 23)	5	1		
Week 52 - No Change (N=38, 23)	2	0		
Week 52 - Minimally Worse (N=38, 23)	0	0		
Week 52 - Much Worse (N=38, 23)	0	1		
Week 52 - Very Much Worse (N=38, 23)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Study Drug Acceptability for Tablets at Week 4

End point title	Study Drug Acceptability for Tablets at Week 4

End point description:

Participants evaluated the taste of the study medication/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 medication/tablets by ticking one of the following categories: "Really Difficult" (0), "Difficult" (1), "Not Difficult, Not Easy" (2), "Easy" (3) and "Really Easy" (4). Analysis population consisted of the FAS (participants on tablets with available data at week 4).

End point type	Secondary

End point timeframe:

Week 4

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: participants				
Taste - Really bad	0	0		
Taste - Bad	0	0		
Taste - Not bad, not good	5	7		
Taste - Good	3	4		
Taste - Really good	1	1		
Swallow - Really difficult	0	0		
Swallow - Difficult	0	0		
Swallow - Not difficult, not easy	1	0		
Swallow - Easy	3	7		
Swallow - Really easy	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Study Drug Acceptability for Oral Suspension at Week 4

End point title	Study Drug Acceptability for Oral Suspension at Week 4

End point description:

Participants evaluated the taste of the study medication/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 medication/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 and the preparation of the study medication/oral suspension by ticking 1 of the following categories: "Really Difficult" (0), "Difficult" (1), "Not Difficult, Not Easy" (2), "Easy" (3) & "Really Easy" (4). Analysis population consisted of the FAS (participants on oral suspension with available data at week 4).

End point type	Secondary

End point timeframe:

Week 4

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	2		
Units: participants				
Taste - Really bad	1	0		
Taste - Bad	3	0		
Taste - Not bad, not good	4	2		
Taste - Good	11	0		
Taste - Really good	3	0		
Smell - Really bad	0	0		
Smell - Bad	1	0		
Smell - Not bad, not good	8	1		
Smell - Good	12	1		
Smell - Really good	1	0		
Take - Really difficult	0	0		
Take - Difficult	0	0		
Take - Not difficult, not easy	4	0		
Take - Easy	7	1		
Take - Really Easy	11	1		
Prepare - Really difficult	0	0		
Prepare - Difficult	0	0		
Prepare - Not difficult, not easy	2	0		
Prepare - Easy	12	0		
Prepare - Really Easy	8	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Study Drug Acceptability for Tablets at Week 24

End point title	Study Drug Acceptability for Tablets at Week 24

End point description:

Participants evaluated the taste of the study medication/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 medication/tablets by ticking one of the following categories: "Really Difficult" (0), "Difficult" (1), "Not Difficult, Not Easy" (2), "Easy" (3) and "Really Easy" (4). Analysis population consisted of the FAS (participants on tablets with available data at week 24).

End point type	Secondary

End point timeframe:

Week 24

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	23		
Units: participants				
Taste - Really bad	1	0		
Taste - Bad	2	0		
Taste - Not bad, not good	6	15		
Taste - Good	4	6		
Taste - Really good	4	2		
Swallow - Really difficult	0	0		
Swallow - Difficult	0	0		
Swallow - Not difficult, not easy	2	2		
Swallow - Easy	3	10		
Swallow - Really easy	12	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Study Drug Acceptability for Oral Suspension at Week 24

End point title	Study Drug Acceptability for Oral Suspension at Week 24

End point description:

Participants evaluated the taste of the study medication/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 medication/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 and the preparation of the study medication/oral suspension by ticking 1 of the following categories: "Really Difficult" (0), "Difficult" (1), "Not Difficult, Not Easy" (2), "Easy" (3) & "Really Easy" (4). Analysis population consisted of the FAS (participants on oral suspension with available data at week 24).

End point type	Secondary

End point timeframe:

Week 24

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	2		
Units: participants				
Taste - Really bad	3	0		
Taste - Bad	1	0		
Taste - Not bad, not good	3	2		
Taste - Good	10	0		
Taste - Really good	6	0		
Smell - Really bad	2	0		
Smell - Bad	0	0		
Smell - Not bad, not good	8	2		
Smell - Good	11	0		
Smell - Really good	2	0		
Take - Really difficult	0	0		
Take - Difficult	2	0		
Take - Not difficult, not easy	2	0		
Take - Easy	6	0		
Take - Really Easy	13	2		
Prepare - Really difficult	0	0		
Prepare - Difficult	1	0		
Prepare - Not difficult, not easy	3	0		
Prepare - Easy	10	2		
Prepare - Really Easy	9	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Study Drug Acceptability for Tablets at Week 52

End point title	Study Drug Acceptability for Tablets at Week 52

End point description:

Participants evaluated the taste of the study medication/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 medication/tablets by ticking one of the following categories: "Really Difficult" (0), "Difficult" (1), "Not Difficult, Not Easy" (2), "Easy" (3) and "Really Easy" (4). Analysis population consisted of the FAS (participants on tablets with available data at week 52).

End point type	Secondary

End point timeframe:

Week 52

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: participants				
Taste - Really bad	0	0		
Taste - Bad	0	0		
Taste - Not bad, not good	8	16		
Taste - Good	6	2		
Taste - Really good	3	2		
Swallow - Really difficult	0	0		
Swallow - Difficult	0	0		
Swallow - Not difficult, not easy	2	2		
Swallow - Easy	4	7		
Swallow - Really easy	11	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Study Drug Acceptability for Oral Suspension at Week 52

End point title	Study Drug Acceptability for Oral Suspension at Week 52

End point description:

Participants evaluated the taste of the study medication/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 medication/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 and the preparation of the study medication/oral suspension by ticking 1 of the following categories: "Really Difficult" (0), "Difficult" (1), "Not Difficult, Not Easy" (2), "Easy" (3) & "Really Easy" (4). Analysis population consisted of the FAS (participants on oral suspension with available data at week 52).

End point type	Secondary

End point timeframe:

Week 52

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	2		
Units: participants				
Taste - Really bad	1	0		
Taste - Bad	2	0		
Taste - Not bad, not good	5	2		
Taste - Good	8	0		
Taste - Really good	6	0		
Smell - Really bad	2	0		
Smell - Bad	1	0		

Smell - Not bad, not good	5	1		
Smell - Good	12	1		
Smell - Really good	2	0		
Take - Really difficult	0	0		
Take - Difficult	1	0		
Take - Not difficult, not easy	3	0		
Take - Easy	7	0		
Take - Really Easy	11	2		
Prepare - Really difficult	0	0		
Prepare - Difficult	0	0		
Prepare - Not difficult, not easy	3	0		
Prepare - Easy	9	2		
Prepare - Really Easy	10	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

An AE was defined as any untoward medical occurrence in a participant who was given the study drug or who had undergone study procedures and did not necessarily have a causal relationship with this treatment. An AE could therefore be any unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. A treatment-emergent adverse event (TEAE) was defined as any AE with date of onset occurring on or after the first dose of study medication and up to the end of study. The analysis population consisted of the safety analysis set (SAF), which consisted of all participants who took at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From the first dose of study drug administration up to end-of-treatment (EoT) (week 52).

End point values	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	31		
Units: participants				
TEAE	33	18		
Drug-related TEAE	8	6		
Serious TEAE	9	5		
Drug-related Serious TEAE	0	0		
TEAE Leading to Death	0	0		
Drug-related TEAE Leading to Death	0	0		
TEAE Leading to Permanent Discontinuation	3	0		
Drug-related TEAE Leading to Permanent Disc.	2	0		

Death	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) of Maximum Plasma Mirabegron Concentration (Cmax)

End point title	Pharmacokinetics (PK) of Maximum Plasma Mirabegron Concentration (Cmax)

End point description:

The analysis population consisted of the pharmacokinetic analysis set (PKAS), which consisted of the subset of the SAF for whom plasma concentration data were available to facilitate derivation of ≥ 1 pharmacokinetic parameter and for whom the time of the last dose prior to sampling was known. The population of the pharmacokinetic analysis included all participants (n=71) that contributed at least one measurable PK sample. This included 5 partcipants who were excluded from the PKAS dataset (n=66) because PK samples were collected outside the protocol specified time window for collection. Due to the low number of participants, data could not be calculated and is denoted as "99999" as applicable.

End point type	Secondary

End point timeframe:

A total of 4 samples were collected over 2 sampling days at 2 separate visits at any of weeks 4, 8, 12, 24, 36, or 52, at the following time points: Sampling day 1, predose; Sampling day 2, predose and 2 samples 2-5 hours postdose more than 1 hour apart.

End point values	Children PED25	Adolescents PED25	Children PED50	Adolescents PED50
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	43	24
Units: ng/mL				
arithmetic mean (standard deviation)	9.386 (± 99999)	9.044 (± 5.407)	20.55 (± 13.63)	18.40 (± 12.45)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Plasma Concentration of Mirabegron Following Drug Administration (Tmax)

End point title	Time to Reach Maximum Plasma Concentration of Mirabegron Following Drug Administration (Tmax)

End point description:

The analysis population consisted of the PKAS. The population of the pharmacokinetic analysis included all participants (n=71) that contributed at least one measurable PK sample. This included 5 partcipants who were excluded from the PKAS dataset (n=66) because PK samples were collected outside the protocol specified time window for collection. Due to the low number of participants, data could not be calculated and is denoted as "99999" as applicable.

End point type	Secondary

End point timeframe:

A total of 4 samples were collected over 2 sampling days at 2 separate visits at any of weeks 4, 8, 12, 24, 36, or 52, at the following time points: Sampling day 1, predose; Sampling day 2, predose and 2 samples 2-5 hours postdose more than 1 hour apart.

End point values	Children PED25	Adolescents PED25	Children PED50	Adolescents PED50
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	43	24
Units: hour				
arithmetic mean (standard deviation)	3.000 (± 99999)	3.500 (± 0.433)	3.419 (± 0.6608)	3.635 (± 1.101)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve From Time Zero to 24 Hours (AUC24) for Mirabegron

End point title	Area Under the Plasma Concentration-Time Curve From Time Zero to 24 Hours (AUC24) for Mirabegron

End point description:

The analysis population consisted of the PKAS. The population of the pharmacokinetic analysis included all participants (n=71) that contributed at least one measurable PK sample. This included 5 partcipants who were excluded from the PKAS dataset (n=66) because PK samples were collected outside the protocol specified time window for collection. Due to the low number of participants, data could not be calculated and is denoted as "99999" as applicable.

End point type	Secondary

End point timeframe:

A total of 4 samples were collected over 2 sampling days at 2 separate visits at any of weeks 4, 8, 12, 24, 36, or 52, at the following time points: Sampling day 1, predose; Sampling day 2, predose and 2 samples 2-5 hours postdose more than 1 hour apart.

End point values	Children PED25	Adolescents PED25	Children PED50	Adolescents PED50
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	43	24
Units: ng*hr/mL				
arithmetic mean (standard deviation)	166.3 (± 99999)	137.8 (± 53.07)	310.1 (± 163.1)	291.6 (± 171.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Mirabegron at the End of a Dosing interval at Steady State (Ctrough)

End point title	Plasma Concentration of Mirabegron at the End of a Dosing interval at Steady State (Ctrough)

End point description:

The analysis population consisted of the PKAS. The population of the pharmacokinetic analysis included all participants (n=71) that contributed at least one measurable PK sample. This included 5 partcipants who were excluded from the PKAS dataset (n=66) because PK samples were collected outside the protocol specified time window for collection. Due to the low number of participants, data could not be calculated and is denoted as "99999" as applicable.

End point type	Secondary

End point timeframe:

A total of 4 samples were collected over 2 sampling days at 2 separate visits at any of weeks 4, 8, 12, 24, 36, or 52, at the following time points: Sampling day 1, predose; Sampling day 2, predose and 2 samples 2-5 hours postdose more than 1 hour apart.

End point values	Children PED25	Adolescents PED25	Children PED50	Adolescents PED50
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	43	24
Units: ng/mL				
arithmetic mean (standard deviation)	5.312 (± 99999)	4.114 (± 1.186)	9.024 (± 5.149)	8.888 (± 5.588)

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Clearance of Mirabegron From Plasma After Oral Administration (CL/F)

End point title	Apparent Total Clearance of Mirabegron From Plasma After Oral Administration (CL/F)

End point description:

The analysis population consisted of the PKAS. The population of the pharmacokinetic analysis included all participants (n=71) that contributed at least one measurable PK sample. This included 5 partcipants who were excluded from the PKAS dataset (n=66) because PK samples were collected outside the protocol specified time window for collection. Due to the low number of participants, data could not be calculated and is denoted as "99999" as applicable.

End point type	Secondary

End point timeframe:

A total of 4 samples were collected over 2 sampling days at 2 separate visits at any of weeks 4, 8, 12, 24, 36, or 52, at the following time points: Sampling day 1, predose; Sampling day 2, predose and 2 samples 2-5 hours postdose more than 1 hour apart.

End point values	Children PED25	Adolescents PED25	Children PED50	Adolescents PED50
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	43	24
Units: L/hr				
arithmetic mean (standard deviation)	192.5 (± 99999)	202.3 (± 83.05)	230.9 (± 162)	279.6 (± 294.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution After Non-intravenous Administration (Vz/F) of Mirabegron

End point title	Apparent Volume of Distribution After Non-intravenous Administration (Vz/F) of Mirabegron

End point description:

The analysis population consisted of the PKAS. The population of the pharmacokinetic analysis included all participants (n=71) that contributed at least one measurable PK sample. This included 5 partcipants who were excluded from the PKAS dataset (n=66) because PK samples were collected outside the protocol specified time window for collection. Due to the low number of participants, data could not be calculated and is denoted as "99999" as applicable.

End point type	Secondary

End point timeframe:

A total of 4 samples were collected over 2 sampling days at 2 separate visits at any of weeks 4, 8, 12, 24, 36, or 52, at the following time points: Sampling day 1, predose; Sampling day 2, predose and 2 samples 2-5 hours postdose more than 1 hour apart.

End point values	Children PED25	Adolescents PED25	Children PED50	Adolescents PED50
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	43	24
Units: Liter				
arithmetic mean (standard deviation)	14450 (± 99999)	15380 (± 6524)	12150 (± 5630)	14770 (± 6792)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first dose of study drug administration up to end-of-treatment (EoT) (week 52).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16

Reporting groups	
Reporting group title	Children (3 to < 12 Years)
Reporting group description:	
Children age 3 to < 12 received initial dose of mirabegron based on weight (pediatric equivalent dose [PED25]) on day 1. At weeks 2, 4 or 8, participant's were up-titrated to the pediatric equivalent dose of 50 mg in adults (PED50) based on the given dose titration criteria. Following week 24, participants stayed on their individual dose level until week 52 end-of-study (EOS) or end-of-treatment (EOT).	
Reporting group title	Adolescents (12 to < 18 Years)
Reporting group description:	
Adolescents age 12 to < 18 received initial dose of mirabegron based on weight (pediatric equivalent dose [PED25]) on day 1. At weeks 2, 4 or 8, participant's were up-titrated to the pediatric equivalent dose of 50 mg in adults (PED50) based on the given dose titration criteria. Following week 24, participants stayed on their individual dose level until week 52 end-of-study (EOS) or end-of-treatment (EOT).	

Serious adverse events	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 55 (16.36%)	5 / 31 (16.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of skin			
subjects affected / exposed	1 / 55 (1.82%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Shunt malfunction			
subjects affected / exposed	0 / 55 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			

Talipes			
subjects affected / exposed	1 / 55 (1.82%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Talipes correction			
subjects affected / exposed	1 / 55 (1.82%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 55 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 55 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device malfunction			
subjects affected / exposed	2 / 55 (3.64%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Epididymitis			

subjects affected / exposed	0 / 55 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash generalised			
subjects affected / exposed	0 / 55 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urethral perforation			
subjects affected / exposed	1 / 55 (1.82%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 55 (1.82%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 55 (1.82%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Viral infection			
subjects affected / exposed	1 / 55 (1.82%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Children (3 to < 12 Years)	Adolescents (12 to < 18 Years)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 55 (30.91%)	9 / 31 (29.03%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 55 (3.64%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 55 (5.45%)	1 / 31 (3.23%)	
occurrences (all)	3	1	
Infections and infestations			
Escherichia urinary tract infection			
subjects affected / exposed	3 / 55 (5.45%)	5 / 31 (16.13%)	
occurrences (all)	5	6	
Nasopharyngitis			
subjects affected / exposed	3 / 55 (5.45%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Respiratory tract infection viral			
subjects affected / exposed	4 / 55 (7.27%)	0 / 31 (0.00%)	
occurrences (all)	6	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 55 (1.82%)	3 / 31 (9.68%)	
occurrences (all)	1	6	
Urinary tract infection			
subjects affected / exposed	4 / 55 (7.27%)	0 / 31 (0.00%)	
occurrences (all)	5	0	
Urinary tract infection bacterial			

subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 5	1 / 31 (3.23%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2016	The changes included: ● The age range of the patients was updated to include children from 3 to < 18 years of age. This study is targeted to fulfill both the EMA and FDA requirements related to the conduct of pediatric studies. A Written Request received from the FDA included a stipulation to decrease the lower limit of the age range from 5 to 3 years of age. ● Mirabegron oral suspension (8 mg/mL) was added to the protocol as a second study drug formulation to enable dosing of the younger patients. ● The weight range for inclusion of patients in the study was lowered to ≥ 11 kg. ● Additional SBPM were included at weeks 1 and 2 after the start of dosing and after a dose escalation to satisfy EMA and FDA comments. ● Nonsubstantial changes corrected administrative-type information. These protocol changes were implemented after enrollment of 38 patients

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported