Clinical trial results:
A Multicentre, Open-label, Single Dose, Phase 1 Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Mirabegron Oral Suspension in Pediatric Subjects from 3 to Less than 12 Years of Age with Neurogenic Detrusor Overactivity (NDO) or Overactive Bladder (OAB)

Summary

EudraCT number	2015-000700-26
Trial protocol	DK
Global end of trial date	30 September 2016

Results information

Result version number	v1 (current)
This version publication date	05 April 2017
First version publication date	05 April 2017

Trial information

Trial identification

Sponsor protocol code	178-CL-203

Additional study identifiers

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

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-PIP02-10, 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	30 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics of mirabegron oral suspension after single dose administration in children with NDO or OAB.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the fed ral, 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 December 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Poland: 4
Worldwide total number of subjects	9
EEA total number of subjects	9

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)	9
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Children were enrolled in sites in Denmark and Poland.

Pre-assignment

Screening details:

Children with NDO aged 3 to less than 12 years of age and with OAB aged 5 to less than 12 years of age who gave assent or whose parents/legal guardians consented to enter this study and fulfilled all the eligibility criteria were enrolled. A wash-out of prohibited medication for 5 half-lives was performed if a participant was using them.

Period 1

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

Arms

Arm title	Total (All participants)

Arm description:

Participants received a single, weight-based dose of mirabegron on day 1.

Arm type	Experimental
Investigational medicinal product name	Mirabegron
Investigational medicinal product code	YM178
Other name	Myrbetriq®, Betmiga™
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants received a single, weight-based dose of mirabegron, resulting in an exposure equivalent to steady state exposure to 50 mg prolonged-release tablets given once daily to adults. Participants were dosed under fed conditions (within 1 hour after completion of the light breakfast and were allowed to have a light lunch > 2 hours after dosing). Mirabegron was provided as granules and reconstituted with vehicle in bottle and was prepared into a modified release oral suspension 2 mg/mL.

Number of subjects in period 1	Total (All participants)
Started	9
Completed	9

Baseline characteristics

Reporting groups	
Reporting group title	Total (All participants)
Reporting group description:	
Participants received a single, weight-based dose of mirabegron on day 1.	

Reporting group values	Total (All participants)	Total	
Number of subjects	9	9	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	7.3		
standard deviation	± 2.2	-	
Gender categorical Units:			
Male	4	4	
Female	5	5	
Diagnosis Units: Subjects			
NDO	6	6	
OAB	3	3	

End points

End points reporting groups

Reporting group title	Total (All participants)
Reporting group description: Participants received a single, weight-based dose of mirabegron on day 1.	

Primary: Maximum Concentration (Cmax) of Mirabegron

End point title	Maximum Concentration (Cmax) of Mirabegron[1]
End point description: The analysis population was the Pharmacokinetic Analysis Set (PKAS) which consisted of participants from the Safety Analysis Set (SAF; consisted of all participants who took the dose of study medication) population for whom sufficient plasma concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom date and time of dosing and sampling were known.	
End point type	Primary
End point timeframe: Day 1: 0.5-2, 3-5, 6-8 hours (h) postdose, Day 2: 24-32 h, Day 3: 48-56 h, Day 4: 72-80 h, Day 5: 96-104 h, Day 6: 120-128 h, Day 7: 144-152 h (2 samples only for Day 3-7)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

End point values	Total (All participants)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: ng/mL				
arithmetic mean (standard deviation)	18.41 (± 11.72)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration-time Curve from Time Zero to Infinity (AUCinf) for Mirabegron

End point title	Area Under the Concentration-time Curve from Time Zero to Infinity (AUCinf) for Mirabegron[2]
End point description: The analysis population was the PKAS.	
End point type	Primary
End point timeframe: Day 1: 0.5-2, 3-5, 6-8 hours (h) postdose, Day 2: 24-32 h, Day 3: 48-56 h, Day 4: 72-80 h, Day 5: 96-104 h, Day 6: 120-128 h, Day 7: 144-152 h (2 samples only for Day 3-7)	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

End point values	Total (All participants)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: ng*h/mL				
arithmetic mean (standard deviation)	464.1 (± 288.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Time After Dosing When Cmax Occurs (tmax) for Mirabegron

End point title	Time After Dosing When Cmax Occurs (tmax) for Mirabegron[3]

End point description:

The analysis population was the PKAS.

End point type	Primary

End point timeframe:

Day 1: 0.5-2, 3-5, 6-8 hours (h) postdose, Day 2: 24-32 h, Day 3: 48-56 h, Day 4: 72-80 h, Day 5: 96-104 h, Day 6: 120-128 h, Day 7: 144-152 h (2 samples only for Day 3-7)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

End point values	Total (All participants)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: hours				
median (full range (min-max))	3.93 (1.25 to 6.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Terminal Elimination Half-life (t1/2) of Mirabegron

End point title	Apparent Terminal Elimination Half-life (t1/2) of Mirabegron[4]

End point description:

The analysis population was the PKAS.

End point type	Primary

End point timeframe:

Day 1: 0.5-2, 3-5, 6-8 hours (h) postdose, Day 2: 24-32 h, Day 3: 48-56 h, Day 4: 72-80 h, Day 5: 96-104 h, Day 6: 120-128 h, Day 7: 144-152 h (2 samples only for Day 3-7)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

End point values	Total (All participants)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: hours				
arithmetic mean (standard deviation)	25.99 (± 5.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration-time Curve from the Time of Dosing (Time Zero) to 24 Hours (AUC24) for Mirabegron

End point title	Area Under the Concentration-time Curve from the Time of Dosing (Time Zero) to 24 Hours (AUC24) for Mirabegron[5]

End point description:

The analysis population was the PKAS.

End point type	Primary

End point timeframe:

Day 1: 0.5-2, 3-5, 6-8 hours (h) postdose, Day 2: 24-32 h, Day 3: 48-56 h, Day 4: 72-80 h, Day 5: 96-104 h, Day 6: 120-128 h, Day 7: 144-152 h (2 samples only for Day 3-7)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

End point values	Total (All participants)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: ng*h/mL				
arithmetic mean (standard deviation)	226.9 (± 136.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration-time Curve from Time Zero to Last Measurable Concentration (AUClast) for Mirabegron

End point title	Area Under the Concentration-time Curve from Time Zero to

	Last Measurable Concentration (AUClast) for Mirabegron[6]

End point description:

The analysis population was the PKAS.

End point type	Primary

End point timeframe:

Day 1: 0.5-2, 3-5, 6-8 hours (h) postdose, Day 2: 24-32 h, Day 3: 48-56 h, Day 4: 72-80 h, Day 5: 96-104 h, Day 6: 120-128 h, Day 7: 144-152 h (2 samples only for Day 3-7)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

End point values	Total (All participants)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: ng*h/mL				
arithmetic mean (standard deviation)	414.3 (± 263.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Oral Clearance (CL/F) for Mirabegron

End point title	Apparent Oral Clearance (CL/F) for Mirabegron[7]

End point description:

The analysis population was the PKAS.

End point type	Primary

End point timeframe:

Day 1: 0.5-2, 3-5, 6-8 hours (h) postdose, Day 2: 24-32 h, Day 3: 48-56 h, Day 4: 72-80 h, Day 5: 96-104 h, Day 6: 120-128 h, Day 7: 144-152 h (2 samples only for Day 3-7)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

End point values	Total (All participants)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: L/h				
arithmetic mean (standard deviation)	338 (± 281.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent volume of Distribution (Vz/F) of Mirabegron

End point title	Apparent volume of Distribution (Vz/F) of Mirabegron[8]

End point description:

The analysis population was the PKAS.

End point type	Primary

End point timeframe:

Day 1: 0.5-2, 3-5, 6-8 hours (h) postdose, Day 2: 24-32 h, Day 3: 48-56 h, Day 4: 72-80 h, Day 5: 96-104 h, Day 6: 120-128 h, Day 7: 144-152 h (2 samples only for Day 3-7)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

End point values	Total (All participants)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: liters				
arithmetic mean (standard deviation)	13726 (± 14036)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

Safety was assessed by collecting AEs, which included abnormalities identified during a medical test (e.g. laboratory tests, vital signs, electrocardiogram, PVR volume, etc.) if the abnormality induced clinical signs or symptoms, needed active intervention, interruption or discontinuation of study medication or was clinically significant. A serious AE (SAE) was an event resulting in death, persistent or significant disability/incapacity or congenital anomaly or birth defect, was life-threatening, required or prolonged hospitalization or was considered medically important A treatment-emergent adverse event (TEAE) was defined as an AE observed after starting administration of the test drug, and no later than 7 days after the last dose of study drug received over the whole investigational period. The analysis population was the SAF.

End point type	Secondary

End point timeframe:

From first dose of study drug up to 30 days after last dose of study drug (up to 37 days)

End point values	Total (All participants)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: participants				
Any TEAE	1			
Drug-related TEAEs	0			
Deaths	0			

Serious TEAEs	0			
Drug-related Serious TEAEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability and Palatability of Mirabegron using a Visual Analog Scale (VAS): Taste

End point title	Acceptability and Palatability of Mirabegron using a Visual Analog Scale (VAS): Taste

End point description:

Acceptability (drug intake) and palatability (taste and smell) of mirabegron (oral suspension) was assessed using a 5-point VAS questionnaire, which was completed by the participant (or by parent/guardian based on input from the participant). The taste assessment scales ranged from "really bad" to "really good". Not available was regarded as response not available. The analysis population was the SAF.

End point type	Secondary

End point timeframe:

Day 1

End point values	Total (All participants)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: participants				
Really bad	4			
Bad	1			
Not bad, not good	1			
Good	2			
Really Good	1			
Not available	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability and Palatability of Mirabegron using a Visual Analog Scale (VAS): Smell

End point title	Acceptability and Palatability of Mirabegron using a Visual Analog Scale (VAS): Smell

End point description:

Acceptability (drug intake) and palatability (taste and smell) of mirabegron was assessed using a 5-point VAS questionnaire, which was completed by the participant (or by parent/guardian based on input from the participant). The smell assessment scales ranged from "really bad" to "really good". Not available was regarded as response not available. The analysis population was the SAF.

End point type	Secondary

End point timeframe:

Day 1

End point values	Total (All participants)			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: participants				
Really bad	1			
Bad	1			
Not bad, not good	4			
Good	2			
Really good	0			
Not available	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability and Palatability of Mirabegron using a Visual Analog Scale (VAS): Drug Intake

End point title	Acceptability and Palatability of Mirabegron using a Visual Analog Scale (VAS): Drug Intake

End point description:

Acceptability (drug intake) and palatability (taste and smell) of mirabegron was assessed using a 5-point VAS questionnaire, which was completed by the participant (or by parent/guardian based on input from the participant). The smell assessment scales ranged from "really bad" to "really good". Not available was regarded as response not available. The analysis population was the SAF.

End point type	Secondary

End point timeframe:

Day 1

End point values	Total (All participants)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: participants				
Really difficult	2			
Difficult	1			
Not difficult, not easy	2			
Easy	2			
Really easy	2			
Not available	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug up to 30 days after last dose of study drug (up to 37 days)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0
Reporting groups	
Reporting group title	Total (All participants)
Reporting group description:	
Participants received a single, weight-based dose of mirabegron on day 1.	

Serious adverse events	Total (All participants)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Total (All participants)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 November 2015	In this global amendment, changes include: (1) The exclusion criterion for pulse rate has been amended to exclude subjects with a (mean) resting pulse rate > 99th percentile. The age-specific centiles used for heart rate in children were based on a systematic review of all studies, which measured these vital signs in healthy children. Taking into account the high variability in pulse rate in children, inclusion would become more feasible if this criterion was followed; (2) The exclusion criteria on systolic blood pressure (SBP) and diastolic blood pressure (DBP) have been combined and amended to exclude subjects with established hypertension and a SBP or DBP greater than the 99th percentile of their normal range determined by sex, age and height, plus 5 mmHg. The previous criteria on blood pressure rates were based on normal ranges in healthy children. However, children with spina bifida have a higher prevalence of hypertension. Therefore, the exclusion criteria had to be amended to allow inclusion of NDO subjects, but still exclude subjects with established hypertension; (3) It was amended that a serious adverse event (SAE) had to be reported to INC Research LCC and not to Astellas Pharma Europe BV; (4) The contact details for the Medical Monitor and the Medical Expert were updated; (5) The list of references was updated; (6) Minor administrative-type changes were implemented.
08 July 2016	In this global amendment, changes include: (1) The age range for the study population was expanded to include male and female children with NDO from 3 years to less than 12 years of age to enter the study, in order to fulfill the FDA Written Request requirement regarding age range for this study; (2) The protocol was amended to allow a total of 6 subjects with NDO in the study to fulfill an FDA Written Request stipulating that Study 178-CL-203 should include a total of 6 subjects with NDO. By allowing a total of 6 subjects with NDO (adding 3 NDO subjects to the already recruited group of subjects [3 NDO and 3 OAB]), this study was designed to fulfill both the Pediatric Investigation Plan and the FDA Written Request, without the need to setup a new study and expose more subjects. The total number of 9 subjects as indicated in the initially approved protocol was not exceeded. A subgroup analysis for the 6 subjects with NDO was added to the protocol to allow for separate reporting of the NDO data. Because subjects with NDO are more difficult to recruit, the planned study period was also prolonged; (3) The calculation of the estimated glomerular filtration rate (eGFR) according to the modified Schwartz formula was added to the protocol in line with the Advice/Information Request, dated 14 Mar 2016, which was received a few days before the FDA Written Request. The eGFR calculated using the Larsson equation was erroneously not listed amongst the laboratory parameters, but only mentioned in the exclusion criterion for the determination of the eGFR. This omission was corrected; (4)The procedure of reporting of expedited safety reports was updated to reflect the actual process.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

22 December 2015	Recruitment of Study 178-CL-203 was temporarily halted after an abnormal postdose ECG without symptoms, had been observed in 1 subject that caused concern to the investigator. After review of patient data and all available information, the abnormal ECG was attributed to artifacts that render the ECG nonevaluable. No safety concerns had been identified for this subject; therefore, APEB considered it acceptable to resume recruitment in Study 178-CL-203.	08 February 2016

Notes:

Limitations and caveats

None reported