Clinical trial results:
A Phase 1, Single Dose, 4-Period Crossover Study to Assess the Bioavailability of an Mirabegron Oral Suspension Relative to the Mirabegron Prolonged Release Tablet and to Assess the Effect of Food on the Pharmacokinetics of Mirabegron Oral Suspension in Healthy Young Male and Female Subjects

Summary

EudraCT number	2014-001446-24
Trial protocol	DE
Global end of trial date	21 January 2015

Results information

Result version number	v1 (current)
This version publication date	18 August 2016
First version publication date	18 August 2016

Trial information

Trial identification

Sponsor protocol code	178-CL-201

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe BV
Sponsor organisation address	Sylviusweg 62, Leiden, Netherlands, 2333 BE
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., 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, EMEA-000597-PIP02-10
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the bioavailability of 50 mg mirabegron oral suspension relative to that of the 50 mg mirabegron modified release tablet when dosed under fasted conditions.

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	14 October 2014
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	Germany: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	25

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthy male and female participants were enrolled at one site in Germany and were resident for a period of 5 days in each of 4 treatment periods. On day -1 of each treatment period, the subjects were admitted to the clinical unit and discharged on day 4. Ambulant visits occurred on days 5, 6, 7, 9 and 11.

Pre-assignment

Screening details:

Participants who fulfilled all eligibility criteria were randomized to 1 of 4 treatment sequences (in first treatment period only) following the William's design in this 4-period crossover study. There was a washout period of at least 14 days between treatment periods.

Period 1

Period 1 title	Overall Study (Periods 1-4) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This is an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Sequence 1: ACBD

Arm description:

Participants who received a single dose of 50 mg mirabegron oral suspension administered under fasted conditions (A) on day 1 of period 1, a single dose of 50 mg mirabegron modified release tablets administered under fasted conditions (C) on day 1 of period 2, a single dose of 50 mg mirabegron oral suspension administered under fed conditions (B) on day 1 of period 3 and a single dose of 50 mg mirabegron modified release tablets administered under fed conditions (D) on day 1 of period 4.

Arm type	Experimental
Investigational medicinal product name	Mirabegron 50 mg oral suspension
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 dose of mirabegron 50 mg oral suspension on day 1 in one of 4 treatment periods, depending on their treatment sequence. Mirabegron was provided as granules and reconstituted with vehicle in bottle and was prepared into a modified release oral suspension 2 mg/mL and given to participants. Doses were administered under fasted conditions (overnight fast of at least 10 hours prior to dosing and 4 hours after dosing).

Investigational medicinal product name	Mirabegron 50 mg modified release tablets
Investigational medicinal product code	YM178
Other name	Myrbetriq®, Betmiga™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a single dose of mirabegron 50 mg modified release tablet orally on day 1 in one of 4 treatment periods, depending on their treatment sequence. Doses were administered under fasted conditions (overnight fast of at least 10 hours prior to dosing and 4 hours after dosing).

Investigational medicinal product name	Mirabegron 50 mg oral suspension
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 dose of mirabegron 50 mg oral suspension on day 1 in one of 4 treatment periods, depending on their treatment sequence. Mirabegron was provided as granules and reconstituted with vehicle in bottle and was prepared into a modified release oral suspension 2 mg/mL and given to participants. Doses were administered with food (dosing done 30 minutes after completion of the light breakfast and a light lunch 2 hours after).

Investigational medicinal product name	Mirabegron 50 mg modified release tablets
Investigational medicinal product code	YM178
Other name	Myrbetriq®, Betmiga™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a single dose of mirabegron 50 mg modified release tablet orally on day 1 in one of 4 treatment periods, depending on their treatment sequence. Doses were administered with food (dosing was done 30 minutes after completion of the light breakfast and a light lunch 2 hours after).

Arm title	Treatment Sequence 2: BADC

Arm description:

Participants who received a single dose of 50 mg mirabegron oral suspension administered under fed conditions (B) on day 1 of period 1, a single dose of 50 mg mirabegron oral suspension administered under fasted conditions (A) on day 1 of period 2, a single dose of 50 mg mirabegron modified release tablets administered under fed conditions (D) on day 1 of period 3 and a single dose of 50 mg mirabegron modified release tablets administered under fasted conditions (C) on day 1 of period 4.

Arm type	Experimental
Investigational medicinal product name	Mirabegron 50 mg oral suspension
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 dose of mirabegron 50 mg oral suspension on day 1 in one of 4 treatment periods, depending on their treatment sequence. Mirabegron was provided as granules and reconstituted with vehicle in bottle and was prepared into a modified release oral suspension 2 mg/mL and given to participants. Doses were administered under fasted conditions (overnight fast of at least 10 hours prior to dosing and 4 hours after dosing).

Investigational medicinal product name	Mirabegron 50 mg modified release tablets
Investigational medicinal product code	YM178
Other name	Myrbetriq®, Betmiga™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a single dose of mirabegron 50 mg modified release tablet orally on day 1 in one of 4 treatment periods, depending on their treatment sequence. Doses were administered under fasted conditions (overnight fast of at least 10 hours prior to dosing and 4 hours after dosing).

Investigational medicinal product name	Mirabegron 50 mg oral suspension
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 dose of mirabegron 50 mg oral suspension on day 1 in one of 4 treatment periods, depending on their treatment sequence. Mirabegron was provided as granules and reconstituted with vehicle in bottle and was prepared into a modified release oral suspension 2 mg/mL and given to participants. Doses were administered with food (dosing done 30 minutes after completion of the light breakfast and a light lunch 2 hours after).

Investigational medicinal product name	Mirabegron 50 mg modified release tablets
Investigational medicinal product code	YM178
Other name	Myrbetriq®, Betmiga™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a single dose of mirabegron 50 mg modified release tablet orally on day 1 in one of 4 treatment periods, depending on their treatment sequence. Doses were administered with food (dosing was done 30 minutes after completion of the light breakfast and a light lunch 2 hours after).

Arm title	Treatment Sequence 3: CDAB

Arm description:

Participants who received a single dose of 50 mg mirabegron modified release tablets administered under fasted conditions (C) on day 1 of period 1, a single dose of 50 mg mirabegron modified release tablets administered under fed conditions (D) on day 1 of period 2, a single dose of 50 mg mirabegron oral suspension administered under fasted conditions (A) on day 1 of period 3 and a single dose of 50 mg mirabegron oral suspension administered under fed conditions (B) on day 1 of period 4.

Arm type	Experimental
Investigational medicinal product name	Mirabegron 50 mg oral suspension
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 dose of mirabegron 50 mg oral suspension on day 1 in one of 4 treatment periods, depending on their treatment sequence. Mirabegron was provided as granules and reconstituted with vehicle in bottle and was prepared into a modified release oral suspension 2 mg/mL and given to participants. Doses were administered under fasted conditions (overnight fast of at least 10 hours prior to dosing and 4 hours after dosing).

Investigational medicinal product name	Mirabegron 50 mg modified release tablets
Investigational medicinal product code	YM178
Other name	Myrbetriq®, Betmiga™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a single dose of mirabegron 50 mg modified release tablet orally on day 1 in one of 4 treatment periods, depending on their treatment sequence. Doses were administered under fasted conditions (overnight fast of at least 10 hours prior to dosing and 4 hours after dosing).

Investigational medicinal product name	Mirabegron 50 mg oral suspension
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 dose of mirabegron 50 mg oral suspension on day 1 in one of 4 treatment periods, depending on their treatment sequence. Mirabegron was provided as granules and reconstituted with vehicle in bottle and was prepared into a modified release oral suspension 2 mg/mL and given to participants. Doses were administered with food (dosing done 30 minutes after completion of the light breakfast and a light lunch 2 hours after).

Investigational medicinal product name	Mirabegron 50 mg modified release tablets
Investigational medicinal product code	YM178
Other name	Myrbetriq®, Betmiga™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a single dose of mirabegron 50 mg modified release tablet orally on day 1 in one of 4 treatment periods, depending on their treatment sequence. Doses were administered with food

(dosing was done 30 minutes after completion of the light breakfast and a light lunch 2 hours after).

Arm title	Treatment Sequence 4: DBCA

Arm description:

Participants who received a single dose of 50 mg mirabegron modified release tablets administered under fed conditions (D) on day 1 of period 1, a single dose of 50 mg mirabegron oral suspension administered under fed conditions (B) on day 1 of period 2, a single dose of 50 mg mirabegron modified release tablets administered under fasted conditions (C) on day 1 of period 3 and a single dose of 50 mg mirabegron oral suspension administered under fasted conditions (A) on day 1 of period 4.

Arm type	Experimental
Investigational medicinal product name	Mirabegron 50 mg oral suspension
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 dose of mirabegron 50 mg oral suspension on day 1 in one of 4 treatment periods, depending on their treatment sequence. Mirabegron was provided as granules and reconstituted with vehicle in bottle and was prepared into a modified release oral suspension 2 mg/mL and given to participants. Doses were administered under fasted conditions (overnight fast of at least 10 hours prior to dosing and 4 hours after dosing).

Investigational medicinal product name	Mirabegron 50 mg modified release tablets
Investigational medicinal product code	YM178
Other name	Myrbetriq®, Betmiga™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a single dose of mirabegron 50 mg modified release tablet orally on day 1 in one of 4 treatment periods, depending on their treatment sequence. Doses were administered under fasted conditions (overnight fast of at least 10 hours prior to dosing and 4 hours after dosing).

Investigational medicinal product name	Mirabegron 50 mg oral suspension
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 dose of mirabegron 50 mg oral suspension on day 1 in one of 4 treatment periods, depending on their treatment sequence. Mirabegron was provided as granules and reconstituted with vehicle in bottle and was prepared into a modified release oral suspension 2 mg/mL and given to participants. Doses were administered with food (dosing done 30 minutes after completion of the light breakfast and a light lunch 2 hours after).

Investigational medicinal product name	Mirabegron 50 mg modified release tablets
Investigational medicinal product code	YM178
Other name	Myrbetriq®, Betmiga™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a single dose of mirabegron 50 mg modified release tablet orally on day 1 in one of 4 treatment periods, depending on their treatment sequence. Doses were administered with food (dosing was done 30 minutes after completion of the light breakfast and a light lunch 2 hours after).

Number of subjects in period 1	Treatment Sequence 1: ACBD	Treatment Sequence 2: BADC	Treatment Sequence 3: CDAB
Started	7	6	6
Completed Treatment Period 1	6	6	6
Completed Treatment Period 2	6	6	6
Completed Treatment Period 3	6	5	6
Completed Treatment Period 4	6	5	5
Completed	6	5	5
Not completed	1	1	1
Consent withdrawn by subject	-	1	-
Protocol violation	1	-	-
Adverse event	-	-	1

Number of subjects in period 1	Treatment Sequence 4: DBCA
Started	6
Completed Treatment Period 1	6
Completed Treatment Period 2	6
Completed Treatment Period 3	6
Completed Treatment Period 4	6
Completed	6
Not completed	0
Consent withdrawn by subject	-
Protocol violation	-
Adverse event	-

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Sequence 1: ACBD
Reporting group description:	
Participants who received a single dose of 50 mg mirabegron oral suspension administered under fasted conditions (A) on day 1 of period 1, a single dose of 50 mg mirabegron modified release tablets administered under fasted conditions (C) on day 1 of period 2, a single dose of 50 mg mirabegron oral suspension administered under fed conditions (B) on day 1 of period 3 and a single dose of 50 mg mirabegron modified release tablets administered under fed conditions (D) on day 1 of period 4.	
Reporting group title	Treatment Sequence 2: BADC
Reporting group description:	
Participants who received a single dose of 50 mg mirabegron oral suspension administered under fed conditions (B) on day 1 of period 1, a single dose of 50 mg mirabegron oral suspension administered under fasted conditions (A) on day 1 of period 2, a single dose of 50 mg mirabegron modified release tablets administered under fed conditions (D) on day 1 of period 3 and a single dose of 50 mg mirabegron modified release tablets administered under fasted conditions (C) on day 1 of period 4.	
Reporting group title	Treatment Sequence 3: CDAB
Reporting group description:	
Participants who received a single dose of 50 mg mirabegron modified release tablets administered under fasted conditions (C) on day 1 of period 1, a single dose of 50 mg mirabegron modified release tablets administered under fed conditions (D) on day 1 of period 2, a single dose of 50 mg mirabegron oral suspension administered under fasted conditions (A) on day 1 of period 3 and a single dose of 50 mg mirabegron oral suspension administered under fed conditions (B) on day 1 of period 4.	
Reporting group title	Treatment Sequence 4: DBCA
Reporting group description:	
Participants who received a single dose of 50 mg mirabegron modified release tablets administered under fed conditions (D) on day 1 of period 1, a single dose of 50 mg mirabegron oral suspension administered under fed conditions (B) on day 1 of period 2, a single dose of 50 mg mirabegron modified release tablets administered under fasted conditions (C) on day 1 of period 3 and a single dose of 50 mg mirabegron oral suspension administered under fasted conditions (A) on day 1 of period 4.	

Reporting group values	Treatment Sequence 1: ACBD	Treatment Sequence 2: BADC	Treatment Sequence 3: CDAB
Number of subjects	7	6	6
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	22.9	22.2	21.7
standard deviation	± 1.3	± 1.6	± 3
Gender categorical Units:			
Male	3	2	5
Female	4	4	1

Reporting group values	Treatment Sequence 4: DBCA	Total	
Number of subjects	6	25	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	22.5		
standard deviation	± 2.2	-	
Gender categorical Units:			
Male	1	11	
Female	5	14	

End points

End points reporting groups

Reporting group title	Treatment Sequence 1: ACBD

Reporting group description:

Participants who received a single dose of 50 mg mirabegron oral suspension administered under fasted conditions (A) on day 1 of period 1, a single dose of 50 mg mirabegron modified release tablets administered under fasted conditions (C) on day 1 of period 2, a single dose of 50 mg mirabegron oral suspension administered under fed conditions (B) on day 1 of period 3 and a single dose of 50 mg mirabegron modified release tablets administered under fed conditions (D) on day 1 of period 4.

Reporting group title	Treatment Sequence 2: BADC

Reporting group description:

Participants who received a single dose of 50 mg mirabegron oral suspension administered under fed conditions (B) on day 1 of period 1, a single dose of 50 mg mirabegron oral suspension administered under fasted conditions (A) on day 1 of period 2, a single dose of 50 mg mirabegron modified release tablets administered under fed conditions (D) on day 1 of period 3 and a single dose of 50 mg mirabegron modified release tablets administered under fasted conditions (C) on day 1 of period 4.

Reporting group title	Treatment Sequence 3: CDAB

Reporting group description:

Participants who received a single dose of 50 mg mirabegron modified release tablets administered under fasted conditions (C) on day 1 of period 1, a single dose of 50 mg mirabegron modified release tablets administered under fed conditions (D) on day 1 of period 2, a single dose of 50 mg mirabegron oral suspension administered under fasted conditions (A) on day 1 of period 3 and a single dose of 50 mg mirabegron oral suspension administered under fed conditions (B) on day 1 of period 4.

Reporting group title	Treatment Sequence 4: DBCA

Reporting group description:

Participants who received a single dose of 50 mg mirabegron modified release tablets administered under fed conditions (D) on day 1 of period 1, a single dose of 50 mg mirabegron oral suspension administered under fed conditions (B) on day 1 of period 2, a single dose of 50 mg mirabegron modified release tablets administered under fasted conditions (C) on day 1 of period 3 and a single dose of 50 mg mirabegron oral suspension administered under fasted conditions (A) on day 1 of period 4.

Subject analysis set title	Mirabegron Suspension Fasted
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who received mirabegron 50 mg oral suspension under fasted conditions in 1 of 4 treatment periods, taken according to their treatment sequence.

Subject analysis set title	Mirabegron Suspension Fed
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who received mirabegron 50 mg oral suspension under fed conditions in 1 of 4 treatment periods, taken according to their treatment sequence.

Subject analysis set title	Mirabegron Tablets Fasted
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who received mirabegron 50 mg modified release tablets under fasted conditions in 1 of 4 treatment periods, taken according to their treatment sequence.

Subject analysis set title	Mirabegron Tablets Fed
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who received mirabegron 50 mg modified release tablets under fed conditions in 1 of 4 treatment periods, taken according to their treatment sequence.

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

End point title	Area Under the Concentration-time Curve from the Time of Dosing Extrapolated to Time Infinity (AUCinf) for Mirabegron

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS) which consisted of the subset of participants of the Safety Analysis Set (SAF) population (all randomized participants who received at least 1 dose of study drug) for whom sufficient plasma concentration data were available to facilitate derivation of at least 1 pharmacokinetic (PK) parameter for the fasted mirabegron oral suspension and the fasted mirabegron tablet.

End point type	Primary

End point timeframe:

Day 1 predose, 30 minutes (min), 1 hour (h), 1h 30min, 2h, 2h 30min, 3h, 4h, 5h, 6h, 8h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, 192h, 240h postdose

End point values	Mirabegron Suspension Fasted	Mirabegron Suspension Fed	Mirabegron Tablets Fasted	Mirabegron Tablets Fed
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	19[1]	23	23
Units: ng*h/mL				
arithmetic mean (standard deviation)	185.2 (± 87.47)	76.37 (± 27.8)	391.3 (± 151.9)	172.3 (± 83.92)

Notes:

[1] - Participants with samples available

Statistical analyses

Statistical analysis title	Relative Bioavailability of Mirabegron

Statistical analysis description:

Relative bioavailability of mirabegron oral suspension formulation vs. tablets when dosed under fasted conditions. AUCinf was analyzed using a linear mixed effects model applied to the natural logarithm log-transformed PK parameter with treatment (suspension fasted, suspension fed, tablets fasted, tablets fed) and investigational period as fixed effects, and subject as a random effect. The number of participants analyzed is calculated by the system and cannot be changed; actual N=23.

Comparison groups	Mirabegron Tablets Fasted v Mirabegron Suspension Fasted
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Least Squares Mean Ratio
Point estimate	47.95
Confidence interval	
level	90 %
sides	2-sided
lower limit	40.91
upper limit	56.21

Statistical analysis title	Food Effect of Mirabegron Oral Suspension

Statistical analysis description:

Food effect of mirabegron oral suspension formulation. AUCinf was analyzed using a linear mixed effects

model applied to the natural logarithm log-transformed PK parameter with treatment (suspension fasted, suspension fed, tablets fasted, tablets fed) and investigational period as fixed effects, and subject as a random effect. The number of participants analyzed is calculated by the system and cannot be changed; actual N=23.

Comparison groups	Mirabegron Suspension Fasted v Mirabegron Suspension Fed
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Least Squares Mean Ratio
Point estimate	40.12
Confidence interval	
level	90 %
sides	2-sided
lower limit	33.95
upper limit	47.41

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

End point title	Area Under the Concentration-time Curve from the Time of Dosing to the Last Measurable Concentration (AUClast) for Mirabegron

End point description:

The analysis population was PKAS.

End point type	Primary

End point timeframe:

Day 1 predose, 30 minutes (min), 1 hour (h), 1h 30min, 2h, 2h 30min, 3h, 4h, 5h, 6h, 8h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, 192h, 240h postdose

End point values	Mirabegron Suspension Fasted	Mirabegron Suspension Fed	Mirabegron Tablets Fasted	Mirabegron Tablets Fed
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	23	23
Units: ng*h/mL				
arithmetic mean (standard deviation)	166.5 (± 82.76)	56.55 (± 24.22)	370.1 (± 150.8)	154.5 (± 82.23)

Statistical analyses

Statistical analysis title	Relative Bioavailability of Mirabegron

Statistical analysis description:

Relative bioavailability of mirabegron oral suspension formulation vs. tablets when dosed under fasted conditions. AUClast was analyzed using a linear mixed effects model applied to the natural logarithm log-transformed PK parameter with treatment (suspension fasted, suspension fed, tablets fasted, tablets fed) and investigational period as fixed effects, and subject as a random effect.The number of participants analyzed is calculated by the system and cannot be changed; actual N=23.

Comparison groups	Mirabegron Suspension Fasted v Mirabegron Tablets Fasted

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Least Squares Mean Ratio
Point estimate	45.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	38.46
upper limit	52.8

Statistical analysis title	Food Effect of Mirabegron Oral Suspension

Statistical analysis description:

Food effect of mirabegron oral suspension formulation. AUClast was analyzed using a linear mixed effects model applied to the natural logarithm log-transformed PK parameter with treatment (suspension fasted, suspension fed, tablets fasted, tablets fed) and investigational period as fixed effects, and subject as a random effect.The number of participants analyzed is calculated by the system and cannot be changed; actual N=23.

Comparison groups	Mirabegron Suspension Fasted v Mirabegron Suspension Fed
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Least Squares Mean Ratio
Point estimate	33.54
Confidence interval	
level	90 %
sides	2-sided
lower limit	28.68
upper limit	39.23

Primary: Maximum Concentration (Cmax) of Mirabegron

End point title	Maximum Concentration (Cmax) of Mirabegron

End point description:

The analysis population is PKAS.

End point type	Primary

End point timeframe:

Day 1 predose, 30 minutes (min), 1 hour (h), 1h 30min, 2h, 2h 30min, 3h, 4h, 5h, 6h, 8h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, 192h, 240h postdose

End point values	Mirabegron Suspension Fasted	Mirabegron Suspension Fed	Mirabegron Tablets Fasted	Mirabegron Tablets Fed
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	23	23
Units: ng/mL				
arithmetic mean (standard deviation)	12.19 (± 9.328)	2.54 (± 1.239)	35.15 (± 16.26)	15.45 (± 9.682)

Statistical analyses

Statistical analysis title	Relative Bioavailability of Mirabegron

Statistical analysis description:

Relative bioavailability of mirabegron oral suspension formulation vs. tablets when dosed under fasted conditions. Cmax was analyzed using a linear mixed effects model applied to the natural logarithm log-transformed PK parameter with treatment (suspension fasted, suspension fed, tablets fasted, tablets fed) and investigational period as fixed effects, and subject as a random effect. The number of participants analyzed is calculated by the system and cannot be changed; actual N=23.

Comparison groups	Mirabegron Suspension Fasted v Mirabegron Tablets Fasted
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Least Squares Mean Ratio
Point estimate	30.76
Confidence interval	
level	90 %
sides	2-sided
lower limit	23.76
upper limit	39.81

Statistical analysis title	Food Effect of Mirabegron Oral Suspension

Statistical analysis description:

Food effect of mirabegron oral suspension formulation. Cmax was analyzed using a linear mixed effects model applied to the natural logarithm log-transformed PK parameter with treatment (suspension fasted, suspension fed, tablets fasted, tablets fed) and investigational period as fixed effects, and subject as a random effect. The number of participants analyzed is calculated by the system and cannot be changed; actual N=23.

Comparison groups	Mirabegron Suspension Fasted v Mirabegron Suspension Fed
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Least Squares Mean Ratio
Point estimate	22.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	17.35
upper limit	28.92

Secondary: Percentage of AUCinf Due to Extrapolation from Time to Last Measurable Concentration (tlast) to Time Infinity (AUC[%extrap]) for Mirabegron

End point title	Percentage of AUCinf Due to Extrapolation from Time to Last Measurable Concentration (tlast) to Time Infinity (AUC[%extrap]) for Mirabegron

End point description:

The analysis population was PKAS.

End point type	Secondary

End point timeframe:

Day 1 predose, 30 minutes (min), 1 hour (h), 1h 30min, 2h, 2h 30min, 3h, 4h, 5h, 6h, 8h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, 192h, 240h postdose

End point values	Mirabegron Suspension Fasted	Mirabegron Suspension Fed	Mirabegron Tablets Fasted	Mirabegron Tablets Fed
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	19[2]	23	23
Units: percentage extrapolated				
arithmetic mean (standard deviation)	11.14 (± 4.189)	21.7 (± 5.896)	6.149 (± 2.74)	12.31 (± 5.758)

Notes:

[2] - Participants with samples available

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Systemic Clearance After Extravascular Dosing (CL/F) of Mirabegron

End point title	Apparent Total Systemic Clearance After Extravascular Dosing (CL/F) of Mirabegron

End point description:

The analysis population was PKAS.

End point type	Secondary

End point timeframe:

Day 1 predose, 30 minutes (min), 1 hour (h), 1h 30min, 2h, 2h 30min, 3h, 4h, 5h, 6h, 8h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, 192h, 240h postdose

End point values	Mirabegron Suspension Fasted	Mirabegron Suspension Fed	Mirabegron Tablets Fasted	Mirabegron Tablets Fed
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	19[3]	23	23
Units: L/h				
arithmetic mean (standard deviation)	329.1 (± 147.1)	745.3 (± 276.4)	150.3 (± 68.3)	364.8 (± 181.9)

Notes:

[3] - Participants with samples available

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Rate Constant (λz) for Mirabgron

End point title	Terminal Elimination Rate Constant (λz) for Mirabgron

End point description:

The analysis population was PKAS.

End point type	Secondary

End point timeframe:

Day 1 predose, 30 minutes (min), 1 hour (h), 1h 30min, 2h, 2h 30min, 3h, 4h, 5h, 6h, 8h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, 192h, 240h postdose

End point values	Mirabegron Suspension Fasted	Mirabegron Suspension Fed	Mirabegron Tablets Fasted	Mirabegron Tablets Fed
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	19[4]	23	23
Units: 1/h				
arithmetic mean (standard deviation)	0.01557 (± 0.00415)	0.01657 (± 0.004918)	0.01456 (± 0.003525)	0.01516 (± 0.004157)

Notes:

[4] - Participants with samples available

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time from the Time of Dosing Extrapolated to Time Infinity (MRTinf) of Mirabegron

End point title	Mean Residence Time from the Time of Dosing Extrapolated to Time Infinity (MRTinf) of Mirabegron

End point description:

The analysis population was PKAS.

End point type	Secondary

End point timeframe:

Day 1 predose, 30 minutes (min), 1 hour (h), 1h 30min, 2h, 2h 30min, 3h, 4h, 5h, 6h, 8h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, 192h, 240h postdose

End point values	Mirabegron Suspension Fasted	Mirabegron Suspension Fed	Mirabegron Tablets Fasted	Mirabegron Tablets Fed
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	19[5]	23	23
Units: hours				
arithmetic mean (standard deviation)	58.22 (± 18)	64.58 (± 23.42)	53.44 (± 15.06)	61.01 (± 23.54)

Notes:

[5] - Participants with samples available

Statistical analyses

No statistical analyses for this end point

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

End point title	Terminal Elimination Half-life (t1/2) of Mirabegron

End point description:

The analysis population was PKAS.

End point type	Secondary

End point timeframe:

Day 1 predose, 30 minutes (min), 1 hour (h), 1h 30min, 2h, 2h 30min, 3h, 4h, 5h, 6h, 8h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, 192h, 240h postdose

End point values	Mirabegron Suspension Fasted	Mirabegron Suspension Fed	Mirabegron Tablets Fasted	Mirabegron Tablets Fed
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	19[6]	23	23
Units: hours				
arithmetic mean (standard deviation)	47.89 (± 14.15)	46.25 (± 17.12)	50.3 (± 12.01)	50.02 (± 17.6)

Notes:

[6] - Participants with samples available

Statistical analyses

No statistical analyses for this end point

Secondary: Time Prior to the Time Corresponding to the First Measurable (Nonzero) Concentration (tlag) of Mirabegron

End point title	Time Prior to the Time Corresponding to the First Measurable (Nonzero) Concentration (tlag) of Mirabegron

End point description:

The analysis population was PKAS.

End point type	Secondary

End point timeframe:

Day 1 predose, 30 minutes (min), 1 hour (h), 1h 30min, 2h, 2h 30min, 3h, 4h, 5h, 6h, 8h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, 192h, 240h postdose

End point values	Mirabegron Suspension Fasted	Mirabegron Suspension Fed	Mirabegron Tablets Fasted	Mirabegron Tablets Fed
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	23	23
Units: hours				
arithmetic mean (standard deviation)	0 (± 0)	0.2 (± 0.3)	0.1 (± 0.2)	0.7 (± 0.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Time of Maximum Concentration (tmax) of Mirabgeron

End point title	Time of Maximum Concentration (tmax) of Mirabgeron
End point description:	
The analysis population was PKAS.	
End point type	Secondary
End point timeframe:	
Day 1 predose, 30 minutes (min), 1 hour (h), 1h 30min, 2h, 2h 30min, 3h, 4h, 5h, 6h, 8h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, 192h, 240h postdose	

End point values	Mirabegron Suspension Fasted	Mirabegron Suspension Fed	Mirabegron Tablets Fasted	Mirabegron Tablets Fed
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	23	23
Units: hours				
median (full range (min-max))	4.08 (2 to 5.33)	3 (1.03 to 12)	4.02 (1.98 to 5.03)	3.02 (1.98 to 6)

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution During the Terminal Elimination Phase after Extravascular Dosing (Vz/F) of Mirabegron

End point title	Apparent Volume of Distribution During the Terminal Elimination Phase after Extravascular Dosing (Vz/F) of Mirabegron
End point description:	
The analysis population was PKAS.	
End point type	Secondary

End point timeframe:

Day 1 predose, 30 minutes (min), 1 hour (h), 1h 30min, 2h, 2h 30min, 3h, 4h, 5h, 6h, 8h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, 192h, 240h postdose

End point values	Mirabegron Suspension Fasted	Mirabegron Suspension Fed	Mirabegron Tablets Fasted	Mirabegron Tablets Fed
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	19[7]	23	23
Units: Liters				
arithmetic mean (standard deviation)	21663 (± 9196)	45348 (± 10665)	10688 (± 4932)	25559 (± 12989)

Notes:

[7] - Participants with samples available

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:

An adverse event (AE) was assigned to the last treatment dose received prior to onset (or worsening). A treatment-emergent adverse event (TEAE) was defined as an adverse event which started after first administration of the study drug (day 1 of treatment period 1) up to the end-of-study visit (5 to 9 days after last [early] discharge from the clinical unit). Drug-related events can be possible or probable, as assessed by the investigator, or records where relationship is missing. The analysis population was SAF.

End point type	Secondary

End point timeframe:

From first dose of study drug in first treatment period up to end of study visit in last treatment period (up to 95 days)

End point values	Mirabegron Suspension Fasted	Mirabegron Suspension Fed	Mirabegron Tablets Fasted	Mirabegron Tablets Fed
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	24	23	23
Units: participants				
Any TEAE	13	11	8	8
Drug-related TEAEs	2	1	4	2
Deaths	0	0	0	0
Serious TEAEs	0	1	0	0
Drug-related serious TEAEs	0	0	0	0
TEAEs leading to discontinuation of drug	0	0	0	0
Drug-related TEAEs leading to Discont. of drug	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability Visual Analogue Scale (VAS) Scores of Mirabegron (oral suspension)

End point title	Palatability Visual Analogue Scale (VAS) Scores of Mirabegron (oral suspension)

End point description:

Palatability of mirabegron (oral suspension) was assessed using a VAS questionnaire, which consisted of 7 separate VAS scales (bitter, salty, sweet, sour, taste in general, aftertaste and acceptance) which were 100 mm in length (ranged from 0 mm “not at all” or "good" to 100 mm “very much” or "bad"). The analysis population was the SAF.

End point type	Secondary

End point timeframe:

Day 1 postdose of each treatment period

End point values	Mirabegron Suspension Fasted	Mirabegron Suspension Fed		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	24		
Units: mm				
arithmetic mean (standard deviation)				
Bitter	26.8 (± 25.2)	37.2 (± 30.4)		
Salty	13 (± 16.9)	13.6 (± 15.9)		
Sweet	49.2 (± 26.5)	50.2 (± 27.3)		
Sour	12.2 (± 18.4)	15.2 (± 24.1)		
Taste in General	55.2 (± 26.7)	56.5 (± 23)		
Aftertaste	52.2 (± 29.6)	49.5 (± 28.7)		
Acceptable (for taste and palatibility)	51.4 (± 27.2)	48.7 (± 21.1)		

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 in first treatment period up to end of study visit in last treatment period (up to 95 days)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Mirabegron Suspension Fed

Reporting group description:

Participants who received mirabegron 50 mg oral suspension under fed conditions in 1 of 4 treatment periods, taken according to their treatment sequence.

Reporting group title	Mirabegron Suspension Fasted

Reporting group description:

Participants who received mirabegron 50 mg oral suspension under fasted conditions in 1 of 4 treatment periods, taken according to their treatment sequence.

Reporting group title	Mirabegron Tablets Fasted

Reporting group description:

Participants who received mirabegron 50 mg modified release tablets under fasted conditions in 1 of 4 treatment periods, taken according to their treatment sequence.

Reporting group title	Mirabegron Tablets Fed

Reporting group description:

Participants who received mirabegron 50 mg modified release tablets under fed conditions in 1 of 4 treatment periods, taken according to their treatment sequence.

Serious adverse events	Mirabegron Suspension Fed	Mirabegron Suspension Fasted	Mirabegron Tablets Fasted
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 23 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Mirabegron Tablets Fed		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)		
number of deaths (all causes)	0		

number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Mirabegron Suspension Fed	Mirabegron Suspension Fasted	Mirabegron Tablets Fasted
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 24 (37.50%)	7 / 25 (28.00%)	4 / 23 (17.39%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 24 (12.50%)	2 / 25 (8.00%)	4 / 23 (17.39%)
occurrences (all)	3	2	5
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 24 (0.00%)	2 / 25 (8.00%)	0 / 23 (0.00%)
occurrences (all)	0	3	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 24 (8.33%)	1 / 25 (4.00%)	1 / 23 (4.35%)
occurrences (all)	2	1	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 24 (25.00%)	2 / 25 (8.00%)	0 / 23 (0.00%)
occurrences (all)	6	2	0

Non-serious adverse events	Mirabegron Tablets Fed		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	7 / 23 (30.43%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 4 / 23 (17.39%) 5		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	 1 / 23 (4.35%) 1		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	 0 / 23 (0.00%) 0		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	 2 / 23 (8.70%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 2 / 23 (8.70%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported