

**Clinical trial results:****A Phase 4, Double-Blind, Randomized, Placebo-controlled, Multi-Center Study to Evaluate the Efficacy, Safety, and Tolerability of Mirabegron in Men with Overactive Bladder (OAB) Symptoms While Taking the Alpha Blocker Tamsulosin Hydrochloride for Lower Urinary Tract Symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH)****Summary**

EudraCT number	2015-004036-36
Trial protocol	CZ DE PL ES GB IT
Global end of trial date	11 September 2018

Results information

Result version number	v1
This version publication date	30 August 2019
First version publication date	30 August 2019

Trial information**Trial identification**

Sponsor protocol code	178-MA-1008
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02757768
WHO universal trial number (UTN)	-
Other trial identifiers	Acronym: PLUS

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc.
Sponsor organisation address	1 Astellas Way, Northbrook, IL, United States, 60062
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)	No
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	11 September 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 September 2018
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 study the efficacy of mirabegron versus placebo in men with OAB symptoms while taking tamsulosin for LUTS due to BPH.

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	13 June 2016
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	Canada: 28
Country: Number of subjects enrolled	Czech Republic: 105
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 91
Country: Number of subjects enrolled	Italy: 92
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	Poland: 150
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	United States: 173
Worldwide total number of subjects	715
EEA total number of subjects	514

Notes:

Subjects enrolled per age group

In utero	0
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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)	312
From 65 to 84 years	402
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study enrolled male participants with overactive bladder (OAB) symptoms who were taking the alpha-blocker tamsulosin for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).

Pre-assignment

Screening details:

Eligible participants who met inclusion criteria and none of the exclusion criteria were enrolled. Participants entered a 4-week open label tamsulosin hydrochloride 0.4 mg once daily (QD) run-in period prior to being randomized in a 1:1 ratio into the 12-week double-blind treatment period of either mirabegron or placebo once daily.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Mirabegron

Arm description:

Participants received initial dose of 25 mg of mirabegron which was increased to 50 mg after 4 weeks. In addition to mirabegron participants received 0.4 mg of oral tamsulosin hydrochloride daily throughout the study.

Arm type	Experimental
Investigational medicinal product name	Mirabegron
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 which was increased to 50 mg after 4 weeks.

Investigational medicinal product name	Tamsulosin Hydrochloride
Investigational medicinal product code	
Other name	Flomax, Omnic
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received once daily treatment with tamsulosin hydrochloride 0.4 mg throughout the study.

Arm title	Placebo
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Arm description:

Participants received matching placebo in addition to oral tamsulosin hydrochloride daily throughout the study.

Arm type	Placebo
Investigational medicinal product name	Tamsulosin Hydrochloride
Investigational medicinal product code	
Other name	Flomax, Omnic
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received once daily treatment with tamsulosin hydrochloride 0.4 mg throughout the study.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received initial dose of 25 mg of matching placebo which was increased to 50 mg after 4 weeks.

Number of subjects in period 1	Mirabegron	Placebo
Started	356	359
Treated	352	354
Completed	323	331
Not completed	33	28
Consent withdrawn by subject	16	9
Adverse event, non-fatal	5	3
Protocol Deviation	2	9
Randomized Never Received Study Drug	3	4
Miscellaneous	4	2
Lost to follow-up	1	-
Lack of efficacy	2	1

Baseline characteristics

Reporting groups

Reporting group title	Mirabegron
Reporting group description:	Participants received initial dose of 25 mg of mirabegron which was increased to 50 mg after 4 weeks. In addition to mirabegron participants received 0.4 mg of oral tamsulosin hydrochloride daily throughout the study.
Reporting group title	Placebo
Reporting group description:	Participants received matching placebo in addition to oral tamsulosin hydrochloride daily throughout the study.

Reporting group values	Mirabegron	Placebo	Total
Number of subjects	356	359	715
Age categorical Units: Subjects			
Age continuous			
The analysis population was the all randomized (RAS), which consisted of participants who received initial doses of 25 mg of mirabegron or matching placebo which was increased after 4 weeks to 50 mg.			
Units: years			
arithmetic mean	65	65	-
standard deviation	± 8.3	± 9.5	-
Gender categorical Units: Subjects			
M	356	359	715
Race/Ethnicity, Customized Units: Subjects			
WHITE	332	325	657
BLACK OR AFRICAN AMERICAN	16	27	43
ASIAN	4	4	8
OTHER	2	2	4
MISSING/UNKNOWN	2	1	3
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	10	12	22
Not Hispanic or Latino	339	336	675
Unknown or Not Reported	7	11	18
Geographic Region Units: Subjects			
Europe	257	257	514
North America	99	102	201
Micturition Episodes per 24 Hours			
This baseline measure is based on the full analysis set (FAS), the FAS was defined as all randomized participants who took at least one dose of double-blind treatment after randomization, reported at least one micturition in the baseline diary and at least one micturition post-baseline.			
Units: micturitions in 24 hours (M24MIC)			
log mean	10.7	10.7	-
standard deviation	± 2.5	± 2.6	-

End points

End points reporting groups

Reporting group title	Mirabegron
Reporting group description: Participants received initial dose of 25 mg of mirabegron which was increased to 50 mg after 4 weeks. In addition to mirabegron participants received 0.4 mg of oral tamsulosin hydrochloride daily throughout the study.	
Reporting group title	Placebo
Reporting group description: Participants received matching placebo in addition to oral tamsulosin hydrochloride daily throughout the study.	

Primary: Change From Baseline to End of Treatment (EoT) in Mean Number of Micturitions Per Day

End point title	Change From Baseline to End of Treatment (EoT) in Mean Number of Micturitions Per Day
End point description: Participants recorded micturitions in the e-diary during three days. The mean number of micturitions was calculated as the average number of times a participant recorded a micturition per day during the 3-day period. Only voluntary micturitions were counted and the episodes of incontinence were not included. The analysis population was the full analysis set (FAS), which consisted of all randomized participants who took at least 1 dose of double-blind study drug, reported at least 1 baseline micturition recorded in the 3-day e-diary and at least 1 postbaseline micturition. Last observation carried forward (LOCF) was used for missing values in the EoT.	
End point type	Primary
End point timeframe: Baseline and Week 12	

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: micturitions				
least squares mean (standard error)				
micturitions	-2.00 (\pm 0.13)	-1.62 (\pm 0.15)		

Statistical analyses

Statistical analysis title	Placebo vs. Mirabegron
Statistical analysis description: Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo

Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean of Difference
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.02
Variability estimate	Standard error of the mean
Dispersion value	0.19

Secondary: Change From Baseline to Week 4, Week 8, and Week 12 in Mean Number of Micturitions Per Day

End point title	Change From Baseline to Week 4, Week 8, and Week 12 in Mean Number of Micturitions Per Day
End point description:	
Participants recorded micturitions in the e-diary during three days. The mean number of micturitions was calculated as the average number of times a participant recorded a micturition per day during the 3-day period. Only voluntary micturitions were counted and the episodes of incontinence were not included. The analysis population was 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, 8, and 12	

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: micturitions				
least squares mean (standard error)				
Week 4 [N=334, 334]	-1.42 (± 0.13)	-1.32 (± 0.13)		
Week 8 [N=328, 326]	-1.89 (± 0.13)	-1.38 (± 0.13)		
Week 12 [N=317, 319]	-1.95 (± 0.13)	-1.56 (± 0.13)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo

Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.558
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.18

Statistical analysis title	Week 8 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 ^[1]
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.19

Notes:

[1] - P-value indicates statistical significance at the 0.05 level.

Statistical analysis title	Week 12 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
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Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041 [2]
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.02
Variability estimate	Standard error of the mean
Dispersion value	0.19

Notes:

[2] - P-value indicates statistical significance at the 0.05 level.

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in Mean Volume Voided Per Micturition

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in Mean Volume Voided Per Micturition
End point description:	
The mean volume voided per micturition collected in the micturition diary during the 3-day period. The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.	
End point type	Secondary
End point timeframe:	
Baseline and Weeks 4, 8, and 12	

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: mL				
least squares mean (standard error)				
Week 4 [N=334, 333]	17.74 (± 1.98)	13.87 (± 1.98)		
Week 8 [N=328, 325]	22.56 (± 2.31)	16.28 (± 2.32)		
Week 12 [N=317, 319]	26.31 (± 2.53)	17.32 (± 2.52)		
EoT [N=337, 339]	25.57 (± 2.42)	16.32 (± 2.42)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Placebo v Mirabegron

Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.167
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	3.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.63
upper limit	9.37
Variability estimate	Standard error of the mean
Dispersion value	2.8

Statistical analysis title	Week 8 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.056
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	6.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	12.73
Variability estimate	Standard error of the mean
Dispersion value	3.28

Statistical analysis title	Week 12 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
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Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	8.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.97
upper limit	16.01
Variability estimate	Standard error of the mean
Dispersion value	3.58

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	9.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.53
upper limit	15.98
Variability estimate	Standard error of the mean
Dispersion value	3.43

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in Mean Number of Incontinence Episodes Per Day

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in Mean Number of Incontinence Episodes Per Day
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End point description:

An incontinence episode was defined as the complaint of any involuntary leakage of urine. The mean number of incontinence episodes per 24 hours was calculated as the average number of times a participant recorded an incontinence episode per day during the 3-day micturition diary period. The analysis population was the full analysis set - incontinence (FAS-I), which consisted of all randomized participants who took at least 1 dose of double-blind study drug and reported 1 micturition at baseline and postbaseline in the 3-day e-diary. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	129		
Units: incontinence episodes				
least squares mean (standard error)				
Week 4 [N=131, 129]	-0.97 (± 0.18)	-0.84 (± 0.18)		
Week 8 [N=130, 121]	-1.29 (± 0.22)	-1.20 (± 0.23)		
Week 12 [N=125, 119]	-1.48 (± 0.22)	-1.23 (± 0.23)		
EoT [N=132, 129]	-1.45 (± 0.21)	-1.15 (± 0.22)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description: Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.747
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	0.38
Variability estimate	Standard error of the mean
Dispersion value	0.26

Statistical analysis title	Week 8 Placebo vs. Mirabegron
Statistical analysis description: Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo

Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.393
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.54
Variability estimate	Standard error of the mean
Dispersion value	0.32

Statistical analysis title	Week 12 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.672
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	0.38
Variability estimate	Standard error of the mean
Dispersion value	0.32

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
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Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.31

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in Mean Number of Urgency Episodes (Grade 3 or 4) Per Day

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in Mean Number of Urgency Episodes (Grade 3 or 4) Per Day
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End point description:

Urgency was defined as a complaint of a sudden, compelling desire to pass urine, which is difficult to defer. An urgency episode was defined as any micturition or incontinence episode with a severity of grade 3 or 4, assessed by participants based on the Patient Perception of Intensity of Urgency Scale (PPIUS), where 0 = No urgency; 1 = Mild urgency; 2 = Moderate urgency, could delay voiding a short while; 3 = Severe urgency, could not delay voiding; 4 = Urge incontinence, leaked before arriving to the toilet. The mean number of urgency episodes (grade 3 and/or 4) per day was calculated as the average number of times a participant recorded an urgency episode (grade 3 and/or 4) with or without incontinence per day during the 3-day micturition diary period. The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: urgency episodes				
least squares mean (standard error)				
Week 4 [N=334, 334]	-1.79 (± 0.15)	-1.53 (± 0.15)		
Week 8 [N=328, 326]	-2.68 (± 0.17)	-1.97 (± 0.17)		
Week 12 [N=317, 319]	-2.86 (± 0.17)	-2.21 (± 0.17)		
EoT [N=337, 339]	-2.90 (± 0.17)	-2.24 (± 0.17)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.222
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.21

Statistical analysis title	Week 8 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [3]
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	-0.24
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

[3] - P-value indicates statistical significance at the 0.05 level.

Statistical analysis title	Week 12 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo

Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008 [4]
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	-0.17
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

[4] - P-value indicates statistical significance at the 0.05 level.

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [5]
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	-0.21
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[5] - P-value indicates statistical significance at the 0.05 level.

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in International Prostate Symptom Score (IPSS) Total Score

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in International Prostate Symptom Score (IPSS) Total Score
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End point description:

The International Prostate Symptom Score (IPSS) consists of 7 questions concerning urinary symptoms and 1 question concerning quality of life (QoL) with total score and subscores (voiding, storage and QoL). The IPSS total score classification ranges from mild (0 to 7) to moderate (8 to 19) or severe (20 to 35). Higher IPSS scored indicated more severe symptoms. The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)				
Week 4 [N=335, 330]	-3.9 (± 0.3)	-4.0 (± 0.3)		
Week 8 [N=327, 331]	-5.0 (± 0.3)	-5.2 (± 0.3)		
Week 12 [N=318, 323]	-5.9 (± 0.3)	-5.5 (± 0.3)		
EoT [N=336, 335]	-5.7 (± 0.3)	-5.6 (± 0.3)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.723
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.4

Statistical analysis title	Week 8 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Placebo v Mirabegron

Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.4

Statistical analysis title	Week 12 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.5

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
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Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.812
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	0.4

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in IPSS Subscale Voiding Score

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in IPSS Subscale Voiding Score
End point description:	
<p>The International Prostate Symptom Score (IPSS) consists of 7 questions concerning urinary symptoms and 1 question concerning quality of life (QoL) with total score and subscores (voiding, storage and QoL). The IPSS total score classification ranges from mild (0 to 7) to moderate (8 to 19) or severe (20 to 35). Higher IPSS scored indicated more severe symptoms. The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.</p>	
End point type	Secondary
End point timeframe:	
Baseline and Weeks 4, 8, and 12	

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)				
Week 4 [N=335, 330]	-1.7 (± 0.2)	-2.1 (± 0.2)		
Week 8 [N=327, 331]	-2.2 (± 0.2)	-2.5 (± 0.2)		
Week 12 [N=318, 323]	-2.5 (± 0.2)	-2.5 (± 0.2)		
EoT [N=336, 335]	-2.5 (± 0.2)	-2.6 (± 0.2)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description:	
<p>Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed</p>	

factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.121
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.3

Statistical analysis title	Week 8 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.241
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	0.3

Statistical analysis title	Week 12 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
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Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.843
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.3

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.679
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.3

Secondary: Change From Baseline to Week 4, Week 8, Week 12, and EoT in IPSS Subscale Storage Score

End point title	Change From Baseline to Week 4, Week 8, Week 12, and EoT in IPSS Subscale Storage Score
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End point description:

The International Prostate Symptom Score (IPSS) consists of 7 questions concerning urinary symptoms and 1 question concerning quality of life (QoL) with total score and subscores (voiding, storage and QoL). The IPSS total score classification ranges from mild (0 to 7) to moderate (8 to 19) or severe (20 to 35). Higher IPSS scored indicated more severe symptoms. The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)				
Week 4 [N=335, 330]	-2.2 (± 0.1)	-1.9 (± 0.1)		
Week 8 [N=327, 331]	-2.8 (± 0.2)	-2.6 (± 0.1)		
Week 12 [N=318, 323]	-3.3 (± 0.2)	-3.0 (± 0.2)		
EoT [N=336, 335]	-3.3 (± 0.2)	-3.0 (± 0.2)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.175
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.2

Statistical analysis title	Week 8 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo

Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.2

Statistical analysis title	Week 12 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.141
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.2

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
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Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.288
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.2

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in IPSS Subscale Quality of Life (QoL) Score

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in IPSS Subscale Quality of Life (QoL) Score
End point description:	
<p>The International Prostate Symptom Score (IPSS) consists of 7 questions concerning urinary symptoms and 1 question concerning quality of life (QoL) with total score and subscores (voiding, storage and QoL). The IPSS total score classification ranges from mild (0 to 7) to moderate (8 to 19) or severe (20 to 35). Higher IPSS scored indicated more severe symptoms. The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.</p>	
End point type	Secondary
End point timeframe:	
Baseline and Weeks 4, 8, and 12	

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)				
Week 4 [N=335, 330]	-0.9 (± 0.1)	-0.7 (± 0.1)		
Week 8 [N=327, 331]	-1.3 (± 0.1)	-1.1 (± 0.1)		
Week 12 [N=318, 323]	-1.5 (± 0.1)	-1.3 (± 0.1)		
EoT [N=336, 335]	-1.4 (± 0.1)	-1.3 (± 0.1)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed	

factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.128
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Week 8 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Week 12 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
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Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.148
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in Mean Number of Urgency Incontinence Episodes Per Day

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in Mean Number of Urgency Incontinence Episodes Per Day
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End point description:

Urgency Incontinence was defined as the complaint of involuntary leakage accompanied by or immediately proceeded by urgency. The mean number of urgency incontinence episodes was calculated as the average number of times a participant recorded an urgency incontinence episode per day during the 3-day micturition diary period. The analysis population was the FAS-I. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8 and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	129		
Units: urgency incontinence episodes				
least squares mean (standard error)				
Week 4 [N=131, 129]	-0.97 (± 0.18)	-0.85 (± 0.18)		
Week 8 [N=130, 121]	-1.29 (± 0.22)	-1.19 (± 0.23)		
Week 12 [N=125, 119]	-1.52 (± 0.22)	-1.24 (± 0.22)		
EoT [N=132, 129]	-1.49 (± 0.21)	-1.16 (± 0.21)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description: Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	0.39
Variability estimate	Standard error of the mean
Dispersion value	0.25

Statistical analysis title	Week 8 Placebo vs. Mirabegron
Statistical analysis description: Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Placebo v Mirabegron

Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.767
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.53
Variability estimate	Standard error of the mean
Dispersion value	0.32

Statistical analysis title	Week 12 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.372
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	0.31

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
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Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.272
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.92
upper limit	0.26
Variability estimate	Standard error of the mean
Dispersion value	0.3

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in Symptom Bother Score

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in Symptom Bother Score
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End point description:

Overactive bladder symptoms were assessed using the Symptom Bother Scale of the Overactive Bladder questionnaire (OAB-q). The OAB-q is a self-reported questionnaire with 33 questions relating to symptom bother and health-related quality of life (HRQoL). The symptom bother portion consists of 8 questions, rated on a 6-point Likert scale (1 through 6). The total symptom bother score was calculated from the 8 answers and then transformed to range from 0 (least severity) to 100 (worst severity). Lower scores on OAB-q symptom bother indicate a better response. The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)				
Week 4 [N=330, 325]	-13.73 (± 0.91)	-11.98 (± 0.92)		
Week 8 [N=323, 325]	-18.72 (± 1.00)	-14.88 (± 0.99)		
Week 12 [N=314, 318]	-20.93 (± 1.07)	-18.03 (± 1.06)		
EoT [N=332, 330]	-20.18 (± 1.04)	-18.07 (± 1.05)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.179
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.29
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	1.3

Statistical analysis title	Week 8 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-3.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	-1.08
Variability estimate	Standard error of the mean
Dispersion value	1.41

Statistical analysis title	Week 12 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Placebo v Mirabegron

Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.86
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	1.51

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.154
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.02
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	1.48

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in Total Health Related Quality of Life (HRQL) Score

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in Total Health Related Quality of Life (HRQL) Score
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End point description:

The OAB-q is a self-reported questionnaire with 33 questions relating to symptom bother and health-related quality of life (HRQoL). The HRQoL portion consists of 25 HRQoL items comprising 4 HRQoL subscales (Coping, Concern, Sleep, and Social Interaction), each item was scored 1-6. The total score was calculated by adding the 4 HRQoL subscale scores and transforming to a scale from 0 to 100, with higher scores indicating better quality of life. A higher score on OAB-q HRQL indicated a better response. The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)				
Week 4 [N=330, 325]	9.08 (± 0.80)	10.43 (± 0.80)		
Week 8 [N=323, 325]	13.06 (± 0.85)	13.53 (± 0.85)		
Week 12 [N=314, 318]	15.90 (± 0.91)	15.00 (± 0.90)		
EoT [N=332, 330]	15.07 (± 0.89)	15.12 (± 0.89)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.233
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.57
upper limit	0.87
Variability estimate	Standard error of the mean
Dispersion value	1.13

Statistical analysis title	Week 8 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo

Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.698
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.89
upper limit	2.82
Variability estimate	Standard error of the mean
Dispersion value	1.2

Statistical analysis title	Week 12 Placebo vs. Mirabegron
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Statistical analysis description:

Week 12 Difference vs. Mirabegron: Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.486
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.62
upper limit	3.4
Variability estimate	Standard error of the mean
Dispersion value	1.28

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
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Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.968
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.52
upper limit	2.42
Variability estimate	Standard error of the mean
Dispersion value	1.26

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in HRQL Subscale Coping Score

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in HRQL Subscale Coping Score
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End point description:

The OAB-q is a self-reported questionnaire with 33 questions relating to symptom bother and health-related quality of life (HRQoL). The HRQoL portion consists of 25 HRQoL items comprising 4 HRQoL subscales (Coping, Concern, Sleep, and Social Interaction), each item was scored 1-6. A higher score on OAB-q HRQL indicated a better response. The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)				
Week 4 [N=330, 325]	10.58 (± 0.96)	12.47 (± 0.97)		
Week 8 [N=323, 325]	16.01 (± 1.00)	15.25 (± 1.00)		
Week 12 [N=314, 318]	18.93 (± 1.09)	18.03 (± 1.08)		
EoT [N=332, 330]	18.05 (± 1.07)	18.02 (± 1.07)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed

factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.165
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.56
upper limit	0.78
Variability estimate	Standard error of the mean
Dispersion value	1.36

Statistical analysis title	Week 8 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.592
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.02
upper limit	3.54
Variability estimate	Standard error of the mean
Dispersion value	1.41

Statistical analysis title	Week 12 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
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Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.559
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.12
upper limit	3.92
Variability estimate	Standard error of the mean
Dispersion value	1.54

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.985
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.94
upper limit	3
Variability estimate	Standard error of the mean
Dispersion value	1.51

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in HRQL Subscale Concern Score

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in HRQL Subscale Concern Score
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End point description:

The OAB-q is a self-reported questionnaire with 33 questions relating to symptom bother and health-related quality of life (HRQoL). The HRQoL portion consists of 25 HRQoL items comprising 4 HRQoL subscales (Coping, Concern, Sleep, and Social Interaction), each item was scored 1-6. A higher score on OAB-q HRQL indicated a better response. The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)				
Week 4 [N=330, 325]	9.06 (± 0.91)	10.87 (± 0.92)		
Week 8 [N=323, 325]	13.34 (± 0.98)	12.99 (± 0.98)		
Week 12 [N=314, 318]	15.64 (± 1.00)	14.47 (± 1.00)		
EoT [N=332, 330]	14.81 (± 0.98)	14.67 (± 0.99)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron:
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.161
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.35
upper limit	0.72
Variability estimate	Standard error of the mean
Dispersion value	1.29

Statistical analysis title	Week 8 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Placebo v Mirabegron

Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.798
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.36
upper limit	3.07
Variability estimate	Standard error of the mean
Dispersion value	1.38

Statistical analysis title	Week 12 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.408
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	3.95
Variability estimate	Standard error of the mean
Dispersion value	1.42

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
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Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.919
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	2.88
Variability estimate	Standard error of the mean
Dispersion value	1.39

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in HRQL Subscale Sleep Score

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in HRQL Subscale Sleep Score
End point description:	
<p>The OAB-q is a self-reported questionnaire with 33 questions relating to symptom bother and health-related quality of life (HRQoL). The HRQoL portion consists of 25 HRQoL items comprising 4 HRQoL subscales (Coping, Concern, Sleep, and Social Interaction), each item was scored 1-6. A higher score on OAB-q HRQL indicated a better response. The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.</p>	
End point type	Secondary
End point timeframe:	
Baseline and Weeks 4, 8 and 12	

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)				
Week 4 [N=330, 325]	10.43 (± 1.05)	10.45 (± 1.06)		
Week 8 [N=323, 325]	15.32 (± 1.10)	14.41 (± 1.09)		
Week 12 [N=314, 318]	17.94 (± 1.15)	16.41 (± 1.15)		
EoT [N=332, 330]	16.87 (± 1.13)	16.62 (± 1.13)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description:	
<p>Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed</p>	

factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.94
upper limit	2.91
Variability estimate	Standard error of the mean
Dispersion value	1.49

Statistical analysis title	Week 8 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.554
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.12
upper limit	3.96
Variability estimate	Standard error of the mean
Dispersion value	1.55

Statistical analysis title	Week 12 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
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Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.348
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	4.73
Variability estimate	Standard error of the mean
Dispersion value	1.63

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.876
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.89
upper limit	3.38
Variability estimate	Standard error of the mean
Dispersion value	1.6

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in HRQL Subscale Social Interaction Score

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in HRQL Subscale Social Interaction Score
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End point description:

The OAB-q is a self-reported questionnaire with 33 questions relating to symptom bother and health-related quality of life (HRQoL). The HRQoL portion consists of 25 HRQoL items comprising 4 HRQoL subscales (Coping, Concern, Sleep, and Social Interaction), each item was scored 1-6. A higher score on OAB-q HRQL indicated a better response. The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)				
Week 4 [N=330, 325]	5.55 (± 0.74)	6.65 (± 0.74)		
Week 8 [N=323, 325]	8.03 (± 0.79)	8.35 (± 0.79)		
Week 12 [N=314, 318]	9.48 (± 0.79)	9.57 (± 0.79)		
EoT [N=332, 330]	8.96 (± 0.77)	9.67 (± 0.78)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.293
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.16
upper limit	0.95
Variability estimate	Standard error of the mean
Dispersion value	1.05

Statistical analysis title	Week 8 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo

Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.773
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.52
upper limit	1.87
Variability estimate	Standard error of the mean
Dispersion value	1.12

Statistical analysis title	Week 12 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.28
upper limit	2.11
Variability estimate	Standard error of the mean
Dispersion value	1.12

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
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Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.516
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.86
upper limit	1.44
Variability estimate	Standard error of the mean
Dispersion value	1.1

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in European Quality of Life in 5 Dimensions and 5 Levels (EQ-5D-5L Questionnaire)

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in European Quality of Life in 5 Dimensions and 5 Levels (EQ-5D-5L Questionnaire)
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End point description:

The EQ-5D-5L is an international standardized non-disease specific generic instrument for describing and valuing health status. It has a multidimensional measure of health-related QoL, capable of being expressed as a single index value and specifically designed to complement other health status measures. The EQ-5D-5L has five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension has 5 response levels (e.g., 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems/unable to perform the activity). In addition, it has a visual analog scale that elicits a self-rating by the respondent of his health status. The analysis population was the FAS. The analysis of the EQ-5D endpoint will be completed by an external vendor outside of the main study report. Astellas anticipates to post the results in April 2020. Data not available is denoted as "99999" as applicable.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in Patient

Perception of Bladder Condition (PPBC)

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in Patient Perception of Bladder Condition (PPBC)
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End point description:

The PPBC is a validated, global assessment tool using a 6-point Likert scale that asks participants to rate their subjective impression of their current bladder condition. Participants assessed their bladder condition using this scale: 1. Does not cause me any problems at all; 2. Causes me some very minor problems; 3. Causes me some minor problems; 4. Causes me (some) moderate problems; 5. Causes me severe problems; 6. Causes me many severe problems. A higher score indicated a worse perception of bladder condition. The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)				
Week 4 [N=330, 325]	-0.6 (± 0.1)	-0.5 (± 0.1)		
Week 8 [N=323, 325]	-0.8 (± 0.1)	-0.7 (± 0.1)		
Week 12 [N=314, 318]	-1.0 (± 0.1)	-0.9 (± 0.1)		
EoT [N=332, 330]	-0.9 (± 0.1)	-0.9 (± 0.1)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.223
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Week 8 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.598
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Week 12 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.312
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Placebo v Mirabegron
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.525
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in Total Urgency and Frequency Score (TUFS)

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in Total Urgency and Frequency Score (TUFS)
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End point description:

The TUFS was calculated by adding the PPIUS scores of every void in a participant's 3-day diary, and dividing this by the number of days recorded in the diary. The analysis population was the FAS. Due to a programming failure in the e-diary data for the number of pads used was not collected. Data not calculable is denoted as "99999" as applicable.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8 and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)				
units on a scale	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in Mean

Number of Nocturia Episodes Per 24 Hours

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in Mean Number of Nocturia Episodes Per 24 Hours
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End point description:

A nocturia episode was defined as waking at night one or more time to void (i.e., any voiding associated with sleep disturbance between the date/time the participant goes to bed with the intention to sleep until the date/time the participant gets up in the morning with the intention to stay awake). A night time episode of incontinence is not considered a nocturia episode. The mean number of nocturia episodes per day (24 hours) was calculated as the average number of times a participant recorded a nocturia episode per day during the 3-day micturition diary period. The analysis population was the full analysis set - nocturia (FAS-N), which consisted of all randomized participants who took at least 1 dose of double-blind study drug and reported 1 micturition at baseline and postbaseline in the 3-day e-diary. N is the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	124		
Units: nocturia episodes				
least squares mean (standard error)				
Week 4 [N=141, 123]	-0.32 (± 0.07)	-0.45 (± 0.08)		
Week 8 [N=135, 118]	-0.48 (± 0.07)	-0.55 (± 0.08)		
Week 12 [N=130, 114]	-0.51 (± 0.08)	-0.52 (± 0.08)		
EoT [N=142, 124]	-0.49 (± 0.07)	-0.52 (± 0.08)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.226
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	0.11

Statistical analysis title	Week 8 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.501
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.28
Variability estimate	Standard error of the mean
Dispersion value	0.11

Statistical analysis title	Week 12 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.984
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.12

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.11

Secondary: Change From Baseline to Week 4, Week 8, Week 12 and EoT in Treatment Satisfaction Visual Analog Scale (TS-VAS)

End point title	Change From Baseline to Week 4, Week 8, Week 12 and EoT in Treatment Satisfaction Visual Analog Scale (TS-VAS)
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End point description:

The TS-VAS is a visual analog scale that asks participants to rate their satisfaction with the treatment by placing a vertical mark on a line that runs from 0 (No, not at all) to 100 (Yes, completely). The analysis population was the FAS. Missing values in the EoT were imputed using the LOCF method. N is the number of participants with available data at each time point.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	339		
Units: units on a scale				
least squares mean (standard error)				
Week 4 [N=328, 324]	15.6 (± 1.3)	12.5 (± 1.4)		
Week 8 [N=321, 325]	18.6 (± 1.4)	16.1 (± 1.4)		
Week 12 [N=313, 317]	19.1 (± 1.5)	16.9 (± 1.5)		
EoT [N=331, 330]	18.4 (± 1.5)	16.9 (± 1.5)		

Statistical analyses

Statistical analysis title	Week 4 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.107
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	6.8
Variability estimate	Standard error of the mean
Dispersion value	1.9

Statistical analysis title	Week 8 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	6.3
Variability estimate	Standard error of the mean
Dispersion value	1.9

Statistical analysis title	Week 12 Placebo vs. Mirabegron
Statistical analysis description:	
Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.	
Comparison groups	Mirabegron v Placebo

Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.297
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	6.3
Variability estimate	Standard error of the mean
Dispersion value	2.1

Statistical analysis title	EoT Placebo vs. Mirabegron
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Statistical analysis description:

Differences of adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, age group (<65, >=65 years) and geographical region as fixed factors and baseline value as a covariate.

Comparison groups	Mirabegron v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.493
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	5.5
Variability estimate	Standard error of the mean
Dispersion value	2.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first double-blind medication intake until 30 days after last double-blind medication intake; 16 weeks

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Mirabegron
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Reporting group description:

Participants received initial dose of 25 mg of mirabegron which was increased to 50 mg after 4 weeks. In addition to mirabegron participants received 0.4 mg of oral tamsulosin hydrochloride daily throughout the study.

Reporting group title	Placebo
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Reporting group description:

Participants received matching placebo in addition to oral tamsulosin hydrochloride daily throughout the study.

Serious adverse events	Mirabegron	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 352 (2.84%)	8 / 354 (2.26%)	
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)			
Glioblastoma			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronotropic incompetence			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar stroke			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			

subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	
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			
Peripheral swelling			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Ankylosing spondylitis			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			

subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 352 (0.00%)	1 / 354 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Neuroborreliosis			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 352 (0.28%)	0 / 354 (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: 2 %

Non-serious adverse events	Mirabegron	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 352 (3.41%)	19 / 354 (5.37%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 352 (1.70%)	11 / 354 (3.11%)	
occurrences (all)	6	12	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 352 (1.70%)	8 / 354 (2.26%)	
occurrences (all)	6	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2016	The changes include: <ul style="list-style-type: none">• Updated mode of administration of tamsulosin to include capsules in the US and tablets in the EU and Canada. Nonsubstantial changes were as follows: <ul style="list-style-type: none">• Added study name PLUS to protocol title• Updated patient e-diary – micturition and incontinence section• Made minor administrative type corrections
10 May 2017	The changes include: <ul style="list-style-type: none">• Updated acceptable PSA range to ≥ 4 ng/mL but < 10 ng/mL if a negative biopsy was obtained within the last year Nonsubstantial changes were minor administrative type corrections.
24 October 2017	The changes include: <ul style="list-style-type: none">• Updated the sample size by reducing the power from 90% to 80%, where approximately 640 patients would be randomized 1:1; with 320 to mirabegron and 320 to placebo• Updated acceptable PSA range if negative biopsy was obtained within the past 2 years Nonsubstantial changes were implemented in addition to the substantial changes mentioned above.
22 January 2018	The changes include: <ul style="list-style-type: none">• Updated reference safety information from the US package insert, Canadian monograph and SmPC to the company core data sheet for mirabegron

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The analysis of the EQ-5D endpoint will be completed by an external vendor outside of the main study report. Astellas anticipates to post the results in April 2020.

Notes: