Clinical trial results:
A Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Adding Mirabegron to Solifenacin in Incontinent OAB Patients who have Received Solifenacin for 4 Weeks and Warrant Additional Relief for their OAB Symptoms

Summary

EudraCT number	2012-005401-41
Trial protocol	SK CZ GB SE IE BE PT NO AT FI GR HU ES SI NL DK PL
Global end of trial date	25 November 2014

Results information

Result version number	v1
This version publication date	21 July 2016
First version publication date	21 July 2016

Trial information

Trial identification

Sponsor protocol code	905-EC-012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01908829
WHO universal trial number (UTN)	-
Other trial identifiers	Acronym: BESIDE

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe Ltd
Sponsor organisation address	2000 Hillswood Drive, Chertsey, United Kingdom, KT16 0RS
Public contact	Clinical Trial Disclosure, Astellas Pharma Europe Ltd, Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Europe Ltd, 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	25 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of solifenacin 5 mg in combination with mirabegron 50 mg (referred to as combination therapy from here on) vs solifenacin 5 mg monotherapy.

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	10 July 2013
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	Algeria: 15
Country: Number of subjects enrolled	Armenia: 52
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Austria: 24
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Canada: 57
Country: Number of subjects enrolled	Czech Republic: 129
Country: Number of subjects enrolled	Denmark: 39
Country: Number of subjects enrolled	Egypt: 11
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Georgia: 23
Country: Number of subjects enrolled	Germany: 106
Country: Number of subjects enrolled	Greece: 53
Country: Number of subjects enrolled	Hungary: 53
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Israel: 43

Country: Number of subjects enrolled	Italy: 49
Country: Number of subjects enrolled	Kazakhstan: 23
Country: Number of subjects enrolled	Norway: 9
Country: Number of subjects enrolled	Poland: 234
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Romania: 84
Country: Number of subjects enrolled	Russian Federation: 241
Country: Number of subjects enrolled	Slovakia: 93
Country: Number of subjects enrolled	Slovenia: 26
Country: Number of subjects enrolled	Spain: 76
Country: Number of subjects enrolled	Sweden: 54
Country: Number of subjects enrolled	Switzerland: 11
Country: Number of subjects enrolled	Turkey: 164
Country: Number of subjects enrolled	Ukraine: 28
Country: Number of subjects enrolled	United Kingdom: 78
Country: Number of subjects enrolled	United States: 320
Country: Number of subjects enrolled	Netherlands: 15
Worldwide total number of subjects	2174
EEA total number of subjects	1183

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1492
From 65 to 84 years	671
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

This multicenter study was conducted at 281 centers globally.

Pre-assignment

Screening details:

Participants who met the screening inclusion/exclusion criteria went through a two week wash-out period and maintained a micturition diary during that the wash-out period. A total of 3815 participants were screened of which 2401 participants received solifenacin 5 mg run-in medication.

Pre-assignment period milestones

Number of subjects started	3815[1]
Intermediate milestone: Number of subjects	Received 1 dose, single-blind run-in: 2401
Number of subjects completed	2174

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Discontinued before run-in solifenacin 5 mg: 1414
Reason: Number of subjects	Exclusion/inclusion criteria not met: 169
Reason: Number of subjects	Patient withdrawn: 32
Reason: Number of subjects	Adverse event: 16
Reason: Number of subjects	Other reasons: 7
Reason: Number of subjects	Lost to follow-up: 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of participants included in the pre-assignment period were the total number screened. The number of participants included in the worldwide number enrolled were the total number of participants randomized.

Period 1

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

Blinding implementation details:

The study is comprised of a 12 week double-blind treatment period (participants were randomized into the double-blind period if they experienced 1 or more incontinence episodes over the 3-day diary period prior to randomization to double-blind period and warranted additional relief for their OAB symptoms). There was 2 week safety follow up period (placebo administered). The active and placebo tablets were made indistinguishable by using a double-dummy packaging system.

Arms

Are arms mutually exclusive?	Yes
Arm title	Combination (solifenacin + mirabegron)

Arm description:

Participants received solifenacin 5 mg, mirabegron 25 mg and solifenacin 10 mg matching placebo once daily for the first 4 weeks of double-blind period. For the last 8 weeks of the double-blind treatment period, the 25 mg mirabegron tablet was replaced by a 50 mg mirabegron tablet. Placebo was given for the 2 week single-blind safety follow-up period.

Arm type	Experimental

Investigational medicinal product name	solifenacin 5 mg
Investigational medicinal product code	YM905
Other name	Vesicare, Vesitrim, Vesikur, solifenacin succinate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Solifenacin was provided as the marketed formulation in the 5 mg strength. Medication was taken orally with a glass of water, with or without food.

Investigational medicinal product name	solifenacin 10 mg matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo of solifenacin succinate 10 mg tablets was supplied. Medication was taken orally with a glass of water, with or without food.

Investigational medicinal product name	mirabegron 25 mg
Investigational medicinal product code	YM178
Other name	Betanis, Betmiga, Myrbetriq
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Mirabegron was supplied as the marketed formulation in the 25 mg OCAS (Oral Controlled Absorption System) modified release tablets. Medication was taken orally with a glass of water, with or without food.

Investigational medicinal product name	mirabegron 50 mg
Investigational medicinal product code	YM178
Other name	Betanis, Betmiga, Myrbetriq
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Mirabegron was supplied as the marketed formulation in the 50 mg OCAS (Oral Controlled Absorption System) modified release tablets. Medication was taken orally with a glass of water, with or without food.

Arm title	Solifenacin 5 mg

Arm description:

Participants received solifenacin 5 mg, mirabegron 25 mg matching placebo and solifenacin 10 mg matching placebo once daily. For the last 8 weeks of the double-blind treatment period, the 25 mg mirabegron matching placebo tablet was replaced by a 50 mg mirabegron matching placebo tablet (to maintain the blind). Placebo was given for the 2 week single-blind safety follow-up period.

Arm type	Active comparator
Investigational medicinal product name	solifenacin 5 mg
Investigational medicinal product code	YM905
Other name	Vesicare, Vesitrim, Vesikur, solifenacin succinate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Solifenacin was provided as the marketed formulation in the 5 mg strength. Medication was taken orally with a glass of water, with or without food.

Investigational medicinal product name	solifenacin 10 mg matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo of solifenacin succinate 10 mg tablets was supplied. Medication was taken orally with a glass of water, with or without food.

Investigational medicinal product name	mirabegron 25 mg matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo of mirabegron OCAS 25 mg tablets was supplied. Medication was taken orally with a glass of water, with or without food.

Investigational medicinal product name	mirabegron 50 mg matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo of mirabegron OCAS 50 mg tablets was supplied. Medication was taken orally with a glass of water, with or without food.

Arm title	Solifenacin 10 mg

Arm description:

Participants received solifenacin 5 mg matching placebo, mirabegron 25 mg matching placebo and solifenacin 10 mg once daily. For the last 8 weeks of the double-blind treatment period, the 25 mg mirabegron matching placebo tablet was replaced by a 50 mg mirabegron matching placebo tablet (to maintain the blind). Placebo was given for the 2 week single-blind safety follow-up period.

Arm type	Active comparator
Investigational medicinal product name	solifenacin 5 mg matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo of solifenacin succinate 5 mg tablets was supplied. Medication was taken orally with a glass of water, with or without food.

Investigational medicinal product name	solifenacin 10 mg
Investigational medicinal product code	YM905
Other name	Vesicare, Vesitrim, Vesikur, solifenacin succinate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Solifenacin was provided as the marketed formulation in the 10 mg strength. Medication was taken orally with a glass of water, with or without food.

Investigational medicinal product name	mirabegron 25 mg matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo of mirabegron OCAS 25 mg tablets was supplied. Medication was taken orally with a glass of water, with or without food.

Investigational medicinal product name	mirabegron 50 mg matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Matching placebo of mirabegron OCAS 50 mg tablets was supplied. Medication was taken orally with a glass of water, with or without food.

Number of subjects in period 1	Combination (solifenacin + mirabegron)	Solifenacin 5 mg	Solifenacin 10 mg
Started	727	728	719
Treated with double-blind drug	725	728	719
Completed	678	679	680
Not completed	49	49	39
Randomized no double-blind drug received	1	-	1
Discontinued (no EoT page)	2	-	-
Other	-	2	-
Adverse event	13	11	13
Protocol Violation	2	2	-
Lost to follow-up	4	2	1
Lack of efficacy	1	3	2
Withdrawal by subject	26	29	22

Baseline characteristics

Reporting groups	
Reporting group title	Combination (solifenacin + mirabegron)
Reporting group description:	
Participants received solifenacin 5 mg, mirabegron 25 mg and solifenacin 10 mg matching placebo once daily for the first 4 weeks of double-blind period. For the last 8 weeks of the double-blind treatment period, the 25 mg mirabegron tablet was replaced by a 50 mg mirabegron tablet. Placebo was given for the 2 week single-blind safety follow-up period.	
Reporting group title	Solifenacin 5 mg
Reporting group description:	
Participants received solifenacin 5 mg, mirabegron 25 mg matching placebo and solifenacin 10 mg matching placebo once daily. For the last 8 weeks of the double-blind treatment period, the 25 mg mirabegron matching placebo tablet was replaced by a 50 mg mirabegron matching placebo tablet (to maintain the blind). Placebo was given for the 2 week single-blind safety follow-up period.	
Reporting group title	Solifenacin 10 mg
Reporting group description:	
Participants received solifenacin 5 mg matching placebo, mirabegron 25 mg matching placebo and solifenacin 10 mg once daily. For the last 8 weeks of the double-blind treatment period, the 25 mg mirabegron matching placebo tablet was replaced by a 50 mg mirabegron matching placebo tablet (to maintain the blind). Placebo was given for the 2 week single-blind safety follow-up period.	

Reporting group values	Combination (solifenacin + mirabegron)	Solifenacin 5 mg	Solifenacin 10 mg
Number of subjects	727	728	719
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	58.2	56.9	57.4
standard deviation	± 13.1	± 13.5	± 13.2
Gender categorical			
Units:			
Male	123	124	119
Female	604	604	600

Reporting group values	Total		
Number of subjects	2174		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units:			
Male	366		
Female	1808		

End points

End points reporting groups

Reporting group title	Combination (solifenacin + mirabegron)

Reporting group description:

Participants received solifenacin 5 mg, mirabegron 25 mg and solifenacin 10 mg matching placebo once daily for the first 4 weeks of double-blind period. For the last 8 weeks of the double-blind treatment period, the 25 mg mirabegron tablet was replaced by a 50 mg mirabegron tablet. Placebo was given for the 2 week single-blind safety follow-up period.

Reporting group title	Solifenacin 5 mg

Reporting group description:

Participants received solifenacin 5 mg, mirabegron 25 mg matching placebo and solifenacin 10 mg matching placebo once daily. For the last 8 weeks of the double-blind treatment period, the 25 mg mirabegron matching placebo tablet was replaced by a 50 mg mirabegron matching placebo tablet (to maintain the blind). Placebo was given for the 2 week single-blind safety follow-up period.

Reporting group title	Solifenacin 10 mg

Reporting group description:

Participants received solifenacin 5 mg matching placebo, mirabegron 25 mg matching placebo and solifenacin 10 mg once daily. For the last 8 weeks of the double-blind treatment period, the 25 mg mirabegron matching placebo tablet was replaced by a 50 mg mirabegron matching placebo tablet (to maintain the blind). Placebo was given for the 2 week single-blind safety follow-up period.

Primary: Change from Baseline to End of Treatment (EoT) in Mean Number of Incontinence Episodes Per 24 Hours During the 3-Day Diary Period

End point title	Change from Baseline to End of Treatment (EoT) in Mean Number of Incontinence Episodes Per 24 Hours During the 3-Day Diary Period

End point description:

The mean number of incontinence episodes (complaint of any involuntary leakage of urine) per day was derived from number of incontinence episodes recorded on valid diary days during the 3-day micturition diary period divided by the number of valid diary days during the 3-day micturition diary period. The analysis population consisted of the Full Analysis Set (FAS) which is comprised of all the Randomized Analysis Set's (RAS) participants who met the following criteria: took at least 1 dose of double-blind study drug after randomization, reported at least 1 micturition in the baseline diary & at least 1 micturition postbaseline & reported at least 1 incontinence episode in the baseline diary. For participants who withdrew before EoT (week 12) and have no measurement available for that diary period, the Last Observation Carried Forward (LOCF) value during the double-blind study period was used as EoT value to derive the primary variable. N=number of participants with available data.

End point type	Primary

End point timeframe:

Baseline and end of treatment (up to 12 weeks)

End point values	Combination (solifenacin + mirabegron)	Solifenacin 5 mg	Solifenacin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	706	704	697	
Units: incontinence episodes				
least squares mean (standard error)				
Adjusted Change from Baseline (FAS)	-1.8 (± 0.08)	-1.53 (± 0.08)	-1.67 (± 0.08)	

Statistical analyses

Statistical analysis title	Adjusted Difference Combination vs Solifenacin 5mg

Statistical analysis description:

Differences of adjusted means were calculated by subtracting adjusted mean of solifenacin monotherapy groups from adjusted mean of combination group based on ANCOVA model. Means (LS means) and 95% CIs are from an ANCOVA model with sex, age group (< 65, ≥ 65 years), geographic region, and 4-week incontinence episode reduction group as fixed factors and mean number of incontinence episodes per 24 hours at baseline as a covariate.

Comparison groups	Combination (solifenacin + mirabegron) v Solifenacin 5 mg
Number of subjects included in analysis	1410
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.001 [2]
Method	ANCOVA
Parameter estimate	Least Squares (LS) Means
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[1] - Primary analysis of the FAS.

[2] - P values for pairwise comparisons are from the stratified rank ANCOVA model. P < 0.05 indicates superiority in favor of treatment group with the largest improvement.

Secondary: Change from Baseline to EoT in Mean Number of Micturitions Per 24 Hours

End point title	Change from Baseline to EoT in Mean Number of Micturitions Per 24 Hours

End point description:

The average number of micturitions (urinations) per 24 hours was derived from number of micturitions recorded on valid diary days during the 3-day micturition diary period divided by the number of valid diary days during the 3-day micturition diary period (excluding incontinence only episodes). LOCF was used. The analysis population included the FAS. N=number of participants with available data.

End point type	Secondary

End point timeframe:

Baseline and end of treatment (up to 12 weeks)

End point values	Combination (solifenacin + mirabegron)	Solifenacin 5 mg	Solifenacin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	706	704	697	
Units: micturitions				
least squares mean (standard error)				
Adjusted Change from Baseline (FAS)	-1.59 (± 0.08)	-1.14 (± 0.08)	-1.12 (± 0.08)	

Statistical analyses

Statistical analysis title	Adjusted Difference Combination vs Solifenacin 5mg

Statistical analysis description:

Differences of adjusted means were calculated by subtracting adjusted mean of solifenacin monotherapy from adjusted mean of combination group. Adjusted change from baseline values as well as 95% CIs for pairwise comparisons and P values are from the ANCOVA model with sex, age group (< 65, ≥ 65 years), geographic region, and 4-week incontinence episode reduction group as fixed factors and mean number of micturitions per 24 hours at baseline as a covariate.

Comparison groups	Combination (solifenacin + mirabegron) v Solifenacin 5 mg
Number of subjects included in analysis	1410
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	ANCOVA
Parameter estimate	LS Means
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	-0.22
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[3] - Primary analysis of the FAS.

[4] - P<0.05 indicates superiority in favor of treatment group with largest improvement.

Secondary: Number of Incontinence Episodes Reported During the 3-Day Diary at EoT

End point title	Number of Incontinence Episodes Reported During the 3-Day Diary at EoT

End point description:

The number of incontinence episodes (complaint of any involuntary leakage of urine) per day was derived from total number of incontinence episodes on valid diary days recorded during the 3-day micturition diary period. The analysis population included the FAS. LOCF was used. N=number of participants with available data at EoT.

End point type	Secondary

End point timeframe:

End of treatment (up to 12 weeks)

End point values	Combination (solifenacin + mirabegron)	Solifenacin 5 mg	Solifenacin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	706	704	697	
Units: incontinence episodes				
least squares mean (standard error)				
EoT (FAS) (N = 706, 704, 697)	4.25 (± 0.29)	4.87 (± 0.28)	4.72 (± 0.31)	

Statistical analyses

Statistical analysis title	Rate Ratio (Combination vs 5 mg solifenacin)

Statistical analysis description:

Rate ratio, 95% CIs, & p-value for number of incontinence episodes during EoT 3-day diary between combination & solifenacin treatment was calculated from Mixed Effects Poisson (negative binomial) regression model including treatment group, sex, age group (<65, >=65 years), geographic region & 4-week incontinence episode reduction group as factors, log of (number of incontinence episodes/number of valid diary days) at baseline as covariate & log of number of valid diary days as offset variable.

Comparison groups	Combination (solifenacin + mirabegron) v Solifenacin 5 mg
Number of subjects included in analysis	1410
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.014 [6]
Method	Mixed Effects Poisson
Parameter estimate	LS Means
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	0.96
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

[5] - Primary analysis of the FAS. Statistical test of hypothesis analysis method was Mixed Effects Poisson (negative binomial) regression.

[6] - P<0.05 indicates superiority in favor of treatment group with lowest rate of incontinence episodes.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of double blind treatment until 30 days after last dose

Adverse event reporting additional description:

Population consisted of the SAF. An AE was defined as any untoward medical occurrence in a subject administered a study drug or who had undergone study procedures and did not necessarily have a causal relationship with this treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Combination

Reporting group description:

Participants received solifenacin 5 mg, mirabegron 25 mg and solifenacin 10 mg matching placebo once daily for the first 4 weeks of double-blind period. For the last 8 weeks of the double-blind treatment period, the 25 mg mirabegron tablet was replaced by a 50 mg mirabegron tablet. Placebo was given for the 2 week single-blind safety follow-up period.

Reporting group title	Solifenacin 5 mg

Reporting group description:

Participants received solifenacin 5 mg, mirabegron 25 mg matching placebo and solifenacin 10 mg matching placebo once daily. For the last 8 weeks of the double-blind treatment period, the 25 mg mirabegron matching placebo tablet was replaced by a 50 mg mirabegron matching placebo tablet (to maintain the blind). Placebo was given for the 2 week single-blind safety follow-up period.

Reporting group title	Solifenacin 10 mg

Reporting group description:

Participants received solifenacin 5 mg matching placebo, mirabegron 25 mg matching placebo and solifenacin 10 mg once daily. For the last 8 weeks of the double-blind treatment period, the 25 mg mirabegron matching placebo tablet was replaced by a 50 mg mirabegron matching placebo tablet (to maintain the blind). Placebo was given for the 2 week single-blind safety follow-up period.

Serious adverse events	Combination	Solifenacin 5 mg	Solifenacin 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 725 (1.79%)	10 / 728 (1.37%)	15 / 719 (2.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	0 / 725 (0.00%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal cancer			

subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 725 (0.00%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 725 (0.00%)	1 / 728 (0.14%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Joint resurfacing surgery			
subjects affected / exposed	0 / 725 (0.00%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin neoplasm excision			
subjects affected / exposed	0 / 725 (0.00%)	1 / 728 (0.14%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adhesion			
subjects affected / exposed	0 / 725 (0.00%)	1 / 728 (0.14%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervix haemorrhage uterine			
subjects affected / exposed	0 / 725 (0.00%)	1 / 728 (0.14%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory tract oedema			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriogram coronary normal			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthroscopy			
subjects affected / exposed	0 / 725 (0.00%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonoscopy			
subjects affected / exposed	0 / 725 (0.00%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 725 (0.00%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 725 (0.00%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 725 (0.00%)	1 / 728 (0.14%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 725 (0.00%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 725 (0.00%)	1 / 728 (0.14%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 725 (0.00%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 725 (0.00%)	1 / 728 (0.14%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 725 (0.00%)	1 / 728 (0.14%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic pain			

subjects affected / exposed	0 / 725 (0.00%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	0 / 725 (0.00%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 725 (0.00%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 725 (0.00%)	1 / 728 (0.14%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 725 (0.00%)	1 / 728 (0.14%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture pain			
subjects affected / exposed	0 / 725 (0.00%)	0 / 728 (0.00%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	1 / 725 (0.14%)	1 / 728 (0.14%)	1 / 719 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis herpes			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 725 (0.14%)	0 / 728 (0.00%)	0 / 719 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Combination	Solifenacin 5 mg	Solifenacin 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 725 (5.93%)	41 / 728 (5.63%)	68 / 719 (9.46%)
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	43 / 725 (5.93%)	41 / 728 (5.63%)	68 / 719 (9.46%)
occurrences (all)	44	44	70

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

One participant was randomized to the Combination arm, but actually received Solifenacin 10 mg. In terms of actual treatment received, the patient was allocated to the solifenacin 10 mg arm.

Notes: