Clinical trial results:
A Phase 3, Open-label, Baseline-controlled, Multicenter, Sequential Dose Titration Study to Assess the Long term Efficacy and Safety, and the Pharmacokinetics of Solifenacin Succinate Suspension in Patients from 5 to Less than 18 years of Age with Neurogenic Detrusor Overactivity (NDO)

Summary

EudraCT number	2011-000330-11
Trial protocol	BE GB NL DK DE FR HU
Global end of trial date	28 April 2016

Results information

Result version number	v1 (current)
This version publication date	10 November 2016
First version publication date	10 November 2016

Trial information

Trial identification

Sponsor protocol code	905-CL-047

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01565694
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe B.V.
Sponsor organisation address	Sylviusweg 62, BE Leiden, Netherlands, 2333
Public contact	Clinical Trial Disclosure, Astellas Pharma Europe B.V., Global Medical Science, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Europe B.V., Global Medical Science, astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000573-PIP02-13
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the long-term efficacy, safety and pharmacokinetics of solifenacin suspension after multiple dose administration.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP). Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Brazil: 7
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Philippines: 16
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 6
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	76
EEA total number of subjects	33

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)	42
Adolescents (12-17 years)	34
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study population consisted of male and female participants with neurogenic detrusor overactivity (NDO) aged 5 years to < 18 years old.

Pre-assignment

Screening details:

After screening and a 14-day washout period, participants were treated with sequential doses of solifenacin oral suspension for 12 weeks (titration period) to determine each participant's optimal dose, after which a fixed dose of solifenacin oral suspension was given for at least 40 weeks (fixed dose assessment period).

Period 1

Period 1 title	Dose-Titration Period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Solifenacin succinate

Arm description:

Participants aged 5 years to < 18 years, received solifenacin orally once a day, with sequential titrated doses for 12 weeks to identify optimal dose during the dose-titration period.

Arm type	Experimental
Investigational medicinal product name	Solifenacin succinate
Investigational medicinal product code	YM905
Other name	solifenacin, solifenacin succinate suspension
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

An initial dose of solifenacin (1 mg/mL) was administered orally once a day via syringe to adolescents (12 Years to < 18 Years) first as a PED5 (5 mg) for 12 weeks. Doses were calculated according to the weight measured at the baseline visit for that visit until and including week 12. The dose was titrated up or down to PED2.5, PED5, PED7.5 or PED10 (2.5 mg, 5 mg, 7.5 mg and 10 mg) according to the titration criteria for the first 12 weeks. The starting dose and titration steps for children (5 Years to < 12 Years) were confirmed after the DSMB reviewed the safety data from the first 10 adolescents who completed week 12 of treatment and the 12 week safety data from solifenacin studies in same aged OAB participants. Most of the participants' doses were up-titrated to PED7.5 or PED10 during the treatment period. The optimal dose for most participants in both age groups (children and adolescents) was PED10.

Number of subjects in period 1	Solifenacin succinate
Started	76
Completed	62
Not completed	14
Adverse event, non-fatal	4
Protocol deviation	10

Period 2

Period 2 title	Fixed-Dose Assessment Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Solifenacin succinate

Arm description:

The participants aged 5 years to < 18 years, who completed dose titration period entered the fixed-dose period and received a fixed dose of solifenacin once a day orally for 40 weeks or until the end of study visit (Week 52).

Arm type	Experimental
Investigational medicinal product name	Solifenacin succinate
Investigational medicinal product code	YM905
Other name	solifenacin, solifenacin succinate suspension
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

After confirming optimal dose in the titration period by Week 12 participants received fixed dose of solifenacin orally once a day for a minimum of 40 weeks or until the end of study visit (Week 52).

Number of subjects in period 2	Solifenacin succinate
Started	62
Completed	58
Not completed	4
Consent withdrawn by subject	4

Baseline characteristics

Reporting groups	
Reporting group title	Solifenacin succinate
Reporting group description:	
Participants aged 5 years to < 18 years, received solifenacin orally once a day, with sequential titrated doses for 12 weeks to identify optimal dose during the dose-titration period.	

Reporting group values	Solifenacin succinate	Total	
Number of subjects	76	76	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 10.8 ± 3.3	 -	
Gender categorical Units:			
Male Female	37 39	37 39	
Weight Units: kilogram (kg) arithmetic mean standard deviation	 38.1 ± 15.5	 -	
Duration of NDO Disease Units: Years median full range (min-max)	 8.24 0.4 to 16.2	 -	

End points

End points reporting groups

Reporting group title	Solifenacin succinate

Reporting group description:

Participants aged 5 years to < 18 years, received solifenacin orally once a day, with sequential titrated doses for 12 weeks to identify optimal dose during the dose-titration period.

Reporting group title	Solifenacin succinate

Reporting group description:

The participants aged 5 years to < 18 years, who completed dose titration period entered the fixed-dose period and received a fixed dose of solifenacin once a day orally for 40 weeks or until the end of study visit (Week 52).

Primary: Change from Baseline to Week 24 in Maximum Cystometric Capacity (MCC)

End point title	Change from Baseline to Week 24 in Maximum Cystometric Capacity (MCC)[1]

End point description:

During urodynamic assessments, the bladder was filled until voiding/leakage begins, or until it was stopped because either the participant experiences pain or discomfort or 135% of expected bladder capacity for age has been reached. MCC is the maximum bladder capacity reached during filling cystometry before either leakage or pain/discomfort was observed. Full Analysis Set (FAS) was used for the endpoint analysis, and it consisted of all participants who took at least one dose of study drug and provided both valid baseline and at least one post-baseline value for the primary efficacy endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 24

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to system limitation it is not possible to report statistical analysis for one arm studies.

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: mL				
arithmetic mean (standard deviation)	57.2 (± 107.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Last Possible Titration Step in Maximum Cystometric Capacity

End point title	Change From Baseline to Last Possible Titration Step in Maximum Cystometric Capacity

End point description:

During urodynamic assessments, the bladder was filled until voiding/leakage begins, or until it was stopped because either the participant experiences pain or discomfort or 135% of expected bladder capacity for age has been reached. MCC is the maximum bladder capacity reached during filling

cystometry before either leakage or pain/discomfort was observed. Based on study requirements, the last possible titration step was Week 9 for participants enrolled under versions 1.0 and 1.1 and Week 12 under later versions. Full Analysis Set (FAS) was used for the endpoint analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 9 or Week 12

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: mL				
arithmetic mean (standard deviation)	57.4 (± 105.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bladder Compliance

End point title	Change from Baseline in Bladder Compliance

End point description:

Bladder compliance was calculated by using urodynamic assessments and dividing the volume change by the change in detrusor pressure during the change in the bladder volume. Full Analysis Set (FAS) was used for the endpoint analysis. Change from baseline to week 24 with and without last observation carried forward (LOCF) imputation are reported. "N" indicates the number of participants included in each analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: mL/cmH2O				
arithmetic mean (standard deviation)				
Change from Baseline Week 24 [N=50]	9.1 (± 28.6)			
Change from Baseline Week 24 LOCF [N=53]	8.8 (± 27.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bladder Volume (mL) Until First Detrusor Contraction > 15 cmH2O as a Percentage of Expected Bladder Capacity

End point title	Change from Baseline in Bladder Volume (mL) Until First Detrusor Contraction > 15 cmH2O as a Percentage of Expected Bladder Capacity

End point description:

Change from baseline in the bladder volume was calculated using urodyanamic assessments. During urodynamic assessments, the bladder is filled until voiding/leakage begins, or until it is stopped because either the subject experiences pain or discomfort or 135% of expected bladder capacity for age has been reached. If no detrusor contraction of at least 15 cmH2O occurs, the bladder volume was imputed with MCC. Full Analysis Set (FAS) set was used for the endpoint analysis. Change from baseline to week 24 with and without last observation carried forward (LOCF) imputation are reported. "N" indicates the number of participants included in each analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: mL				
arithmetic mean (standard deviation)				
Change from Baseline Week 24 [N=50]	30.1 (± 39.8)			
Change from Baseline Week 24 LOCF [N=31]	16.3 (± 36.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bladder Volume at 30 and 40 cmH2O Detrusor Pressure

End point title	Change from Baseline in Bladder Volume at 30 and 40 cmH2O Detrusor Pressure

End point description:

Bladder volumes at 30 cm H2O and 40 cm H2O detrusor pressure were calculated using urodynamic assessments. During urodynamic assessments, the bladder is filled until voiding/leakage begins, or until it is stopped because either the subject experiences pain or discomfort or 135% of expected bladder capacity for age has been reached. Full Analysis Set (FAS) was used for the endpoint analysis. Change from baseline to week 24 with and without last observation carried forward (LOCF) imputation are reported. "N" indicates the number of participants included in each analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: mL				
arithmetic mean (standard deviation)				
Change from Baseline Week 24 (30 cmH20)[N=17]	61.8 (± 80.6)			
Change from Baseline Week 24 LOCF (30 cmH20)[N=21]	71.9 (± 88.3)			
Change from Baseline Week 24 (40 cmH20)[N=10]	67 (± 44.3)			
Change from Baseline Week 24 LOCF (40 cmH20)[N=12]	54.4 (± 52.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Number of Overactive Detrusor Contractions (> 15 cmH2O) Until End of Bladder Filling

End point title	Change from Baseline in Number of Overactive Detrusor Contractions (> 15 cmH2O) Until End of Bladder Filling

End point description:

Change from baseline in number of overactive detrusor contractions until end of bladder filling was measured by urodynamic testing. If leakage occurred, the "Detrusor pressure at leakage" was recorded otherwise the volume of fluid instilled into the bladder was recorded. Full Analysis Set (FAS) set was used for the endpoint analysis. Change from baseline to week 24 with and without last observation carried forward (LOCF) imputation are reported. "N" indicates the number of participants included in each analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Detrusor Contractions				
arithmetic mean (standard deviation)				
Change from Baseline Week 24 [N=50]	-2.3 (± 5.1)			
Change from Baseline Week 24 (LOCF) [N=54]	-1.8 (± 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Detrusor Pressure at the End of Bladder Filling

End point title	Change from Baseline in Detrusor Pressure at the End of Bladder Filling

End point description:

The bladder was filled until voiding/leakage began or until it was stopped because either the participant experiences pain or discomfort or 135% of expected bladder capacity for age has been reached. Pressure was recorded for an extra 5 minutes after leakage began or the end of bladder-filling, whichever is sooner. Full Analysis Set (FAS) set was used for the endpoint analysis. Change from baseline to week 24 with and without last observation carried forward (LOCF) imputation are reported. "N" indicates the number of participants included in each analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: cmH2O				
arithmetic mean (standard deviation)				
Change from Baseline Week 24 [N=46]	-9.2 (± 33.6)			
Change from Baseline Week 24 (LOCF) [N=51]	-8.2 (± 32.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Average Catheterized Volume per Catheterization

End point title	Change from Baseline in Average Catheterized Volume per Catheterization

End point description:

The average catheterized volume per catheterization was calculated using all available (non-zero) catheterized volumes recorded over both of the 2 measuring days in the diary, whether or not these 2 days are concurrent. Full Analysis Set (FAS) set was used for the endpoint analysis. Change from baseline to week 24 with and without last observation carried forward (LOCF) imputation are reported. "N" indicates the number of participants included in each analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: mL				
arithmetic mean (standard deviation)				
Change from Baseline Week 24 [N=51]	46.2 (± 48.3)			
Change from Baseline Week 24 (LOCF) [N=54]	48.8 (± 50.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Maximum Catheterized Volume

End point title	Change from Baseline in Maximum Catheterized Volume

End point description:

The maximum catheterized volume per day was calculated using all available (non-zero) catheterized volumes recorded for the 2 measuring days in the diary, whether or not these 2 days were concurrent. The maximum value was calculated separately for each measuring day and the mean of these two values was used. Full Analysis Set (FAS) set was used for the endpoint analysis. Change from baseline to week 24 with and without last observation carried forward (LOCF) imputation are reported. "N" indicates the number of participants included in each analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: mL				
arithmetic mean (standard deviation)				
Change from Baseline Week 24 [N=51]	67.4 (± 88.07)			
Change from Baseline Week 24 (LOCF) [N=54]	69.6 (± 88.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Average First Morning Catheterized Volume

End point title	Change from Baseline in Average First Morning Catheterized Volume

End point description:

The average first morning catheterized volume was calculated as the average of the available first morning catheterized volumes recorded for the 2 measuring days in the diary, whether or not these 2

days are concurrent. Full Analysis Set (FAS) set was used for the endpoint analysis. Change from baseline to week 24 with and without last observation carried forward (LOCF) imputation are reported. "N" indicates the number of participants included in each analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: mL				
arithmetic mean (standard deviation)				
Change from Baseline Week 24[N=51]	43.2 (± 72.7)			
Change from Baseline Week 24 (LOCF) [N=54]	44.2 (± 73.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours

End point title	Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours

End point description:

The mean of the number of incontinence episodes per 24h was calculated as the mean over the valid diary days in the 7-day diary. Full Analysis Set (FAS) set was used for the endpoint analysis. Change from baseline to week 24 with and without last observation carried forward (LOCF) imputation are reported. "N" indicates the number of participants included in each analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Incontinence Episodes				
arithmetic mean (standard deviation)				
Change from Baseline Week 24 [N=51]	-1.6 (± 2)			
Change from Baseline Week 24 (LOCF) [N=54]	-1.6 (± 2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Number of Dry (Incontinence-free) Days per 7 Days

End point title	Change from Baseline in Number of Dry (Incontinence-free) Days per 7 Days

End point description:

Full Analysis Set (FAS) set was used for the endpoint analysis. Change from baseline to week 24 with and without last observation carried forward (LOCF) imputation are reported. "N" indicates the number of participants included in each analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Days				
arithmetic mean (standard deviation)				
Change from Baseline Week 24 [N=51]	1 (± 2.8)			
Change from Baseline Week 24 (LOCF) [N=54]	1.1 (± 2.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Number of Dry (Incontinence-free) Nights per 7 Days

End point title	Change from Baseline in Number of Dry (Incontinence-free) Nights per 7 Days

End point description:

Full Analysis Set (FAS) set was used for the endpoint analysis. Change from baseline to week 24 with and without last observation carried forward (LOCF) imputation are reported. "N" indicates the number of participants included in each analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Nights				
arithmetic mean (standard deviation)				
Change from Baseline Week 24 [N=51]	1.6 (± 3)			
Change from Baseline Week 24 (LOCF) [N=54]	1.6 (± 3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of Life [QoL] (PinQ Questionnaire Score)

End point title	Change from Baseline in Quality of Life [QoL] (PinQ Questionnaire Score)

End point description:

Pediatric Incontinence Questionnaire (PinQ) is a 20-item questionnaire addressing quality of life for participants with bladder disorders. Each question is answered on a scale from 0 (no, never) to 4 (all the time). The total score ranges from 0 to 80, where higher scores indicate more impact on quality of life. Full Analysis Set (FAS) set was used for the endpoint analysis. Change from baseline to week 24 with and without last observation carried forward (LOCF) imputation are reported. "N" indicates the number of participants included in each analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Change from Baseline Week 24 [N=53]	-0.7 (± 8.3)			
Change from Baseline Week 24 (LOCF) [N=51]	-0.7 (± 8.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

A treatment-emergent adverse event (TEAE) was defined as an adverse event observed after starting

administration of the first dose of study medication on Day 1. All adverse events collected within 7 days after taking the last dose of study drug were also counted as a TEAE.

End point type	Secondary

End point timeframe:

Baseline to End of Study Visit (Week 52)

End point values	Solifenacin succinate			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Participants				
TEAEs	51			
Drug related TEAE	15			
Deaths	0			
Serious TEAEs	7			
Drug related Serious TEAEs	0			
TEAEs Leading to Discontinuation	2			
Drug related TEAEs Leading to Discontinuation	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to the last dose of study drug (up to 54 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Solifenacin succinate

Reporting group description:

Participants aged 5 years to < 18 years, received solifenacin once daily, with sequential titrated doses for 12 weeks to identify optimal dose during the Dose-titration period after which they received fixed dose of solifenacin for 40 weeks until the end of study.

Serious adverse events	Solifenacin succinate		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 76 (9.21%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Spinal cord operation			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Tethered cord syndrome			

subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Megacolon			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Dengue Fever			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orchitis			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection bacterial			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Solifenacin succinate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 76 (55.26%)		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 76 (3.95%)		
occurrences (all)	5		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Renal and urinary disorders			
Bladder pain			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	3 / 76 (3.95%)		
occurrences (all)	5		
Escherichia urinary tract infection			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	7		
Nasopharyngitis			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	6		
Urinary tract infection			
subjects affected / exposed	12 / 76 (15.79%)		
occurrences (all)	12		
Urinary tract infection bacterial			

subjects affected / exposed	14 / 76 (18.42%)		
occurrences (all)	17		
Urinary tract infection pseudomonal			
subjects affected / exposed	3 / 76 (3.95%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2012	Amendment 1 ●Text on the selection of study population was updated to facilitate understanding. ●Participants were allowed to enter the study on a CIC regimen of between 4 and 6 times per day instead of a fixed regimen of 4 CICs per day, which permitted greater flexibility and a regimen tailored to individual patient need. ●The requirement for all participants to be on bowel management program was re-evaluated and amended. Participants with normal bowel function did not require active management to participate in the study. ●Participants with vesicoureteral reflux grade 3 or higher excluded to avoid bias (additional volume in the ureters when determining cystometric bladder capacity) and were at increased risk of renal damage from urodynamic assessments. Due to an error in the original protocol the highest category of vesicoureteral reflux - grade 5 was omitted from this exclusion criteria. ●The exclusion criteria were updated with a threshold value which used the QT interval corrected for heart rate (QTc) by Bazett's formula (QTcB) – the most widely used and best understood measure in pediatric cardiology practice. The discontinuation criteria and criteria for repeating an electrocardiogram (ECG) were also updated to reflect the use of the Bazett's formula for QTc. ●Exclusion criterion 19 was deleted. Participants with severe hepatic impairment were to be excluded on basis of exclusion criteria 15, 18 and 20. ●New exclusion criterion was added to confirm that participants were to be excluded when they failed to meet urodynamic inclusion criteria. This was an additional precaution added at the request of the PDCO to ensure the inclusion of participants that required management with antimuscarinic therapy. ●New exclusion criterion was added. Participants with glaucoma were to be excluded from the study because solifenacin was contraindicated in adults with narrow angle glaucoma. While childhood glaucoma is extremely rare, this exclusion criterion

30 September 2013	Amendment 2 ●Planned study period was extended to address the slower than anticipated enrollment. The last patient last visit date was extended from 4Q2014 to 3Q2015. ●Evaluations of whether recruitment in the younger-aged group could begin were updated to include OAB safety data profile for age-matched groups. These data were included as the safety and tolerability of solifenacin oral suspension was expected to be similar in participants with NDO and OAB and because participants in the OAB studies (905-CL-076 and 905-CL-077) had a corresponding age range to this study. ●Collection of pharmacokinetic blood sampling was changed and could be performed at 1 visit, or could be spread over 2 visits at visit 7, 8 and/or 9. If the final dose titration occurred at visit 7, pharmacokinetic sampling was not undertaken until visit 8 or later. This change allowed sampling to be spread over 2 visits to reduce patient's burden on any single visit day. ●The option to complete study visits 4 and 6 by telephone was included to reduce the burden of travel and waiting time in the clinic. ●Calculation of baseline mean QTcB was revised for the eligibility check and discontinuation criterion to use the average of the QTcB mean from the visit 2 (or visit 1, if visits 1 and 2 were combined) and visit 3 ECG triplicates instead of using the QTcB mean from visit 3 only. This revision allowed for a more precise estimate of QTcB to account for the intra-patient variation in baseline QTcB between visit 2 and visit 3. ●A statement about the evaluation of the mean QTcB was added to allow site staff to understand that the discontinuation criteria were related to the mean QTcB from 2 triplicate measurements not 1. ●The urodynamic assessment from visit 6 was moved to visit 7 to permit visit 6 to be completed by telephone and to reduce the number of study/clinic visits. ●Dose-titration permission changed to 4 occasions rather than 3 so that a new dose could be taken the day after visit 7
29 January 2015	Amendment 3 ●A typographical error in the pharmacokinetics section was corrected to ensure consistency in the pharmacokinetic sampling schedule. ●Urinalysis assessment was added for visit 10 and the relevant sections updated to ensure clarity and consistency throughout the protocol. ●Concomitant medication text was corrected in the relevant sections for consistency and to provide better clarity. ●ECG measurement intervals were clarified to allow more flexibility in taking the ECG in triplicate without affecting the safety of the patient. ●National Cancer Institute-Common Terminology Criteria for AEs grading was removed as it was not applicable to this study. ●SAEs contact was corrected and (S)AE reporting requirements were refined to provide better guidance as per latest regulations. ●A urodynamic measurement was added at visit 3 and the measurement at visit 6 moved to visit 7 to align with the latest protocol design. ●Other minor text adjustments were done.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported