Clinical trial results:
An Open-label, Long-term Extension, Multicenter, Sequential Dose Titration Study to Assess Safety and Efficacy of Solifenacin Succinate Suspension in Pediatric Subjects with Overactive Bladder

Summary

EudraCT number	2011-002047-10
Trial protocol	GB BE NL DE DK SE NO FR
Global end of trial date	08 October 2014

Results information

Result version number	v1
This version publication date	22 February 2016
First version publication date	22 April 2015

Trial information

Trial identification

Sponsor protocol code	905-CL-077

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01655069
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000573-PIP01-09
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	08 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 October 2014
Global end of trial reached?	Yes
Global end of trial date	08 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of solifenacin oral suspension once daily in children and adolescents with overactive bladder (OAB).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH 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 and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 October 2012
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	Norway: 4
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Belgium: 34
Country: Number of subjects enrolled	Denmark: 20
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Philippines: 2
Country: Number of subjects enrolled	Serbia: 16
Country: Number of subjects enrolled	South Africa: 5
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Ukraine: 3
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Korea, Republic of: 7

Worldwide total number of subjects	148
EEA total number of subjects	89

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)	119
Adolescents (12-17 years)	29
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants recruited for this study were children (5 to less than 12 years old) and adolescents (12 to less than 18 years old) with overactive bladder (OAB), who completed the 2-week placebo run-in period and 12-week treatment period of Study 905-CL-076.

Pre-assignment

Screening details:

Children and adolescents with OAB, who completed study 905-CL-076, consented to enter this study and fulfilled all the inclusion/exclusion criteria were enrolled at Week 12/13 (2-3 days after last dose was received during the 905-CL-076 study). The age of participant at informed consent signing in 905-CL-076 determined the age group in this study.

Period 1

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

Blinding implementation details:

All participants in this extension study received open-label solifenacin. However, the treatment which they received (solifenacin or placebo) in Study 905-CL-076 has been reflected to provide clarity on the baseline status of the participants.

Arms

Are arms mutually exclusive?	Yes
Arm title	Children treated with placebo in 905-CL-076

Arm description:

Male and female children aged 5 to less than 12 years old who received placebo in Study 905-CL-076 and received open-label solifenacin once daily for 40 weeks in this 905-CL-077 study

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

Dosage and administration details:

Children were given solifenacin liquid suspension once a day orally via syringe along with the completion of a 7-day diary prior to study visit (start of 905-CL-076 to end of 905-CL-077, 14 visits). The initial dose started with the equivalent of 5 mg in adults (referred to as PED5) except for participants who finished Study 905-CL-076 with PED2.5 (active or placebo), who could start at this dose for this study. Doses were calculated per weight determined at the first visit of this study, targeting to have equivalent doses of 2.5, 5, 7.5 and 10 mg doses of solifenacin once daily in adults (referred to as PED2.5, PED5, PED7.5 and PED10). There was a titration period of up to 12 weeks during which the participants would be up or down-titrated based on a combination of efficacy and safety parameters followed by a fixed dose period during which no dose adjustments were allowed.

Arm title	Children treated with solifenacin in 905-CL-076

Arm description:

Male and female children aged 5 to less than 12 years old who received solifenacin in Study 905-CL-076 and received open-label solifenacin once daily for 40 weeks in this 905-CL-077 study

Arm type	Experimental

Investigational medicinal product name	Solifenacin succinate suspension
Investigational medicinal product code	YM905
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Children were given solifenacin liquid suspension once a day orally via syringe along with the completion of a 7-day diary prior to study visit (start of 905-CL-076 to end of 905-CL-077, 14 visits). The initial dose started with the equivalent of 5 mg in adults (referred to as PED5) except for participants who finished Study 905-CL-076 with PED2.5 (active or placebo), who could start at this dose for this study. Doses were calculated per weight determined at the first visit of this study, targeting to have equivalent doses of 2.5, 5, 7.5 and 10 mg doses of solifenacin once daily in adults (referred to as PED2.5, PED5, PED7.5 and PED10). There was a titration period of up to 12 weeks during which the participants would be up or down-titrated based on a combination of efficacy and safety parameters followed by a fixed dose period during which no dose adjustments were allowed.

Arm title	Adolescents treated with placebo in 905-CL-076

Arm description:

Male and female adolescents aged 12 to less than 18 years old who received placebo in Study 905-CL-076 and received open-label solifenacin once daily for 40 weeks in this 905-CL-077 study

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

Dosage and administration details:

Adolescents were given solifenacin liquid suspension once a day orally via syringe along with the completion of a 7-day diary prior to study visit (start of 905-CL-076 to end of 905-CL-077, 14 visits). The initial dose started with the equivalent of 5 mg in adults (referred to as PED5) except for participants who finished Study 905-CL-076 with PED2.5 (active or placebo), who could start at this dose for this study. Doses were calculated per weight determined at the first visit of this study, targeting to have equivalent doses of 2.5, 5, 7.5 and 10 mg doses of solifenacin once daily in adults (referred to as PED2.5, PED5, PED7.5 and PED10). There was a titration period of up to 12 weeks during which the participants would be up or down-titrated based on a combination of efficacy and safety parameters followed by a fixed dose period during which no dose adjustments were allowed.

Arm title	Adolescents treated with solifenacin in 905-CL-076

Arm description:

Male and female adolescents aged 12 to less than 18 years old who received solifenacin in Study 905-CL-076 and received open-label solifenacin once daily for 40 weeks in this 905-CL-077 study

Arm type	Experimental
Investigational medicinal product name	Solifenacin succinate suspension
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Dosage and administration details:

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Number of subjects in period 1	Children treated with placebo in 905-CL-076	Children treated with solifenacin in 905-CL-076	Adolescents treated with placebo in 905-CL-076
Started	61	58	14
Dispensed study medication	61	58	14
Safety Analysis Set (SAF)	61	57	14
Full Analysis Set (FAS)	60	57	14
Completed	53	46	12
Not completed	8	12	2
Consent withdrawn by subject	2	3	-
Physician decision	-	-	-
No treatment needed	-	1	-
Adverse event	6	7	2
Lack of efficacy	-	1	-

Number of subjects in period 1	Adolescents treated with solifenacin in 905-CL-076
Started	15
Dispensed study medication	15
Safety Analysis Set (SAF)	15
Full Analysis Set (FAS)	15
Completed	11
Not completed	4
Consent withdrawn by subject	-
Physician decision	1
No treatment needed	-
Adverse event	3
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Children treated with placebo in 905-CL-076
Reporting group description:	
Male and female children aged 5 to less than 12 years old who received placebo in Study 905-CL-076 and received open-label solifenacin once daily for 40 weeks in this 905-CL-077 study	
Reporting group title	Children treated with solifenacin in 905-CL-076
Reporting group description:	
Male and female children aged 5 to less than 12 years old who received solifenacin in Study 905-CL-076 and received open-label solifenacin once daily for 40 weeks in this 905-CL-077 study	
Reporting group title	Adolescents treated with placebo in 905-CL-076
Reporting group description:	
Male and female adolescents aged 12 to less than 18 years old who received placebo in Study 905-CL-076 and received open-label solifenacin once daily for 40 weeks in this 905-CL-077 study	
Reporting group title	Adolescents treated with solifenacin in 905-CL-076
Reporting group description:	
Male and female adolescents aged 12 to less than 18 years old who received solifenacin in Study 905-CL-076 and received open-label solifenacin once daily for 40 weeks in this 905-CL-077 study	

Reporting group values	Children treated with placebo in 905-CL-076	Children treated with solifenacin in 905-CL-076	Adolescents treated with placebo in 905-CL-076
Number of subjects	61	58	14
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	7.2	7.5	13.9
standard deviation	± 1.6	± 1.5	± 1.6
Gender categorical			
Units: Subjects			
Female	27	34	13
Male	34	23	1
Not recorded	0	1	0

Reporting group values	Adolescents treated with solifenacin in 905-CL-076	Total	
Number of subjects	15	148	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	14.5		
standard deviation	± 1.8	-	
Gender categorical			
Units: Subjects			
Female	11	85	
Male	4	62	

Not recorded	0	1	

End points

End points reporting groups

Reporting group title	Children treated with placebo in 905-CL-076

Reporting group description:

Male and female children aged 5 to less than 12 years old who received placebo in Study 905-CL-076 and received open-label solifenacin once daily for 40 weeks in this 905-CL-077 study

Reporting group title	Children treated with solifenacin in 905-CL-076

Reporting group description:

Male and female children aged 5 to less than 12 years old who received solifenacin in Study 905-CL-076 and received open-label solifenacin once daily for 40 weeks in this 905-CL-077 study

Reporting group title	Adolescents treated with placebo in 905-CL-076

Reporting group description:

Male and female adolescents aged 12 to less than 18 years old who received placebo in Study 905-CL-076 and received open-label solifenacin once daily for 40 weeks in this 905-CL-077 study

Reporting group title	Adolescents treated with solifenacin in 905-CL-076

Reporting group description:

Male and female adolescents aged 12 to less than 18 years old who received solifenacin in Study 905-CL-076 and received open-label solifenacin once daily for 40 weeks in this 905-CL-077 study

Subject analysis set title	Children (aged 5 to less than 12 years) - FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The analysis population is the Full Analysis Set (FAS), which consisted of participants who received at least one dose of open-label solifenacin, had a valid baseline value (from 905-CL-076) and a valid post-baseline value from diary data completed after the first dose of open-label solifenacin (in 905-CL-077). Two children were not included in the FAS due to visits not performed within the protocol visit windows.

Subject analysis set title	Adolescents (aged 12 to less than 18 years) - FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The analysis population is the FAS, which consisted of participants who received at least one dose of open-label solifenacin, had a valid baseline value (from 905-CL-076) and a valid post-baseline value from diary data completed after the first dose of open-label solifenacin (in 905-CL-077).

Subject analysis set title	Children (aged 5 to less than 12 years old) - SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

The analysis population is the Safety Analysis Set (SAF), which consisted of participants who received at least one dose of open-label solifenacin and had any safety data reported after the first dose of open-label solifenacin. One child was not included in the SAF due to visits not performed within the protocol visit windows.

Subject analysis set title	Adolescents (aged 12 to less than 18 years) - SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

The analysis population is the SAF, which consisted of participants who received at least one dose of open-label solifenacin and had any safety data reported after the first dose of open-label solifenacin.

Primary: Number of participants with and severity of treatment-emergent adverse events (TEAEs)

End point title	Number of participants with and severity of treatment-emergent adverse events (TEAEs)[1]

End point description:

A treatment-emergent adverse event (TEAE) was defined as an AE that occurred after the first dose of study drug and within 7 days after last dose of study drug. The investigator measured the severity of AEs, including abnormal clinical laboratory values, as follows: Mild: No disruption of normal daily activities; Moderate: Affect normal daily activities; Severe: Inability to perform daily activities. To determine if an AE is an TEAE with respect to solifenacin: (1) For participants who received placebo in 905-CL-076, a TEAE was defined as any AE that started or worsened after the first dose of open-label

solifenacin in 905-CL-077 and up to 7 days after the last dose of open-label solifenacin; (2) For subjects who received solifenacin in 905-CL-076, a TEAE is defined as any AE that started or worsened after the first dose of double-blind solifenacin in 905-CL-076 and up to 7 days after the last dose of open-label solifenacin.
The analysis population is the Safety Analysis Set (SAF).

End point type	Primary

End point timeframe:

From first dose of study drug (in Study 905-CL-076) up to 7 days after last dose of open-label study drug (52 weeks)

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: As this was simply an open-label, long-term safety study, there were no statistical analyses performed for the primary safety endpoint. However, statistical analyses were performed for the secondary efficacy endpoints, which used a repeated measures model to provide adjusted means per study period (window) and data is seen in the summary results. There were no comparisons and no p-values that resulted from these analyses.

End point values	Children (aged 5 to less than 12 years old) - SAF	Adolescents (aged 12 to less than 18 years) - SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118	29		
Units: participants				
TEAE - Mild	72	10		
TEAE - Moderate	20	8		
TEAE - Severe	1	2		
Total	93	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of Study 905-CL-076 to end of this study in mean number of incontinence episodes per 24 hours

End point title	Change from baseline of Study 905-CL-076 to end of this study in mean number of incontinence episodes per 24 hours

End point description:

The mean number of incontinence episodes is based on a 7-day diary data completed by a participant prior to a visit from start of 905-CL-076 to end of 905-CL-077. An incontinence episode is defined as an episode with any involuntary loss of urine. Analysis used is a repeated measures ANCOVA (analysis of covariance) considering the change in the total number of incontinence episodes from the baseline mean value. The model includes duration of double-blind and/or open-label solifenacin treatment, gender, geographic region and randomized treatment group in Study 905-CL-076 as fixed effects, baseline as a covariate and "duration" repeated within subject. The analysis population is the Full Analysis Set (FAS) which consisted of participants received at least one dose of open-label solifenacin, and for at least one of the efficacy variables in this study had both a valid baseline value and valid post-baseline from diary data completed after first dose of open-label solifencacin.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Children (aged 5 to less than 12 years) - FAS	Adolescents (aged 12 to less than 18 years) - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	11		
Units: incontinence episodes				
least squares mean (standard error)	-1.93 (± 0.13)	-2 (± 0.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of Study 905-CL-076 to end of this study in number of dry (incontinence-free) days per 7 days

End point title	Change from baseline of Study 905-CL-076 to end of this study in number of dry (incontinence-free) days per 7 days

End point description:

The number of dry (incontinence-free) days data is based on a 7-day diary data completed by a participant prior to a visit from start of 905-CL-076 to end of 905-CL-077. An incontinence-free day is a day without any incontinence episodes. Analysis used is a repeated measures ANCOVA (analysis of covariance) considering the change in the total number of dry days from the baseline mean value. The model includes duration of double-blind and/or open-label solifenacin treatment, gender, geographic region and randomized treatment group in Study 905-CL-076 as fixed effects, baseline as a covariate and "duration" repeated within subject. The analysis population is FAS.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Children (aged 5 to less than 12 years) - FAS	Adolescents (aged 12 to less than 18 years) - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	11		
Units: days				
least squares mean (standard error)	2.84 (± 0.33)	3.93 (± 0.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of Study 905-CL-076 to end of this study in mean number of micturitions per 24 hours

End point title	Change from baseline of Study 905-CL-076 to end of this study in mean number of micturitions per 24 hours

End point description:

The mean number of micturitions (urinations) data is based on a 7-day diary data completed by a

participant prior to a visit from start of 905-CL-076 to end of 905-CL-077. Analysis used is a repeated measures ANCOVA (analysis of covariance) considering the change in the total number of urgency episodes from the baseline mean value. The model includes duration of double-blind and/or open-label solifenacin treatment, gender, geographic region and randomized treatment group in Study 905-CL-076 as fixed effects, baseline as a covariate and "duration" repeated within subject. The analysis population is FAS.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Children (aged 5 to less than 12 years) - FAS	Adolescents (aged 12 to less than 18 years) - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	11		
Units: micturitions				
least squares mean (standard error)	-1.83 (± 0.2)	-1.79 (± 0.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of Study 905-CL-076 to end of this study in mean number of grade 3 or 4 urgency episodes per 24 hours in adolescents

End point title	Change from baseline of Study 905-CL-076 to end of this study in mean number of grade 3 or 4 urgency episodes per 24 hours in adolescents

End point description:

Adolescent participants were also asked to record urgencies for at least 2 of the 7 days using the Perception of Intensity of Urgency Scale (PPIUS): (0 - no urgency, 1 - mild urgency, 2 - moderate urgency, 3 - severe urgency, 4 - urge incontinence). This data is based on a 7-day diary data completed by a participant prior to a visit from start of 905-CL-076 to end of 905-CL-077. Analysis used is a repeated measures ANCOVA (analysis of covariance) considering the change in the total number of urgency episodes from the baseline mean value. The model includes duration of double-blind and/or open-label solifenacin treatment, gender, geographic region and randomized treatment group in Study 905-CL-076 as fixed effects, baseline as a covariate and "duration" repeated within subject. The analysis population is FAS.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Adolescents (aged 12 to less than 18 years) - FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: urgency episodes				
least squares mean (standard error)	-2.2 (± 0.65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety as assessed by laboratory tests, vital signs, 12-lead electrocardiograms (ECGs)

End point title	Safety as assessed by laboratory tests, vital signs, 12-lead electrocardiograms (ECGs)

End point description:

Safety is monitored by collecting AEs, which include abnormal laboratory tests, vital signs or ECG data that were defined as an AE if the abnormality induced clinical signs or symptoms, required active intervention, interruption or discontinuation of study medication or was clinically significant in the investigator's opinion. A treatment-emergent adverse event (TEAE) was defined as an AE that occurred after the first dose of study drug and within 7 days after last dose of study drug.
The analysis population is the SAF.

End point type	Secondary

End point timeframe:

From first dose of study drug (in Study 905-CL-076) up to 7 days after last dose of open-label study drug (52 weeks)

End point values	Children (aged 5 to less than 12 years old) - SAF	Adolescents (aged 12 to less than 18 years) - SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118	29		
Units: participants				
Any TEAE	93	20		
Drug-related TEAEs	41	11		
Deaths	0	0		
Serious TEAEs	1	1		
Drug-related serious TEAEs	0	0		
TEAEs leading to discontinuation	12	5		
Drug-related TEAE leading to permanent discontinue	12	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in postvoid residual (PVR) volume

End point title	Change from baseline in postvoid residual (PVR) volume

End point description:

PVR volume was assessed by ultrasonography or bladder scan.The analysis population is the SAF.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Children (aged 5 to less than 12 years old) - SAF	Adolescents (aged 12 to less than 18 years) - SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118	29		
Units: mL				
arithmetic mean (standard deviation)	1.3 (± 11.9)	0.7 (± 8.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug (in Study 905-CL-076) up to 7 days after last dose of open-label study drug (52 weeks)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Children (aged 5 to less than 12 years)
Reporting group description: -	
Reporting group title	Adolescents (aged 12 to less than 18 years)

Reporting group description: -

Serious adverse events	Children (aged 5 to less than 12 years)	Adolescents (aged 12 to less than 18 years)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 118 (0.85%)	1 / 29 (3.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Children (aged 5 to less than 12 years)	Adolescents (aged 12 to less than 18 years)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 118 (78.81%)	20 / 29 (68.97%)	

Investigations Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	 10 / 118 (8.47%) 10	 4 / 29 (13.79%) 4	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 16 / 118 (13.56%) 21	 1 / 29 (3.45%) 1	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 9 / 118 (7.63%) 11	 0 / 29 (0.00%) 0	
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	 1 / 118 (0.85%) 1	 2 / 29 (6.90%) 2	
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 7 / 118 (5.93%) 10 16 / 118 (13.56%) 19 7 / 118 (5.93%) 7 3 / 118 (2.54%) 3 3 / 118 (2.54%) 4	 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1 2 / 29 (6.90%) 3 2 / 29 (6.90%) 2 3 / 29 (10.34%) 3	
Infections and infestations Escherichia urinary tract infection subjects affected / exposed occurrences (all) Gastroenteritis	 7 / 118 (5.93%) 9	 2 / 29 (6.90%) 4	

subjects affected / exposed	11 / 118 (9.32%)	2 / 29 (6.90%)	
occurrences (all)	11	2	
Nasopharyngitis			
subjects affected / exposed	16 / 118 (13.56%)	4 / 29 (13.79%)	
occurrences (all)	21	4	
Urinary tract infection			
subjects affected / exposed	6 / 118 (5.08%)	2 / 29 (6.90%)	
occurrences (all)	8	2	
Influenza			
subjects affected / exposed	4 / 118 (3.39%)	3 / 29 (10.34%)	
occurrences (all)	4	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2012	Several changes to dose, risk-benefit assessment and other statistical analyses were made to align the current protocol with the updated opinion of the Paediatric Committee (PDCO) of the EMA (published as: opinion of the PDCO on the acceptance of a modification of an agreed PIP (EMEA-000573-PIP01-09-M01). Other changes were: increase in number of sites, inclusion criterion 3 was updated to reflect differences in national legislation with regard to informed consent (IC) for adolescents in clinical studies, inclusion criterion 4 was updated to provide more clarity on who should be subject to birth control, the discontinuation criterion relating to the QT interval was updated to reflect the use of QT interval corrected for heart rate by Bazett formula (QTcB), acute urinary retention (AUR) was defined as "urinary retention for which an intervention is required or has taken place" to provide clarification to investigators, it was added that no important identified risks for solifenacin had been captured in a pediatric population to date, a requirement for leucocyturia, defined as white blood cell (WBC) count > 100/mcL as a prior step to urine culture was added, Tri- and tetracyclic antidepressants were added to the list of restricted medication, the recording of the urgency grade in adolescents according to the PPIUS was reduced from 7 days per diary period to 2 days, the requirement of a sitting position of the patient for these assessments and the use of the same arm for every blood pressure measurement was specified to further standardize the measurement, instructions were changed to repeat the PVR volume assessment only once when the initial PVR volume was > 20 mL, specifications (comparison to age-appropriate norms) were added to aid data interpretation and ensure consistency in the assessment and evaluation of vital signs, laboratory results and height and weight, the SAE reporting instruction was slightly rephrased to provide better guidance to investigators.
19 July 2012	After finalization and first regulatory submissions of Substantial Amendment 1 dated 20 Apr 2012 (Protocol version 2.0), inconsistencies were identified in the changes made to the respective paragraphs across the protocol (e.g., changes made only in the synopsis part of the protocol, but not in the body text of the protocol). These were corrected in Protocol version 2.1, including Substantial Amendment 1 dated 20 Apr 2012.
07 September 2012	Germany country-specific amendment: A local substantial Amendment 1 dated 7 Sep 2012 was issued. This amendment corresponds to the global substantial Amendment 2 dated 30 Oct 2012. In addition, the pharmacokinetic samples scheduled to be taken in Study 905-CL-076 were instead to be taken in this unblinded extension Study 905-CL-077. No patients were enrolled at the study sites in Germany.
24 September 2012	The Netherlands country-specific amendment: A local substantial Amendment 1 dated 24 Sep 2012 was issued. This amendment corresponds to the global substantial Amendment 2 dated 30 Oct 2012. No patients were enrolled at the study sites in the Netherlands before this amendment was implemented.
17 October 2012	UK country-specific amendment: A local substantial Amendment 1 dated 17 Oct 2012 was issued. This amendment corresponds to the global substantial Amendment 2 dated 30 Oct 2012. No patients were enrolled at the study sites in the UK before this amendment was implemented.

30 October 2012	This global amendment was prepared and submitted after approval of the country specific amendments. The sections "Study Design","Dose Rationale", "Discontinuation Criteria for Individual Subjects", "Dose/Dose Regimen and Administration Period", and "Increase or Reduction in Dose of the Study Drugs" were updated to reflect the inclusion of the possibility to down titrate to "no treatment" (i.e., interruption of treatment) for a period of 3 weeks and the subsequent possibility to discontinue the study in case no symptoms of OAB occur in this period. This amendment was developed to limit unnecessary exposure to solifenacin in patients who did no longer require treatment with OAB medication. The objective was to identify patients who did not require treatment with OAB medication.
23 September 2013	Several changes were made to align current protocol with the updated opinion of the PDCO of the EMA regarding solifenacin (published as: opinion of the Paediatric Committee on the acceptance of a modification of an agreed PIP [EMEA-000573-PIP01-09-M04]). Other changes were: the number of patients was changed from at least 120 patients (at least 60 children and 60 adolescents) to at least 120 patients (at least 100 children and at least 20 adolescents) evaluable for the primary endpoint, an additional inclusion criterion was added "Subject agrees not to participate in another interventional study while on treatment", as well as the main analyses of safety and efficacy, which were performed separately in both children and adolescent cohorts, further statistical methods were described that used the data from the patients in this study together with data from adults in the solifenacin phase 3 program, to interpolate between children and adults, and provide estimates of treatment effects in adolescents based on an extensive data set, in assessing the PVR volume, the instruction that the bladder was to be emptied when it was initially filled > 50% of the bladder capacity for age was changed such that the bladder should only be emptied when it was initially filled with preferably > 50% of the bladder capacity for age, the calculation of the baseline QTcB mean was revised to use the average of the QTcB means of the ECG triplicates from the 2 prerandomization visits (i.e., visits 2 and 3) of Study 905-CL-076 instead of using the QTcB mean from visit 3 ECG triplicates only, the definition of SAE was reworded for clarification and the events of interest that may require expedited reporting and/or safety evaluation were defined and categorized.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported