Clinical trial results:
An Open-Label, Long-Term Extension, Multi-center, Sequential Dose Titration Study to Assess Safety and Efficacy of Solifenacin Succinate Suspension in Pediatric Subjects with Overactive Bladder (OAB)

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	v2 (current)
This version publication date	24 February 2018
First version publication date	22 April 2015
Version creation reason	

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 Europe B.V., Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Europe B.V., 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?	No

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:

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 fed ral, national 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 eligibility 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 in this study. The mean time on study drug in this study was 247.9 days in children.

Arm type	Experimental
Investigational medicinal product name	Solifenacin succinate suspension
Investigational medicinal product code	YM905
Other name	solifenacin succinate
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 in this study. The mean time on study drug in this study was 247.9 days in children.

Arm type	Experimental

Investigational medicinal product name	Solifenacin succinate suspension
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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 in this study. The mean time on study drug in this study was 240.1 days in adolescents.

Arm type	Experimental
Investigational medicinal product name	Solifenacin succinate suspension
Investigational medicinal product code	YM905
Other name	solifenacin succinate
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 in this study. The mean time on study drug in this study was 240.1 days in adolescents.

Arm type	Experimental
Investigational medicinal product name	Solifenacin succinate suspension
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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.

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
Safety Analysis Set (SAF)	61	57	14
Full Analysis Set (FAS)	60	57	14
Completed	53	46	12
Not completed	8	12	2
Lack of Efficacy	-	1	-
No Treatment Needed	-	1	-
Adverse Event	6	7	2
Physician Decision	-	-	-
Withdrawal by Subject	2	3	-

Number of subjects in period 1	Adolescents Treated With Solifenacin in 905-CL-076
Started	15
Safety Analysis Set (SAF)	15
Full Analysis Set (FAS)	15
Completed	11
Not completed	4
Lack of Efficacy	-
No Treatment Needed	-
Adverse Event	3
Physician Decision	1
Withdrawal by Subject	-

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 in this study. The mean time on study drug in this study was 247.9 days in children.	
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 in this study. The mean time on study drug in this study was 247.9 days in children.	
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 in this study. The mean time on study drug in this study was 240.1 days in adolescents.	
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 in this study. The mean time on study drug in this study was 240.1 days in adolescents.	

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			
The analysis population is Safety Analysis Set (SAF), which consisted of all participants who received at least 1 dose of open-label solifenacin and had any safety data reported after the first dose of open-label solifenacin. The baseline values measured for study 905-CL-076 were used as the baseline values for the present study.			
Units: years			
arithmetic mean	7.2	7.5	13.9
standard deviation	± 1.6	± 1.5	± 1.6
Gender categorical Units:			
Male	34	23	1
Female	27	34	13
Not recorded	0	1	0
Ethnicity Units: Subjects			
Hispanic or Latino	7	7	2
Not Hispanic or Latino	54	50	12
Unknown or Not Reported	0	1	0
Race Units: Subjects			
American Indian or Alaska Native	3	3	1
Asian	4	5	1

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	1
White	49	47	11
More than one race	0	0	0
Other	3	0	0
Unknown or Not Reported	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			
The analysis population is Safety Analysis Set (SAF), which consisted of all participants who received at least 1 dose of open-label solifenacin and had any safety data reported after the first dose of open-label solifenacin. The baseline values measured for study 905-CL-076 were used as the baseline values for the present study.			
Units: years			
arithmetic mean	14.5		
standard deviation	± 1.8	-	
Gender categorical Units:			
Male	4	62	
Female	11	85	
Not recorded	0	1	
Ethnicity Units: Subjects			
Hispanic or Latino	1	17	
Not Hispanic or Latino	14	130	
Unknown or Not Reported	0	1	
Race Units: Subjects			
American Indian or Alaska Native	0	7	
Asian	1	11	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	2	7	
White	12	119	
More than one race	0	0	
Other	0	3	
Unknown or Not Reported	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 in this study. The mean time on study drug in this study was 247.9 days in children.

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 in this study. The mean time on study drug in this study was 247.9 days in children.

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 in this study. The mean time on study drug in this study was 240.1 days in adolescents.

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 in this study. The mean time on study drug in this study was 240.1 days in adolescents.

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

Subject analysis set description:

Children aged 5 to less than 12 years old with OAB who received placebo or solifenacin in 905-CL-076, received a weight-based dose of open-label solifenacin oral suspension once daily for 40 weeks in this study. At the start of the 12-week titration period, the dose was adjusted according to the weight of the participant in order to deliver a plasma drug exposure equivalent to the 2.5 mg, 5 mg, 7.5 mg and 10 mg once daily oral tablet dose of solifenacin in adults. The full analysis set (FAS) consisted of participants who received at least one dose of open-label solifenacin and for at least 1 efficacy variable had a valid baseline value (from 905-CL-076 study) and a valid postbaseline value from diary data completed after the first dose of open-label solifenacin (in 905-CL-077 study).

Subject analysis set title	Adolescents (Aged 12 to Less Than 18 Years) - FAS
Subject analysis set type	Full analysis

Subject analysis set description:

Adolescents aged 12 to less than 18 years old with OAB who received placebo or solifenacin in 905-CL-076, received a weight-based dose of open-label solifenacin oral suspension once daily for 40 weeks in this study. At the start of the 12-week titration period, the dose was adjusted according to the weight of the participant in order to deliver a plasma drug exposure equivalent to the 2.5 mg, 5 mg, 7.5 mg and 10 mg once daily oral tablet dose of solifenacin in adults. This group is part of the FAS.

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

Subject analysis set description:

Children aged 5 to less than 12 years old with OAB who received placebo or solifenacin in 905-CL-076, received a weight-based dose of open-label solifenacin oral suspension once daily for 40 weeks in this study. At the start of the 12-week titration period, the dose was adjusted according to the weight of the participant in order to deliver a plasma drug exposure equivalent to the 2.5 mg, 5 mg, 7.5 mg and 10 mg once daily oral tablet dose of solifenacin in adults. The safety analysis set (SAF) consisted of all participants who received at least 1 dose of open-label solifenacin and had any safety data reported after the first dose of open-label solifenacin.

Subject analysis set title	Adolescents (Aged 12 to Less Than 18 Years) - SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Adolescents aged 12 to less than 18 years old with OAB who received placebo or solifenacin in 905-CL-076, received a weight-based dose of open-label solifenacin oral suspension once daily for 40 weeks in this study. At the start of the 12-week titration period, the dose was adjusted according to the weight of

the participant in order to deliver a plasma drug exposure equivalent to the 2.5 mg, 5 mg, 7.5 mg and 10 mg once daily oral tablet dose of solifenacin in adults. This group is part of the SAF.

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:

The investigator assessed the severity of AEs, including abnormal clinical laboratory values, electrocardiogram (ECG), vital signs, as follows: (1) Mild: No disruption of normal daily activities; (2) Moderate: Affect normal daily activities; (3) Severe: Inability to perform daily activities. In participants treated with placebo in Study 905-CL-076, a TEAE was defined as an AE that started/worsened after the first dose of open-label solifenacin in Study 905-CL-077 up to 7 days after the last dose of solifenacin. In participants treated with solifenacin in Study 905-CL-076, a TEAE was defined as an AE that started/worsened after the first dose of double-blind solifenacin in Study 905-CL-076 up to 7 days after last dose of open-label solifenacin in Study 905-CL-077. The analysis population was the SAF. Participants who received placebo and participants who received solifenacin in Study 905-CL-076 are combined for analyses of efficacy and safety in this study.

End point type	Primary

End point timeframe:

From first dose of solifenacin (in Study 905-CL-076 or in current study) up to 7 days after last dose of open-label solifenacin (41 weeks for participants who received placebo in 076 and 53 weeks for those who received solifenacin in 076)

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				
number (not applicable)				
TEAE - Mild	72	10		
TEAE - Moderate	20	8		
TEAE - Severe	1	2		
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 TEAEs leading to permanent discont.	12	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 number of incontinence episodes was based on 7-day diary data completed by participants prior to each visit from the start of 905-CL-076 to the end of 905-CL-077. An Incontinence episode is defined as an episode with any involuntary loss of urine. Data are reported by duration of solifenacin treatment based on the number of days from the date of first dose of solifenacin in either study 905-CL-076 or 905-CL-077 up to and including the study visit. Using equivalent treatment duration periods, data were combined for participants who received placebo and solifenacin in study 905-CL-076 within each age group. The analysis population was the FAS. N indicates the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline (of 905-CL-076 study) and after 3, 6, 9, 12, 24, 40, and 52 weeks of solifenacin treatment

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	117	29		
Units: Incontinence episodes				
arithmetic mean (standard error)				
3 weeks solifenacin treatment [N=114, 28]	-0.92 (± 0.18)	-1.05 (± 0.34)		
6 weeks solifenacin treatment [N=116, 26]	-1.11 (± 0.17)	-1.40 (± 0.33)		
9 weeks solifenacin treatment [N=115, 29]	-1.28 (± 0.19)	-1.48 (± 0.38)		
12 weeks solifenacin treatment [N=111, 29]	-1.39 (± 0.20)	-1.66 (± 0.39)		
24 weeks solifenacin treatment [N=108, 27]	-1.61 (± 0.19)	-1.73 (± 0.39)		
40 weeks solifenacin treatment [N=97, 23]	-1.66 (± 0.23)	-1.49 (± 0.36)		
52 weeks solifenacin treatment [N=44, 11]	-1.56 (± 0.22)	-1.34 (± 0.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours – Repeated Measures ANCOVA

End point title	Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours – Repeated Measures ANCOVA

End point description:

Repeated measures ANCOVA (analysis of covariance) was used in this analysis, which included double-blind and/or open-label solifenacin treatment duration, gender, geographic region and randomized treatment group in Study 905-CL-076 as fixed effects, baseline as a covariate and "duration" repeated within participant. The analysis population was the FAS. N indicates the number of participants with

available data at each time point.

End point type	Secondary

End point timeframe:

Baseline (of 905-CL-076 study) and after 3, 6, 9, 12, 24, 40, and 52 weeks of solifenacin treatment

End point values	Children (aged 5 to less than 12 years) - FAS	Children (aged 5 to less than 12 years old) - SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	29		
Units: Incontinence episodes				
least squares mean (standard error)				
3 weeks solifenacin treatment [N=114, 28]	-0.95 (± 0.12)	-0.93 (± 0.35)		
6 weeks solifenacin treatment [N=116, 26]	-1.11 (± 0.12)	-1.38 (± 0.36)		
9 weeks solifenacin treatment [N=115, 29]	-1.26 (± 0.13)	-1.40 (± 0.35)		
12 weeks solifenacin treatment [N=111, 29]	-1.39 (± 0.12)	-1.58 (± 0.35)		
24 weeks solifenacin treatment [N=108, 27]	-1.54 (± 0.11)	-1.80 (± 0.35)		
40 weeks solifenacin treatment [N=97, 23]	-1.56 (± 0.13)	-1.57 (± 0.36)		
52 weeks solifenacin treatment [N=44, 11]	-1.93 (± 0.13)	-2.00 (± 0.42)		

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:

The number of dry (incontinence-free) days was based on 7-day diary data completed by participants prior to each visit from start of 905-C L-076 to end of 905-C L-077. An incontinence-free day is a day without any incontinence episodes. Data are reported by duration of solifenacin treatment based on the number of days from the date of first dose of solifenacin in either study 905-CL-076 or 905-CL-077 up to and including the study visit. Using equivalent treatment duration periods, data were combined for participants who received placebo and solifenacin in study 905-CL-076 within each age group. The analysis population was the FAS. N indicates the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline (of 905-CL-076 study) and after 3, 6, 9, 12, 24, 40, and 52 weeks of solifenacin treatment

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	117	29		
Units: days				
arithmetic mean (standard error)				
3 weeks solifenacin treatment [N=114, 28]	1.17 (± 0.16)	1.69 (± 0.53)		
6 weeks solifenacin treatment [N=116, 26]	1.28 (± 0.19)	2.21 (± 0.56)		
9 weeks solifenacin treatment [N=115, 29]	1.59 (± 0.21)	1.94 (± 0.50)		
12 weeks solifenacin treatment [N=111, 29]	1.60 (± 0.21)	2.89 (± 0.51)		
24 weeks solifenacin treatment [N=108, 27	2.09 (± 0.22)	3.19 (± 0.51)		
40 weeks solifenacin treatment [N=97, 23]	2.15 (± 0.25)	2.71 (± 0.59)		
52 weeks solifenacin treatment [N=44, 11]	2.57 (± 0.40)	3.27 (± 0.73)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Repeated measures ANCOVA (analysis of covariance) was used in this analysis, which included double-blind and/or open-label solifenacin treatment duration, gender, geographic region and randomized treatment group in Study 905-CL-076 as fixed effects, baseline as a covariate and "duration" repeated within participant. The analysis population was the FAS. N indicates the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline (of 905-CL-076 study) and after 3, 6, 9, 12, 24, 40, and 52 weeks of solifenacin treatment

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	117	29		
Units: days				
least squares mean (standard error)				
3 weeks solifenacin treatment [N=114, 28]	1.35 (± 0.19)	1.53 (± 0.69)		
6 weeks solifenacin treatment [N=116, 26]	1.43 (± 0.20)	1.90 (± 0.70)		

9 weeks solifenacin treatment [N=115, 29]	1.72 (± 0.22)	1.75 (± 0.69)		
12 weeks solifenacin treatment [N=111, 29]	1.80 (± 0.22)	2.69 (± 0.69)		
24 weeks solifenacin treatment [N=108, 27]	2.21 (± 0.23)	3.07 (± 0.69)		
40 weeks solifenacin treatment [N=97, 23]	2.28 (± 0.25)	2.45 (± 0.71)		
52 weeks solifenacin treatment [N=44, 11]	2.84 (± 0.33)	3.93 (± 0.81)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The mean number of micturitions (urinations) was based on 7-day diary data completed by participants prior to each visit from start of 905-CL-076 to end of 905-CL-077. Data are reported by duration of solifenacin treatment based on the number of days from the date of first dose of solifenacin in either study 905-CL-076 or 905-CL-077 up to and including the study visit. Using equivalent treatment duration periods, data were combined for participants who received placebo and solifenacin in study 905-CL-076 within each age group. The analysis population was the FAS. N indicates the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline (of 905-CL-076 study) and after 3, 6, 9, 12, 24, 40, and 52 weeks of solifenacin treatment

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	117	29		
Units: Micturitions				
arithmetic mean (standard error)				
3 weeks solifenacin treatment [N=114, 28]	-0.78 (± 0.18)	-1.29 (± 0.39)		
6 weeks solifenacin treatment [N=116, 26]	-0.96 (± 0.20)	-1.38 (± 0.63)		
9 weeks solifenacin treatment [N=115, 29]	-1.15 (± 0.20)	-1.15 (± 0.61)		
12 weeks solifenacin treatment [N=111, 29]	-1.09 (± 0.21)	-1.24 (± 0.49)		
24 weeks solifenacin treatment [N=108, 27]	-1.42 (± 0.21)	-1.01 (± 0.49)		
40 weeks solifenacin treatment [N=97, 23]	-1.43 (± 0.24)	-1.39 (± 0.75)		
52 weeks solifenacin treatment [N=44, 11]	-1.80 (± 0.43)	-0.81 (± 0.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Number of Micturitions per 24 Hours – Repeated Measures ANCOVA

End point title	Change from Baseline in Mean Number of Micturitions per 24 Hours – Repeated Measures ANCOVA

End point description:

Repeated measures ANCOVA (analysis of covariance) was used in this analysis, which included double-blind and/or open-label solifenacin treatment duration, gender, geographic region and randomized treatment group in Study 905-CL-076 as fixed effects, baseline as a covariate and "duration" repeated within participant. The analysis population was the FAS. N indicates the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline (of 905-CL-076 study) and after 3, 6, 9, 12, 24, 40, and 52 weeks of solifenacin treatment

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	117	29		
Units: Micturitions				
least squares mean (standard error)				
3 weeks solifenacin treatment [N=114, 28]	-0.98 (± 0.15)	-0.93 (± 0.39)		
6 weeks solifenacin treatment [N=116, 26]	-1.15 (± 0.15)	-0.94 (± 0.26)		
9 weeks solifenacin treatment [N=115, 29]	-1.31 (± 0.15)	-0.81 (± 0.31)		
12 weeks solifenacin treatment [N=111, 29]	-1.22 (± 0.15)	-0.91 (± 0.30)		
24 weeks solifenacin treatment [N=108, 27]	-1.50 (± 0.15)	-0.71 (± 0.52)		
40 weeks solifenacin treatment [N=97, 23]	-1.52 (± 0.16)	-1.18 (± 0.36)		
52 weeks solifenacin treatment [N=44, 11]	-1.83 (± 0.20)	-1.79 (± 0.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Number of Grade 3 or 4 Urgency Episodes per 24 Hours in Adolescents

End point title	Change from Baseline 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 diary 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 7-day diary data completed by participants prior to each visit from the start of 905-CL-076 to the end of 905-CL-077. Data are reported by duration of solifenacin treatment based on the number of days from the date of first dose of solifenacin in either study 905-CL-076 or 905-CL-077 up to and including the study visit. Using equivalent treatment duration periods, data were combined for participants who received placebo and solifenacin in study 905-CL-076 within each age group. The analysis population was the FAS. N indicates the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline (of 905-CL-076 study) and after 3, 6, 9, 12, 24, 40, and 52 weeks of solifenacin treatment

End point values	Adolescents (Aged 12 to Less Than 18 Years) - FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Urgency episodes				
arithmetic mean (standard error)				
3 weeks solifenacin treatment [N=27]	-0.79 (± 0.26)			
6 weeks solifenacin treatment [N=25]	-1.36 (± 0.53)			
9 weeks solifenacin treatment [N=27]	-1.15 (± 0.54)			
12 weeks solifenacin treatment [N=28]	-1.31 (± 0.38)			
24 weeks solifenacin treatment [N=26]	-1.11 (± 0.47)			
40 weeks solifenacin treatment [N=22]	-2.18 (± 0.81)			
52 weeks solifenacin treatment [N=10]	-1.87 (± 0.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Number of Grade 3 or 4 Urgency Episodes per 24 Hours in Adolescents – Repeated Measures ANCOVA

End point title	Change from Baseline in Mean Number of Grade 3 or 4 Urgency Episodes per 24 Hours in Adolescents – Repeated Measures ANCOVA

End point description:

Repeated measures ANCOVA (analysis of covariance) was used in this analysis, which included double-blind and/or open-label solifenacin treatment duration, gender, geographic region and randomized treatment group in Study 905-CL-076 as fixed effects, baseline as a covariate and "duration" repeated within participant. The analysis population was the FAS. N indicates the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline (of 905-CL-076 study) and after 3, 6, 9, 12, 24, 40, and 52 weeks of solifenacin treatment

End point values	Adolescents (Aged 12 to Less Than 18 Years) - FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: Urgency episodes				
least squares mean (standard error)				
3 weeks solifenacin treatment [N=27]	-0.74 (± 0.46)			
6 weeks solifenacin treatment [N=25]	-1.30 (± 0.47)			
9 weeks solifenacin treatment [N=27]	-1.14 (± 0.47)			
12 weeks solifenacin treatment [N=28]	-1.28 (± 0.46)			
24 weeks solifenacin treatment [N=26]	-1.04 (± 0.46)			
40 weeks solifenacin treatment [N=22]	-1.96 (± 0.49)			
52 weeks solifenacin treatment [N=10]	-2.20 (± 0.65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Final Visit in Postvoid Residual (PVR) Volume

End point title	Change from Baseline to Final Visit in Postvoid Residual (PVR) Volume

End point description:

PVR volume was assessed by ultrasonography or bladder scan during 905-CL-076 and 905-CL-077. The value reported is the last PVR volume value after first dose of solifenacin up to 52 weeks.

End point type	Secondary

End point timeframe:

Baseline (of 905-CL-076 study) to final visit (the most recent value after first dose of solifenacin up to 40 weeks for participants who received placebo in 076 and 52 weeks for those who received solifenacin in 076)

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 error)	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 solifenacin (in Study 905-CL-076 or in current study) up to 7 days after last dose of open-label solifenacin (41 weeks for participants who received placebo in 076 and 53 weeks for those who received solifenacin in 076).

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:

Children aged 5 to less than 12 years old with OAB who received placebo or solifenacin in 905-CL-076, received a weight-based dose of open-label solifenacin oral suspension once daily for 40 weeks in this study. At the start of the 12-week titration period, the dose was adjusted according to the weight of the participant in order to deliver a plasma drug exposure equivalent to the 2.5 mg, 5 mg, 7.5 mg and 10 mg once daily oral tablet dose of solifenacin in adults.

Reporting group title	Adolescents (Aged 12 to Less Than 18 Years)

Reporting group description:

Adolescents aged 12 to less than 18 years old with OAB who received placebo or solifenacin in 905-CL-076, received a weight-based dose of open-label solifenacin oral suspension once daily for 40 weeks in this study. At the start of the 12-week titration period, the dose was adjusted according to the weight of the participant in order to deliver a plasma drug exposure equivalent to the 2.5 mg, 5 mg, 7.5 mg and 10 mg once daily oral tablet dose of solifenacin in adults.

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			
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%)	29 / 29 (100.00%)	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	10 / 118 (8.47%)	4 / 29 (13.79%)	
occurrences (all)	10	4	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 118 (13.56%)	1 / 29 (3.45%)	
occurrences (all)	21	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 118 (7.63%)	0 / 29 (0.00%)	
occurrences (all)	11	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 118 (0.85%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	7 / 118 (5.93%)	1 / 29 (3.45%)	
occurrences (all)	10	1	
Constipation			
subjects affected / exposed	16 / 118 (13.56%)	1 / 29 (3.45%)	
occurrences (all)	19	1	
Diarrhoea			
subjects affected / exposed	7 / 118 (5.93%)	2 / 29 (6.90%)	
occurrences (all)	7	3	
Abdominal pain			
subjects affected / exposed	3 / 118 (2.54%)	2 / 29 (6.90%)	
occurrences (all)	3	2	
Nausea			

subjects affected / exposed	3 / 118 (2.54%)	3 / 29 (10.34%)	
occurrences (all)	4	3	
Infections and infestations			
Escherichia urinary tract infection			
subjects affected / exposed	7 / 118 (5.93%)	2 / 29 (6.90%)	
occurrences (all)	9	4	
Gastroenteritis			
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