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Long-Term Safety and Efficacy of Solifenacin in Children and Adolescents with Overactive Bladder

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ABSTRACT

Purpose: To evaluate long-term safety and efficacy of once-daily oral solifenacin suspension in children (aged 5–<12 years) and adolescents (aged 12–<18 years) with overactive bladder.

Materials and Methods: 40-week, open-label extension of a 12-week double-blind, placebo-controlled trial. Outcome measures: incidence and severity of adverse events (primary endpoint), laboratory variables, vital signs, 12-lead electrocardiogram, post-void residual volume, change from baseline to end of treatment in: mean number of micturitions and incontinence episodes/24 hours, number of incontinence-free days/7 days, number of grade 3 or 4 urgency episodes/24 hours (adolescents only).

Results: Patients enrolled: 119 children, 29 adolescents. Incidence of drug-related treatment-emergent adverse events: 34.7% (children), 37.9% (adolescents), the most common of which were: children, constipation (11.9%), electrocardiogram QT prolonged (8.5%), dry mouth (4.2%); adolescents, electrocardiogram QT prolonged (13.8%), nausea (6.9%). Adverse events resulted in 10.2% (children) and 13.8% (adolescents) discontinuing treatment. No cases of urinary retention or increase in post-void residual volume, and no clinically relevant changes in laboratory variables or vital signs. Two cases of dizziness but no other CNS drug-related treatment-emergent adverse events reported. Improvements in all efficacy parameters and grade 3 or 4 urgencies observed by 3 weeks were improved and/or maintained during the study.

Conclusions: Once-daily solifenacin oral suspension was well tolerated for up to 52 weeks in children aged 5–<12 years and adolescents aged 12–<18 years diagnosed with overactive bladder, with constipation and electrocardiogram QT prolonged the most common adverse reactions, respectively. Improvements in efficacy at 3 weeks were sustained over the study.

This study is registered at ClinicalTrials.gov NCT01655069

INTRODUCTION

Overactive bladder (OAB), which is often accompanied by urinary incontinence, is a bothersome condition in the pediatric population. Daytime urinary incontinence may affect up to 16.9% of children[1] and can result in psychological comorbidities.[2] First-line management is urotherapy, with adjunctive antimuscarinic therapy recommended for those who do not respond,[3] but treatment options are limited (oxybutynin is the only approved therapy in many countries for pediatric patients with OAB; trospium is approved for those aged ≥12 years and propiverine for children aged ≥5 years in Germany, the Czech Republic and Slovakia). Side effects frequently result in early treatment discontinuation.[4,5] Nevertheless, few prospective, blinded, controlled clinical trials have evaluated antimuscarinics in the pediatric population with OAB[6-8] and long-term trials are scarce.[9-12] There is a need for dedicated studies in pediatric patients that evaluate new, effective and well-tolerated OAB therapies with convenient, flexible dosing.

The competitive muscarinic receptor antagonist solifenacin succinate (VESIcare®, Astellas Pharma Europe, B.V., The Netherlands), available in daily doses of 5 mg and 10 mg tablets, is approved for the treatment of urinary frequency, urinary incontinence or urgency associated with OAB in adults. In a 12-week clinical trial (the LION study), once-daily oral solifenacin suspension demonstrated superiority over placebo in change from baseline to end of treatment (EoT) in the primary endpoint of mean volume voided (MVV)/micturition in children aged 5–<12 years diagnosed with OAB and was well tolerated, with low incidences of dry mouth and constipation.[13]

We tested the hypothesis that safety and efficacy of once-daily oral solifenacin suspension in patients with OAB aged 5–<18 years would be maintained over a longer term.

MATERIALS AND METHODS

Study Design

This 40-week, phase III, open-label, safety trial of once-daily solifenacin in children aged 5–<12 years and adolescents aged 12–<18 years (the LEOPARD study) was an extension of a 12-week, double-blind, randomized, placebo-controlled, solifenacin dose-titration study with concomitant urotherapy.[13] The end-of-study visit in the 12-week trial (visit 8) coincided with the first visit of the extension study (figure 1).

The study was conducted from October 2012 to October 2014 in 16 countries worldwide. Children and adolescents who completed the 12-week study were entered into the trial if they satisfied the inclusion/exclusion criteria (table 1). Solifenacin was titrated to optimal dose as for the 12-week study (appendix A1); patients continued urotherapy at the discretion of the study site. To identify those who did not require further antimuscarinic treatment, patients who demonstrated a complete treatment response during the titration phase were down-titrated to no treatment for 3 weeks. Individuals who exhibited a sustained response were withdrawn from the study. Further discontinuation criteria are provided in table 1. Patients who were withdrawn from the study due to an ongoing adverse event (AE) were followed up until the condition stabilized or was no longer clinically significant.

Methodology for the 12-week study has been published previously and is described briefly in appendix A1.[13]

Safety Endpoints

Safety parameters were recorded at each visit. The primary endpoint was the incidence and severity of AEs. Secondary safety variables included measurements of clinical laboratory

variables (hematology, biochemistry and urinalysis), vital signs (systolic and diastolic blood pressure, pulse rate and body temperature), 12-lead electrocardiogram (ECG) and post-void residual (PVR) volume. Treatment-emergent adverse events (TEAEs) reported as related to solifenacin treatment by the study investigator were considered to be drug-related. In addition, all TEAEs were evaluated by the sponsor for a potential relationship with solifenacin.

Efficacy Endpoints

Efficacy variables were change from baseline to end of treatment (EoT) in: mean number of micturitions and incontinence episodes/24 hours, number of incontinence-free days/7 days, and number of grade 3 or 4 urgency episodes/24 hours in adolescents according to the Patient Perception of Intensity of Urgency Scale (PPIUS).[10]

To assess the need for dose titration and to evaluate efficacy, patients or their parent/caregiver were required to complete a 7-day diary of micturitions and incontinence episodes prior to study visits 9–14. Urgency episodes in adolescents were recorded over 2 diary days.

Statistical Methodology

Baseline measurements for the 12-week study were considered baseline values for the current study so that solifenacin data could be combined from both studies for analyses of up to 52 weeks. Data from children and adolescents were analysed separately. The planned sample size was ≥100 children and ≥20 adolescents. Safety parameters, and patient demographics and characteristics were analysed for the safety analysis set (SAF; patients who had received ≥1 dose of open-label solifenacin and who reported safety data after the first dose). Efficacy analyses were performed on the full analysis set (FAS; patients who had received ≥1 dose open-label solifenacin and for at least 1 efficacy variable had both a valid baseline value from the double-blind study and a valid post-baseline value from diary data completed after the first

open-label solifenacin dose). Last observation carried forward (LOCF) methodology was applied to efficacy, vital signs and ECG endpoints where data were missing. Data from assessments at baseline or when the patient was receiving placebo during the double-blind study were not carried forward.

The efficacy and secondary safety endpoints were assigned to solifenacin treatment-duration windows so that data from solifenacin-treated patients in the double-blind study could be combined with that from placebo-treated patients in the double-blind study who received solifenacin only in the open-label study (figure 2). The data were summarized by treatment duration and dose group. As safety measurements relate to the pre-assessment dose and some treatment-duration windows incorporated more than 1 study visit per patient, 2 rules were applied to assign the measurement and dose group to these windows (appendix A2).

Baseline and demographic characteristics, drug exposure, treatment compliance and laboratory values were summarized by descriptive statistics. For each efficacy variable, change from baseline to each solifenacin treatment-duration window was assessed using an analysis of covariance (ANCOVA) model including duration of all treatment (double-blind and/or open-label), sex, geographic region and randomized treatment group in the 12-week study as fixed effects, baseline as covariate and duration repeated within patient. For the assessment of laboratory parameters, values below the lower limit of quantification were set to 0.

The study was conducted in accordance with ethical principles of the Declaration of Helsinki, Good Clinical Practice and International Conference on Harmonization guidelines, and applicable laws and regulations. For each study site, an independent ethics committee/institutional review board approved the study before initiation. Informed consent was provided by the patient's parent/legal representative and, where appropriate, the patient provided written assent.

RESULTS

Patient Demographics

Of 163 patients (131 children, 32 adolescents) who completed the double-blind study, 148 (90.8%; 119 children, 29 adolescents) were enrolled in the open-label extension (figure 3). A total of 122 patients (74.8%; 99 children, 21 adolescents) completed the study. Of those who discontinued treatment, (20 [16.8%] children, 6 [20.7%] adolescents), an AE was the most commonly reported reason (13 children, 5 adolescents). In children, treatment discontinuation also resulted from withdrawal by patient (n=5), lack of efficacy (n=1) and resolution of OAB symptoms (n=1). One adolescent was withdrawn due to protocol non-compliance and was not included in the SAF or FAS, and 1 child treated with placebo in the 12-week study was not included in the FAS. The SAF comprised 118 children and 29 adolescents: 51.7% of children and 82.8% of adolescents were female; mean age was 7.3 years (children) and 14.2 years (adolescents; table 2).

Solifenacin Exposure and Treatment Compliance

The majority of doses were uptitrated from an initial pediatric equivalent dose 5mg (PED5) to a maximum PED10. At week 52, 77 of 99 (78%) children and 16 of 23 (70%) adolescents received a solifenacin PED10 dose. The median (interquartile range: Q1, Q3) duration of exposure to solifenacin was 278 days (271, 280 days) in children and 277 days (271, 279 days) in adolescents (SAF). Treatment compliance ranged from ≥80%–<120% in 86.4% of children (n=102) and 89.7% of adolescents (n=26).

Safety

The incidence of drug-related TEAEs was 34.7% (children, n=41) and 37.9% (adolescents, n=11). The most commonly reported drug-related TEAEs in children were constipation (n=14, 11.9%), ECG QT prolonged (n=10, 8.5%) and dry mouth (n=5, 4.2%), and in adolescents ECG QT prolonged (n=4, 13.8%) and nausea (n=2, 6.9%; table 3). Most TEAEs were considered mild or moderate in intensity. Aside from 2 cases of dizziness, no other CNS-related drug-related TEAEs were reported. Two serious TEAEs were reported, which were of severe intensity but considered unrelated to solifenacin treatment: gastroenteritis (female aged 7 years) and appendicitis (female aged 12 years).

There were no cases of urinary retention and no evidence of a solifenacin-induced increase in PVR volume (table 4). Three cases of a treatment-emergent UTI concurrent with PVR volume increase were successfully treated prior to study end without treatment interruption, dose reduction or withdrawal from the study. There were no clinically relevant changes observed in clinical laboratory evaluations or vital signs. Mean change from baseline in systolic and diastolic blood pressure, pulse rate and body temperature is shown in table 4.

There were no clinically-relevant abnormalities observed in any post-baseline ECG measurements. The mean increase in QT interval corrected for heart rate using Bazett's formula (QTcB) observed at final visit compared with baseline was 6.1 ms (children) vs 3.8 ms (adolescents; table 5). Increase from baseline to final visit in QTcB interval >30 ms (maximum 39 ms) was reported in 5 (4.3%) children and 1 (3.4%) adolescent (table 5). Patients with an increase of QTcB >30 ms were reported as TEAEs, in accordance with the protocol (10 children, 4 adolescents). None of these was associated with clinical symptoms or tachyarrhythmia.

From study start to final visit, mean weight (SD) increased from 27.8 (7.8) kg to 31.3 (9.5) kg (children) and from 57.3 (12.3) kg to 60.3 (13.1) kg (adolescents). Mean height (SD) increased

from 127.8 (10.3) cm to 133.2 (10.6) cm (children) and from 160.2 (7.5) cm to 162.4 (8.0) cm (adolescents).

Treatment was also discontinued due to TEAEs in four other patients, which included one case of tic, two cases of constipation and one patient who was exposed to solifenacin during the first trimester of pregnancy and who delivered a healthy baby following treatment discontinuation.

No dose-dependent effects were identified with solifenacin for TEAEs or other safety measures.

Efficacy

Change from baseline to final visit was similar between the 2 age groups for adjusted mean number of incontinence episodes/24 hours, micturitions/24 hours and incontinence-free days/7 days (figure 4a–c). Reductions in mean incontinence episodes/24 hours were observed at 3 weeks (children: 1.0; adolescents: 0.9) and continued to improve over 52 weeks (children: 1.9; adolescents: 2.0). Similarly, by 3 weeks reductions in mean micturitions/24 hours were 1.0 (children) and 0.9 (adolescents), improving to 1.8 for both age groups at 52 weeks. An improvement in the mean number of incontinence-free days/7days was observed at 3 weeks (children: 1.4, adolescents 1.5 days), increasing to 2.8 and 3.9 days, respectively, at 52 weeks. Reductions in the mean number of grade 3 or 4 urgencies/24 hours (adolescents only; figure 4d) was observed from 3–52 weeks (0.7 to 2.2, respectively).

DISCUSSION

Data from this open-label safety extension study of solifenacin in a pediatric population were combined with those from a 12-week, double-blind, placebo-controlled trial.[13] Solifenacin was well tolerated with no additional safety signals observed over the 12-week study and with a continued improvement in efficacy over baseline.

To our knowledge, this is the first, prospective, long-term study of solifenacin in a pediatric population with OAB. The incidence and severity of AEs was similar to 2 prospective and 1 retrospective study of long-term solifenacin therapy in children with refractory OAB[10-12] and 1 long-term study in adults with OAB.[14] In adults, the incidence of dry mouth, the most common antimuscarinic AE, is lower with solifenacin than other treatments.[15,16] The low incidence of dry mouth in our pediatric population (4.2%) is of particular note: an incidence of 0−15.3% has been reported with solifenacin in children with refractory OAB[10-12] and 23.3% with oxybutynin in a non-refractory population.[17] Nevertheless, long-term data in the pediatric population are limited.

The incidence of constipation (11.9%) in children was higher than reported in children with refractory OAB (2.2–8.2%),[10-12] although no dose-dependent effects were apparent and no case was classified as severe. The incidence compares favorably with that in adults with OAB (19.2%).[14] Importantly, constipation in children is a common complaint and the incidence within the general pediatric population is variable,[18] possibly as high as 50% in those with lower urinary tract dysfunction.[19,20]

Three other common TEAEs, nasopharyngitis, headache and nausea, are also common complaints among the pediatric population and considered unlikely to be due to solifenacin treatment.

Small increases in mean DBP and SBP (1.5 and 2.7 mmHg, respectively) and a reduction in mean pulse rate (2.2 bpm) were observed in children during the study, which approximate to the expected annual age-related increases.[21,22] There were no apparent changes in SBP, DBP or pulse rate in adolescents. Overall, there were no clinically relevant changes in vital signs.

There were no clinically-relevant abnormalities observed in any post-baseline ECG measurements. As with many other antimuscarinic agents, solifenacin induces a small increase

in QTc interval (QT interval corrected for heart rate) in adults, which is below the threshold of clinical concern (5 ms).[23] A discontinuation threshold of QTcB >30 ms from baseline was implemented, resulting in 13 discontinuations. An analysis of repeat ECG measures recorded before treatment initiation demonstrated that the observed incidence of patients exceeding the 30 ms threshold was equivalent to the expected incidence based on random variation. Following a protocol amendment to increase the precision of the baseline ECG assessment, no further patients were discontinued. The largest observed increases from baseline and the highest absolute measured values of QTcB were not indicative of a safety concern. These data support the conclusion that solifenacin has no clinically relevant adverse effects on cardiac function in the pediatric population. Therefore, an ECG before or during solifenacin treatment is not required unless otherwise indicated.

A further four patients discontinued treatment due to TEAEs (one case each of pregnancy and of tic and two cases of constipation). Overall, solifenacin was well-tolerated and the absence of CNS associated side effects contrasts with the clinical profile of oxybutynin.[24]

Solifenacin did not affect growth in children or adolescents. Changes in these parameters were as expected.[25]

Improvements in efficacy endpoints observed within 3 weeks were sustained during the study. Furthermore, the magnitude of improvements over the longer term were larger than those observed during the 12-week study. While we cannot exclude the possibility that some participants improved during extended urotherapy treatment, it is unlikely that patients would have continued to improve based on urotherapy alone.[26] However, these improvements in efficacy should be interpreted with caution as the study did not include a placebo or active comparator.

CONCLUSIONS

Data from this open-label study suggest that a once-daily solifenacin oral suspension appears to be well tolerated for up to 52 weeks in children and adolescents aged 5–<18 years diagnosed with OAB.

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Legends

Figure 1. Study flow chart

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Figure 2. Solifenacin treatment-duration windows

Data from solifenacin-treated patients in the double-blind phase was combined with that from patients who started solifenacin treatment in the open-label study according to the treatment-duration windows. For example, patients who received solifenacin in the double-blind study reached 84 days' treatment by visit 7, whereas those who received placebo reached 81 days' treatment by visit 12 – these groups were combined into a treatment-duration window of 74–126 days.

For patients who had received solifenacin during the double-blind study, data from visits 9, 10 and 11 were not used for efficacy analyses as this was during the titration phase of the open-label study when patients may not have been receiving the optimal dose.

For diary data, the assessment date for the whole diary was considered to be the last diary day. If more than 1 diary had an assessment date within the same treatment-duration window resulting in ≥1 value, the mean of the values was used.

Figure 3. Patient disposition

*Allocation to patient age group was the same whether age at screening or age at signing the informed consent/assent was used.

[†]Patients who completed the double-blind study but who did not give informed consent for the open-label extension study.

[‡]Patients with informed consent for the double-blind study.

[§]Patient with no OAB symptoms after being titrated to 0 dose for 3 weeks.

[¶]Patient was non-compliant with protocol.

Figure 4. Change from baseline to end of treatment in mean number of a) incontinence episodes/24 hours, b) micturitions/24 hours, c) incontinence-free days/7 days and d) grade 3 or 4 urgency episodes (full analysis set)

Means generated from ANCOVA model with duration of all treatment (double-blind and/or open label), sex, geographic region and randomized treatment group in 12-week study as fixed effects, baseline as covariate and duration repeated within patient

Appendices

A1. Methodology for the 12-week double-blind study

A2. Assignment of secondary safety endpoints to treatment-duration windows

Table 1. *Inclusion, exclusion and discontinuation criteria*

Inclusion Criteria	Exclusion Criteria
• Patients completed 12-week study (for patient selection criteria in the 12-week study, refer to appendix A1) • Patients and their parents/legal representatives were willing and able to comply with study requirements, such as completion of patient diary and concomitant medication restrictions • Sexually active female patients of childbearing age had a negative serum pregnancy test at the end of the previous 12-week study and agreed to use a reliable form of birth control for the duration of the study and until at least 1 month after • Independent Ethics Committee/Institutional Review Board-approved written informed consent and assent provided, where applicable	• Patient was pregnant or breastfeeding • Patient was using or had used prohibited and/or concomitant medication (including antimuscarinics/antispasmodics, antidiuretics, α-blockers, strong CYP3A4 inhibitors, antidepressants) • Patient had known or suspected hypersensitivity to solifenacin (or other antimuscarinics) • Patient was unlikely to complete the trial in the opinion of the investigator • Patient had a clinically significant unstable medical condition, which in the opinion of the investigator precluded the patient's participation in the study

Discontinuation Criteria

Patients could withdraw from the study at any time. However, there were 4 discontinuation criteria for individual patients:

- QTcB interval >460 ms or QTcB interval prolonged by >30 ms relative to baseline value
- Acute urinary retention
- Signs or symptoms of hypersensitivity (anaphylactic reaction, angioedema, erythema multiforme, exfoliate dermatitis)
- If in the titration phase a complete response was sustained following no treatment for 3 weeks

Table 2. *Demographic characteristics (safety analysis set)*

	Children (aged 5–<12 years)			Adolescents (aged 12–<18 years)		
	Previous double-blind treatment			Previous double-blind treatment		
	Solifenacin (n=57)	**Placebo (n=61)**	**Total (n=118)**	**Solifenacin (n=15)**	**Placebo (n=14)**	**Total (n=29)**
Sex, n (%)						
Male	23 (40.4)	34 (55.7)	57 (48.3)	4 (26.7)	1 (7.1)	8 (17.2)
Female	34 (59.6)	27 (44.3)	61 (51.7)	11 (73.3)	13 (92.9)	24 (82.8)
Race, n (%)						
White	47 (82.5)	49 (80.3)	96 (81.4)	12 (80.0)	11 (78.6)	23 (79.3)
Black/African American	2 (3.5)	2 (3.3)	4 (3.4)	2 (13.3)	1 (7.1)	3 (10.3)

	Children (aged 5–<12 years)			Adolescents (aged 12–<18 years)		
	Previous double-blind treatment			Previous double-blind treatment		
	Solifenacin (n=57)	Placebo (n=61)	Total (n=118)	Solifenacin (n=15)	Placebo (n=14)	Total (n=29)
Asian	5 (8.8)	4 (6.6)	9 (7.6)	1 (6.7)	1 (7.1)	2 (6.9)
American Indian/Alaskan Native	3 (5.3)	3 (4.9)	6 (5.1)	0	1 (7.1)	1 (3.4)
Other	0	3 (4.9)	3 (2.5)	0	0	0
Age, years	7.5 (1.5)	7.2 (1.6)	7.3 (1.6)	14.5 (1.8)	13.9 (1.6)	14.2 (1.7)
BMI, mean (SD)	17.5 (3.0)	16.0 (2.2)	16.7 (2.7)	22.1 (4.6)	22.4 (3.0)	22.2 (3.8)

Table 3. *Incidence of a) drug-related and b) common treatment-emergent adverse events in children and adolescents (safety analysis set)*

a) Drug-related treatment-emergent adverse events (>4% in either children or adolescents)*

	Patients, n (%)	
	Children (n=118)	**Adolescents (n=29)**
Constipation	14 (11.9)	1 (3.4)
Electrocardiogram QT prolonged	10 (8.5)	4 (13.8)
Dry mouth	5 (4.2)	1 (3.4)
Nausea	0	2 (6.9)

b) Common treatment-emergent adverse events (>5% in either children or adolescents)*

	Patients, n (%)	
	Children (n=118)	**Adolescents (n=29)**
Nasopharyngitis	16 (13.6)	4 (13.8)
Constipation	16 (13.6)	1 (3.4)
Headache	16 (13.6)	1 (3.4)

	Patients, n (%)	
	Children (n=118)	**Adolescents (n=29)**
Urinary tract infection	13 (11.0)	4 (13.8)
Gastroenteritis	12 (10.2)	2 (6.9)
Electrocardiogram QT prolonged	10 (8.5)	4 (13.8)
Pyrexia	9 (7.6)	0
Diarrhea	7 (5.9)	2 (6.9)
Abdominal pain upper	7 (5.9)	1 (3.4)
Influenza	4 (3.4)	3 (10.3)
Nausea	3 (2.5)	3 (10.3)
Abdominal pain	3 (2.5)	2 (6.9)
Seasonal allergy	1 (0.8)	2 (6.9)

*Individual patients may have experienced 1 or more TEAEs.

Age groups: Children, 5–<12 years of age; adolescents, 12–<18 years of age.

Table 4. *Change from baseline to end of study in vital signs (safety analysis set)*

	Patients, n (%)	
Criteria	**Children (n=118)***	**Adolescents (n=29)**
Mean systolic blood pressure, mmHg		
Baseline (SD)	101.9 (11.1)	114.3 (7.9)
Change from baseline (SD)	2.7 (9.9)	-0.5 (7.3)
Mean diastolic blood pressure, mmHg		
Baseline (SD)	62.7 (7.6)	71.0 (8.5)
Change from baseline (SD)	1.5 (8.4)	−0.6 (8.6)
Mean pulse rate, bpm		
Baseline (SD)	85.7 (10.5)	77.1 (10.9)
Change from baseline (SD)	−2.2 (11.1)	0.9 (9.3)
Mean body temperature, ℃		
Baseline (SD)	36.4 (0.5)	36.5 (0.4)
Change from baseline (SD)	−0.1 (0.5)	−0.1 (0.4)
Mean PVR volume, mL		

	Patients, n (%)	
Criteria	**Children (n=118)***	**Adolescents (n=29)**
Baseline (SD)	4.5 (5.7)	4.8 (6.8)
Change from baseline (SD)	1.3 (11.9)	0.7 (8.8)

*n=116 at final visit.

Age groups: Children, 5–<12 years of age; adolescents, 12–<18 years of age.

Expected annual age-related increase in systolic and diastolic blood pressure in children is 2–3 mmHg.[27]

Table 5. *Mean and categorized absolute value and change from baseline in QTc – Bazett's Correction (safety analysis set)*

	Patients, n (%)	
Criteria	**Children (n=118)**	**Adolescents (n=29)**
Value at baseline (ms)		
n	118	29
<450	118 (100)	29 (100)
≥450	0	0
Value at final visit (ms)*		
n	116	29
<450	111 (95.7)	29 (100)
450 to <480	5 (4.3)	0
≥480	0	0
Change from baseline to final visit (ms)*		
n	116	29
<0	38 (32.8)	11 (37.9)

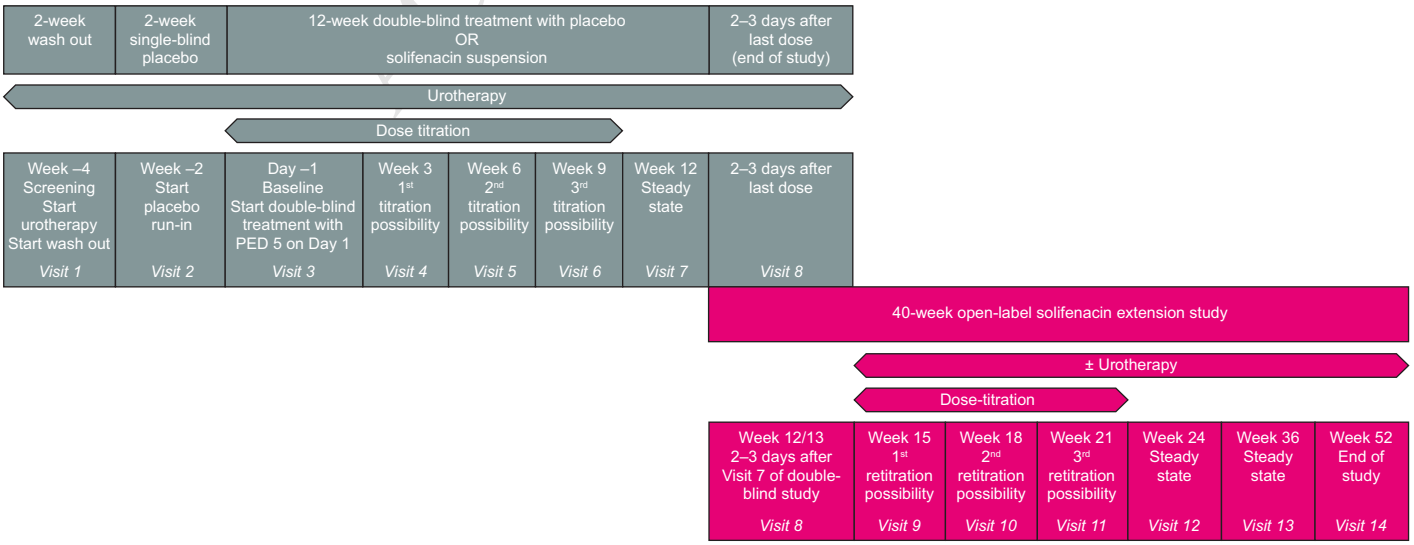
Criteria	Patients, n (%) Children (n=118)	Adolescents (n=29)
0 to <30	73 (62.9)	17 (58.6)
30 to <60	5 (4.3)	1 (3.4)
≥60	0	0
Mean QTcB		
Mean baseline, ms (SD)†	411.2 (13.1)	411.4 (13.4)
Mean final visit, ms (SD)*	417.4 (16.3)	415.2 (11.8)
Mean change, ms (SD)	6.1 (13.5)	3.8 (11.8)

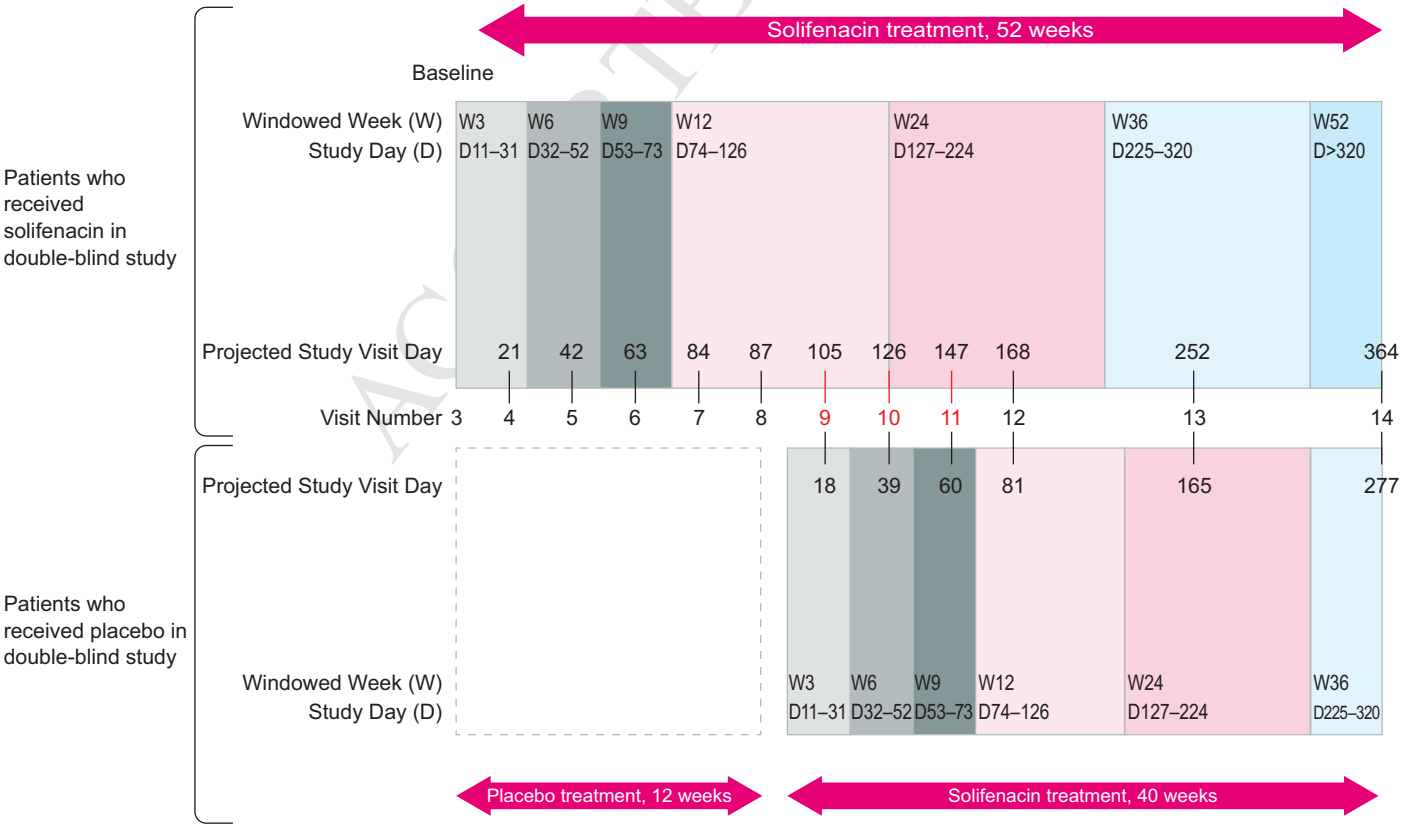
*Value at final visit is the most recent value after the first solifenacin dose up to and including visit 14.

†Value at baseline is the mean of the triplicate at visit 2 and 3 in the 12-week study.

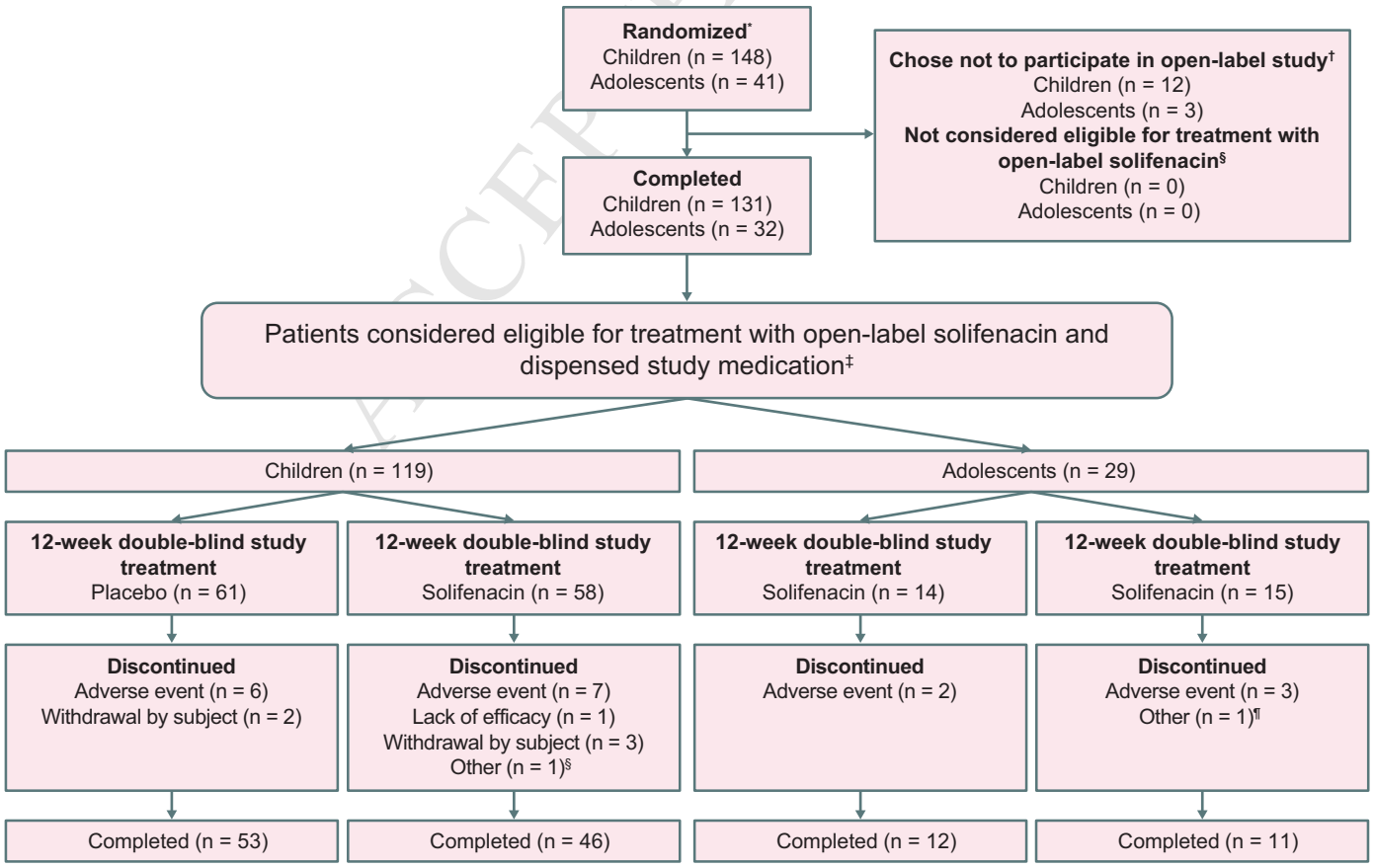
Age groups: Children, 5–<12 years of age; adolescents, 12–<18 years of age.

QTc, QT interval corrected for heart rate; QTcB, QTc corrected using Bazett's formula.



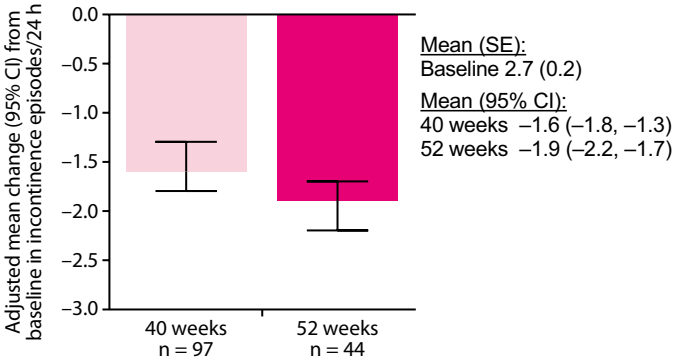


Data from color matching windows (presenting the duration of solifenacin exposure) are combined in the windowed analysis.


Randomized*
Children (n = 148)
Adolescents (n = 41)
Chose not to participate in open-label study†
Children (n = 12)
Adolescents (n = 3)
Not considered eligible for treatment with open-label solifenacin§
Children (n = 0)
Adolescents (n = 0)
Completed
Children (n = 131)
Adolescents (n = 32)
Patients considered eligible for treatment with open-label solifenacin and dispensed study medication‡
Children (n = 119)
Adolescents (n = 29)
12-week double-blind study treatment
Placebo (n = 61)
12-week double-blind study treatment
Solifenacin (n = 58)
12-week double-blind study treatment
Solifenacin (n = 14)
12-week double-blind study treatment
Solifenacin (n = 15)
Discontinued
Adverse event (n = 6)
Withdrawal by subject (n = 2)
Discontinued
Adverse event (n = 7)
Lack of efficacy (n = 1)
Withdrawal by subject (n = 3)
Other (n = 1)§
Discontinued
Adverse event (n = 2)
Discontinued
Adverse event (n = 3)
Other (n = 1)¶
Completed (n = 53)
Completed (n = 46)
Completed (n = 12)
Completed (n = 11)

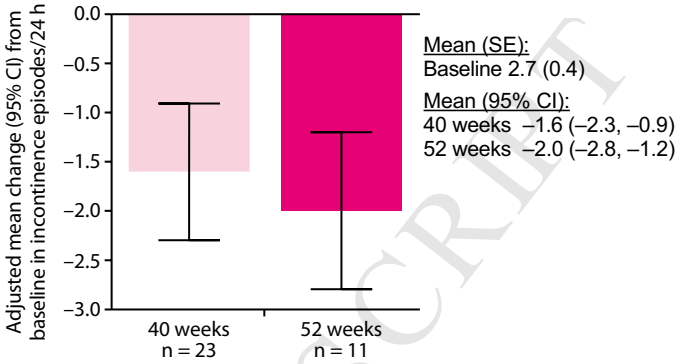
a) Incontinence episodes/24 hours

Children



Mean (SE):
Baseline 2.7 (0.2)
Mean (95% CI):
40 weeks −1.6 (−1.8, −1.3)
52 weeks −1.9 (−2.2, −1.7)

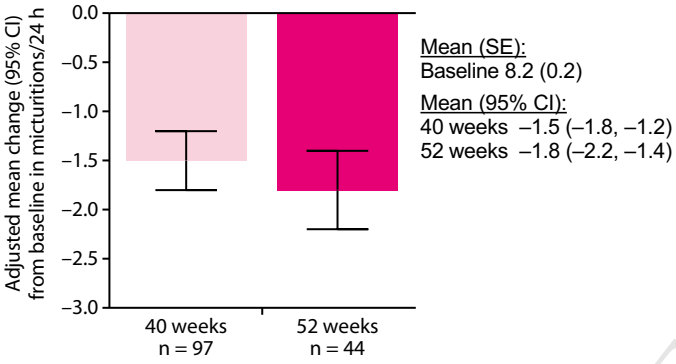
Adolescents



Mean (SE):
Baseline 2.7 (0.4)
Mean (95% CI):
40 weeks −1.6 (−2.3, −0.9)
52 weeks −2.0 (−2.8, −1.2)

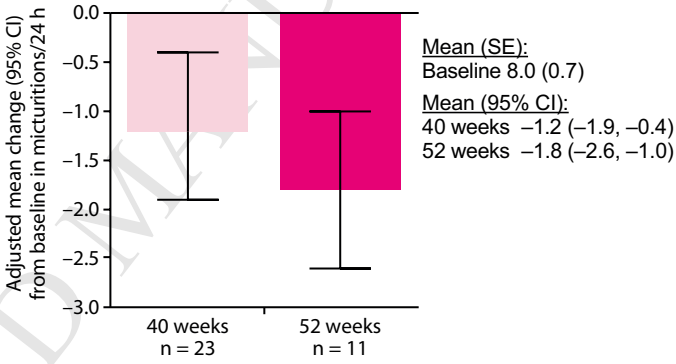
b) Micturitions/24 hours

Children



Mean (SE):
Baseline 8.2 (0.2)
Mean (95% CI):
40 weeks −1.5 (−1.8, −1.2)
52 weeks −1.8 (−2.2, −1.4)

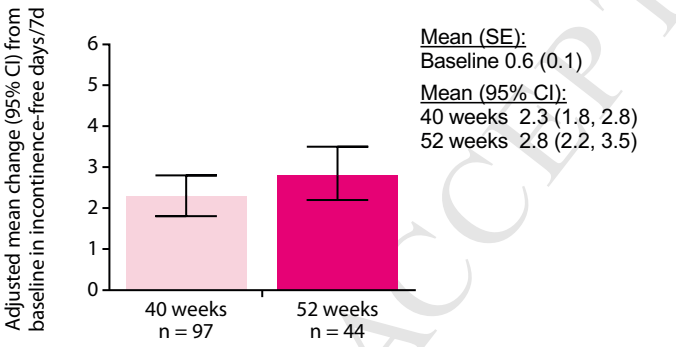
Adolescents



Mean (SE):
Baseline 8.0 (0.7)
Mean (95% CI):
40 weeks −1.2 (−1.9, −0.4)
52 weeks −1.8 (−2.6, −1.0)

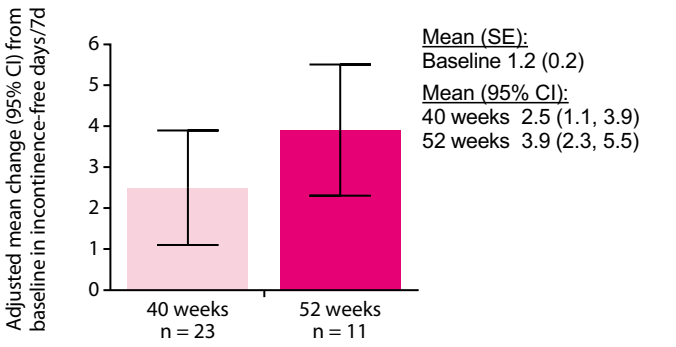
c) Incontinence-free days/7 days

Children



Mean (SE):
Baseline 0.6 (0.1)
Mean (95% CI):
40 weeks 2.3 (1.8, 2.8)
52 weeks 2.8 (2.2, 3.5)

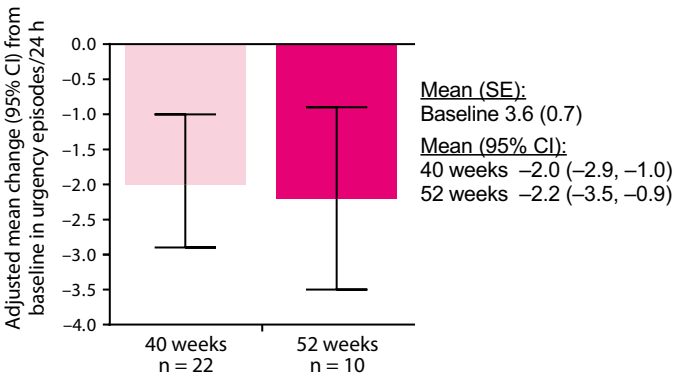
Adolescents



Mean (SE):
Baseline 1.2 (0.2)
Mean (95% CI):
40 weeks 2.5 (1.1, 3.9)
52 weeks 3.9 (2.3, 5.5)

d) Grade 3 or 4 urgency episodes/24 hours (adolescents)

Adolescents



Mean (SE):
Baseline 3.6 (0.7)
Mean (95% CI):
40 weeks −2.0 (−2.9, −1.0)
52 weeks −2.2 (−3.5, −0.9)

ABBREVIATIONS USED THREE TIMES OR MORE

AE, adverse event

ANCOVA, analysis of covariance

ECG, electrocardiogram

EoT, end of treatment

FAS, full analysis set

OAB, Overactive bladder

PED, pediatric equivalent dose

PVR, post-void residual

QTcB, QT interval corrected for heart rate using Bazett's formula

SAF, safety analysis set

SD, standard deviation

TEAE, treatment-emergent adverse event

Appendices

A1. Methodology for the 12-week double-blind study[14]

Methodology for the 12-week study has been published previously.[14] Briefly, patients were included into the study if they had a diagnosis of OAB with ≥4 episodes of daytime incontinence during a 7-day pre-baseline diary period, and height and weight within normal percentiles for age according to the Centers for Disease Control and Prevention growth charts (3rd to 97th percentile)[25]. Prior to screening, patients were excluded if they experienced extraordinary daytime urinary frequency (voiding frequency ≥1/h with a mean voided volume <50% of estimated bladder capacity [EBC] and normal nocturnal bladder behavior for age). They were also ineligible for study entry if they had: lower urinary tract pathologies other than OAB; any condition/treatment that could cause urinary symptoms or interfere with assessment of efficacy parameters. Following screening, patients were excluded if maximum voided volume (excluding morning volume) was greater than EBC for age [(age +1) x 30] mL or >390 mL; PVR volume was >20 mL; or if they had a current urinary tract infection confirmed by urinalysis (>1x10^5 cfu/mL).

Patients who satisfied the inclusion/exclusion criteria underwent a 4-week urotherapy run-in period with single-blind placebo treatment added at week 2. At baseline, eligible patients were randomized 1:1 and stratified by country to receive urotherapy plus double-blind solifenacin oral suspension or placebo once daily for 12 weeks. Based on the patient's weight at screening the dose aimed to deliver steady-state plasma drug exposure equivalent to that of the 5 mg tablet dose in adults (PED5).The solifenacin or placebo dose could be titrated up or down every 3 weeks up to a maximum of 3 times (week 9) to a final dose of PED2.5, PED5, PED7.5 or PED10 (equivalent to 2.5 mg, 5.0 mg, 7.5 mg or 10.0 mg in adults, respectively).

A2. Assignment of secondary safety endpoints to treatment-duration windows

Two rules were used to assign an overall measurement and dose group to a treatment-duration window when the window contained target days for more than 1 visit. The rules were dependent on whether the expected distribution of the endpoint was 2-tailed or 1-tailed and which tails of the distribution indicated a safety signal.

Safety endpoint	**Indication of safety signal**	**Values assigned to window**
ECG: pulse rate, QRS duration, QT interval, RR interval, heart rate **Vital signs:** systolic and diastolic blood pressure **Urinalysis:** urine pH	Two-tailed distribution with measurement (values) in both tails	Mean of the measurement within the window and the lowest of their assigned dose groups
ECG: QT interval corrected for heart rate by Bazett's or Fridericia's formula **Vital signs:** body temperature **PVR volume** **Urinalysis:** all qualitative and quantitative endpoints except urine pH	Two-tailed distribution with measurements in the upper tail One-tailed distribution with measurements in the tail	Highest or worst measurements in the window and the lowest of their assigned dose groups