Long-term efficacy and safety of solifenacin in pediatric patients aged 6 months to 18 years with neurogenic detrusor overactivity: results from two phase 3 prospective open-label studies

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Journal limits

Summary word count (maximum 400 words, plus a figure/table): 400 words

Body text word count (maximum 3000 words): 3066 words (we have received confirmation from the Editorial Office for the *Journal of Pediatric Urology* that we could increase the number of words in the manuscript slightly in order to amend the manuscript according to the reviewers' comments)

Figures/Tables (maximum four items): four items (two figures and two tables) plus appendices

References (maximum 30 references): 32 references (we have received confirmation from the Editorial Office for the *Journal of Pediatric Urology* that we could increase the number of references in the manuscript slightly in order to amend the manuscript according to the reviewers' comments)

Competing interests

Israel Franco is an investigator and consultant for Astellas Pharma; Małgorzata Baka-Ostrowska, Piet Hoebeke and Johan Vande Walle have received personal fees from Astellas Pharma; Leon N. Davies has received grants and consultancy fees from Astellas Pharma; Robert Snijder is an Astellas Pharma employee; Ellen Dahler, Otto Stroosma, Frank Verheggen, Brigitte Bosman, and Donald Newgreen were previously Astellas Pharma employees at the time of the study. All authors received support for the development of the manuscript.

Summary

Introduction

The standard recommended treatment for neurogenic detrusor overactivity (NDO) is clean intermittent catheterization combined with an antimuscarinic agent. However, the adverse systemic side effects of oxybutynin, the most widely used agent, are of concern.

Objective

To evaluate the efficacy and safety of solifenacin in pediatric patients with NDO, aged 6 months–<5 years and 5–<18 years.

Study design

Two open-label, baseline-controlled, phase 3 studies were conducted in pediatric patients with NDO. Patients were treated with sequential doses of solifenacin oral suspension (pediatric equivalent doses 2.5–10 mg) for 12 weeks to determine each patient's optimal dose, followed by a fixed dose ≥40-week treatment period. Primary efficacy endpoint was change from baseline in maximum cystometric capacity (MCC) after 24 weeks. Secondary endpoints included bladder compliance, bladder volume until first detrusor contraction (>15 cmH_2O), number of overactive detrusor contractions (>15 cmH_2O), maximum catheterized volume (MCV)/24 h and incontinence episodes/24 h. Safety parameters were treatment-emergent adverse events (TEAEs), serious adverse events, laboratory variables, vital signs, electrocardiograms, and ocular accommodation and cognitive function assessments.

Results

After 24 weeks, MCC had significantly increased compared with baseline in patients aged 6 months–<5 years and 5–<18 years (37.0 ml and 57.2 ml, respectively; *P* < 0.001; Fig.). Improvement was also observed after 52 weeks' treatment. Significant changes were observed from baseline to week 24 in all secondary endpoints in both age groups: increase in bladder compliance, increase in bladder volume to first detrusor contraction as a percentage of expected bladder capacity, reduction in the number of overactive detrusor contractions, increase in MCV, and decreased incontinence episodes. TEAEs were mostly mild or moderate and there were no new drug-related TEAEs compared with adult studies. Age-related improvements were noted in ocular accommodation and cognitive function.

Discussion

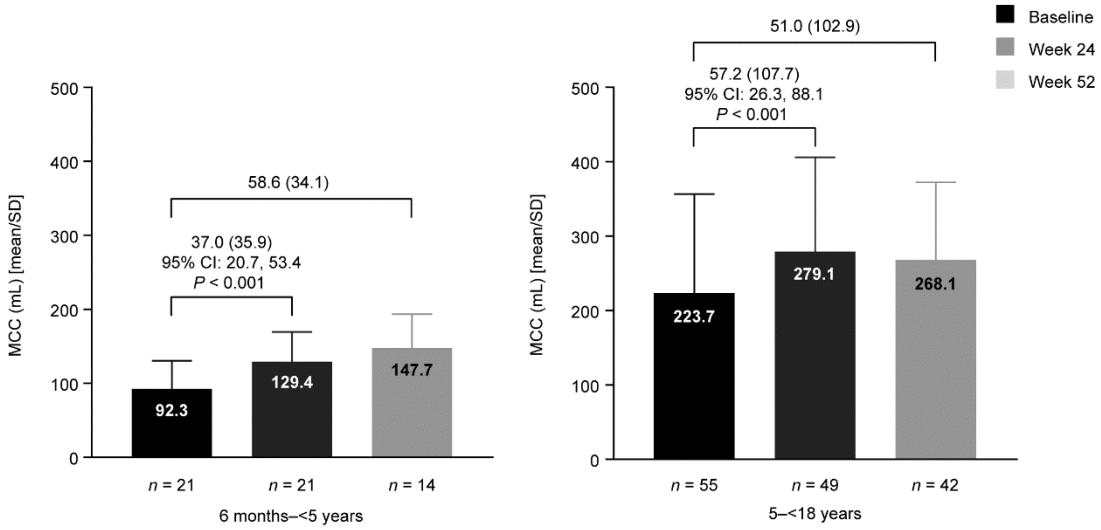
These long-term multicenter investigations demonstrated the efficacy and safety of solifenacin in pediatric patients with NDO. The observed increases in MCC were clinically relevant and demonstrated that an increase in fluid volume can be accommodated in the bladder prior to reaching intravesical pressures that endanger kidney function and/or are associated with leakage or discomfort. Solifenacin was well tolerated with low incidences of constipation and dry mouth (typically associated with antimuscarinics), central nervous system-related side effects and facial flushing.

Conclusion

Solifenacin was effective and well tolerated in pediatric patients with NDO, aged

6 months–<18 years, suggesting that it is a viable alternative to oxybutynin, the current standard of care.

Studies are registered at ClinicalTrials.gov: NCT01981954 and NCT01565694



Summary Fig. MCC of patients aged 6 months–<5 years and 5–<18 years at baseline and week 24 (primary endpoint) and week 52 (secondary endpoint; full analysis set).

Keywords (three to six)

Children; Adolescents; Neurogenic urinary bladder; Solifenacin

Introduction

Neurogenic detrusor overactivity (NDO) is defined as the occurrence of involuntary detrusor contractions during filling cystometry that have a relevant neurological cause [1]. Epidemiology data in the pediatric population are limited; in 2009, an estimated 17 170 pediatric patients in the EU were diagnosed with NDO (prevalence: 1.8/10 000 children) [2]. NDO is predominantly caused by a congenital neural tube defect in children [3]. The detrusor of patients with NDO contracts involuntarily during bladder filling, which simultaneously coincides with sphincter dyssynergia, and results in high bladder pressure and eventual renal damage [4]. Clinically, we typically find the majority of children with congenital neural tube defects present with both detrusor instability and sphincter dyssynergia.

Goals for NDO management are to prevent or minimize upper urinary tract damage and achieve social continence [5]. Clean intermittent catheterization (CIC) combined with antimuscarinic agents is the standard recommended treatment [6]. The antimuscarinic oxybutynin is approved in patients aged ≥5 years and trospium is approved for older children (≥12 years) in some countries [7]. Although widely used, oxybutynin has been associated with adverse systemic effects including cognitive impairment in children [8,9], a well-known undesirable effect in adults. Concerns about adverse central nervous system (CNS) effects in pediatric patients with NDO have resulted in a need for a drug with a lower potential for such effects.

The antimuscarinic solifenacin succinate (VESIcare®, Astellas Pharma Europe, B.V., The Netherlands) is approved worldwide for the treatment of adult overactive bladder (OAB) symptoms [10], and is effective and well tolerated in adults with either OAB [11-13] or NDO [14].

An oral suspension of solifenacin, developed to enable comfortable administration and flexible dosing in the pediatric population, has proven to be efficacious and well tolerated in pediatric patients with OAB [15,16]. In a prospective open-label study, an adjusted-dose solifenacin regimen had high subjective and objective success rates for the treatment of NDO in pediatric patients refractory to oxybutynin or tolterodine [17]. Following this previous investigation, the current studies were conducted to assess whether the efficacy and safety of solifenacin oral suspension could be maintained long term in pediatric patients with NDO. Results from these studies contributed to European approval of solifenacin treatment for NDO in patients aged 2–18 years.

Materials and methods

Study design

Two open-label, baseline-controlled, multicenter, sequential-dose titration, phase 3 studies were conducted in pediatric patients, aged 6 months–<5 years (MARMOSET; NCT01981954; September 2013–December 2015) and 5–<18 years (MONKEY; NCT01565694; August 2012–April 2016), diagnosed with NDO according to International Children's Continence Society (ICCS) criteria and using CIC [18]. A staggered approach was followed during enrollment, starting with the adolescents and conducting a safety assessment before

enrolling children aged 5–<12 years, 2–<5 years, and 6 months–<2 years. Enrolled patients who satisfied the inclusion criteria during screening (Appendix Table A) were administered solifenacin oral suspension. The starting dose in children aged ≥2 years was initially an allometrically scaled pediatric equivalent of the adult 5 mg dose (PED5), revised to a physiologically based pharmacokinetic-determined dose of PED2.5 for children aged 6 months–<5 years following a protocol amendment to include patients who were 6 months–<2 years. Solifenacin was titrated up or down every 3 weeks over a 12-week period to an optimal once-daily final dose of PED2.5, PED5, PED7.5, or PED10 (Fig. 1). The decision to titrate was according to investigator discretion based on diary and safety parameters: (i) if the patient was incontinent but did not experience intolerable adverse events (AEs), or if there were high pressure contractions (>40 cmH_2O) and/or a bladder compliance of <10 mL/cmH_2O, the dose was titrated up to next highest dose; (ii) if the patient experienced intolerable AEs, the dose was titrated down to next lowest dose (iii) if the patient was incontinence-free and did not experience intolerable AEs, the dose remained the same. A minimum 40-week fixed dose assessment period started when the optimal dose for each patient was reached (i.e., a maximum 52 weeks' treatment).

Recruitment of patients was dependent on satisfactory review of data and recommendations made by an independent Data and Safety Monitoring Board who met at regular intervals. No concerns were raised at any of the meetings.

Both studies were approved by the Independent Ethics Committee/Institutional Review Board for each site. The patient's parent(s)/legal guardian(s) provided

informed consent, and where appropriate, the patient provided written assent. The studies were conducted in accordance with Good Clinical Practice, International Council for Harmonisation guidelines and the ethical principles of the Declaration of Helsinki.

Efficacy assessments

Urodynamic assessments were performed in unsedated patients at baseline, during the titration period and at week 24; an optional assessment was performed at week 52. Patients and/or parent(s)/legal representative(s) completed a 3-day diary for patients aged 6 months–<5 years or a 7-day diary for patients aged 5–<18 years, on the number of catheterizations, catheterized volumes, and incontinence episodes (leakage) before visit 2 and all subsequent visits.

The primary efficacy endpoint was change from baseline to week 24 in maximum cystometric capacity (MCC), defined as maximum bladder capacity reached during filling cystometry before either leakage or pain/discomfort was observed or 135% of expected bladder capacity (EBC) was reached [19]. The secondary efficacy variables based on urodynamic assessments were change from baseline to week 52 in MCC and change from baseline to week 24 and week 52 in bladder compliance (measured at a point agreed by two investigators prior to a detrusor contraction or sudden spike in pressure), bladder volume until first detrusor contraction (>15 cmH_2O) expressed as a percentage of EBC, bladder volume at 10, 20 and 30 cmH_2O (individuals aged 6 months–<5 years) or 20, 30 and 40 cmH_2O (individuals aged 5–<18 years),

and number of overactive detrusor contractions (>15 cmH_2O) until leakage or end of bladder filling. Secondary efficacy variables based on patient diaries were changes from baseline to each post-baseline visit (up to week 52) in maximum catheterized volume (MCV)/24 h and incontinence episodes/24 h. Exploratory analyses were performed to express MCC as a percentage of EBC or MCV.

Safety assessments

Safety assessments performed at each study visit included incidences of treatment-emergent adverse events (TEAEs), vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, and body temperature versus standard norms) [20], laboratory variables (hematology, biochemistry, and urinalysis), 12-lead electrocardiograms (ECGs), height and weight versus growth charts [21], and ultrasound assessments of the upper urinary tract. Patients aged 5–<18 years underwent tests for ocular accommodation (accommodative response profile over 0 to 4.5 diopters and the accommodative error index) and cognitive function (assessed by trained staff using a computerized cognitive test battery [CogState Ltd, Melbourne, Australia] to measure psychomotor function, attention, working memory and learning).

Statistical methodology

The planned sample size is described in Appendix A. Efficacy analyses were performed on the full analysis set (FAS; patients who received ≥1 dose of solifenacin and provided valid baseline and ≥1 post-baseline values for the

primary efficacy endpoint). Safety analyses were performed on the safety analysis set (SAF; patients who received ≥1 solifenacin dose). All statistical analyses used SAS® version 9.1.3 or higher. Demographics and baseline characteristics and efficacy and safety data were summarized by descriptive statistics. Unless mentioned otherwise, changes from baseline to week 24 in primary and secondary efficacy endpoints were analyzed using a paired two-sided *t*-test at $\alpha = 0.05$ significance level. The Wilcoxon signed-rank test was used to analyze the statistical significance of change from baseline to week 24 in bladder volume and in exploratory analyses where MCC was expressed as a percentage of EBC or MCV. Missing data were not imputed.

Results

Patient demographics and dosing

A total of 23 patients aged 6 months–<5 years and 76 patients aged 5–<18 years were enrolled (Appendix Fig. A); all were included in the SAF. Of these, 21 and 55 patients aged 6 months–<5 years and 5–<18 years, respectively, had valid baseline and post-baseline measurements for MCC and were included in the FAS (exclusions listed in Appendix Table B). Mean age was 35.3 months (6 months–<5 years age group), and 10.8 years (5–<18 years age group; Table 1). More than half of the patients were female (60.9% aged 6 months–<5 years; 51.3% aged 5–<18 years).

Overall, 14 (66.7%) and 41 (70.7%) patients aged 6 months–<5 years and 5–<18 years, respectively, were receiving a PED10 dose of solifenacin by week 52.

Efficacy assessments

After 24 weeks' solifenacin treatment, there was a statistically significant increase in MCC versus baseline in patients aged 6 months–<5 years and 5–<18 years (mean [standard deviation (SD)]: 37.0 [35.9] ml and 57.2 [107.7 ml, respectively; *P* < 0.001; Fig. 2). Improvement in MCC was also observed after 52 weeks' treatment in patients aged 6 months–<5 years and 5–<18 years (mean [SD]: 58.6 [34.1] ml and 51.0 [102.9] ml, respectively).

Compared with baseline, at 24 weeks, solifenacin treatment significantly improved bladder compliance in patients aged 6 months–<5 years and 5–<18 years (mean [SD]: 5.1 [6.8] ml/cmH_2O, *P* = 0.003 and 9.1 [28.6] ml/cmH_2O, *P* = 0.029, respectively), increased bladder volume until first detrusor contraction (>15 cmH_2O) expressed as a percentage of EBC (*P* = 0.001, *P* < 0.001, respectively) and decreased the number of overactive detrusor contractions (mean [SD]: −7.0 [8.6], *P* = 0.001 and −2.3 [5.1], *P* = 0.003, respectively; Appendix Fig. B). Compared with baseline, at 24 weeks there was a decrease in the number of patients reaching a detrusor pressure threshold of 30 cmH_2O in both age groups (from seven to three of 21 children aged 6 months–<5 years and from 25 of 55 to 22 of 49 patients aged 5–<18 years). For those reaching 30 cmH_2O at both baseline and week 24 there was an increase in bladder volume (mean [SD] change: 67.5 [118] mL, *P* = 0.567 [6 months–<5 years]; 61.8 [80.6] mL; *P* = 0.006 [5–<18 years]).

There were significant improvements in diary endpoints at week 24 versus baseline: MCV/24 h increased (mean [SD]: 40.6 [51.5] ml, *P* = 0.004 and 67.5

[88.1] ml, $P < 0.001$, respectively) and number of incontinence episodes/24 h decreased (mean [SD]: −1.3 [1.4], $P = 0.001$ and −1.6 [2.0], $P < 0.001$, respectively). Improvements were sustained up to 52 weeks.

In both age groups, solifenacin treatment significantly increased MCC expressed as a percentage of EBC or MCV from baseline to week 24 (mean [SD]: EBC, 35.1 [35.7], $P < 0.001$ and 16.3 [31.0], $P < 0.001$, respectively; MCV, 62.4 [92.7] ml, $P = 0.002$ and 37.5 [62.1] ml, $P < 0.001$, respectively; Appendix Fig. C).

Safety assessments

The incidences of drug-related TEAEs were 21.7% and 19.7% in patients aged 6 months–<5 years and 5–<18 years, respectively (Table 2). In both age groups, the most common drug-related TEAE was constipation. All drug-related TEAEs were considered mild-to-moderate in intensity. Serious AEs were reported in three patients aged 6 months–<5 years and seven patients aged 5–<18 years, respectively (Appendix Table C); none were considered to be solifenacin related.

There were no clinically relevant changes in blood pressure, heart rate, body temperature, or laboratory parameters. Compared with baseline, all changes in vital signs were consistent with normal age-adjusted ranges at week 52 (Appendix Table D). Moreover, according to the investigator, there were no clinically relevant changes in ultrasound assessments of the upper urinary tract. Height and weight increases were consistent with standard norms.

Most 12-lead ECGs were considered to be normal, and no abnormality was assessed as clinically significant. Mean changes from baseline to week 52 for all ECG measurements were negligible in patients from both age groups (Appendix Table E). Four patients aged 5–<18 years were discontinued from treatment (Appendix Table F) as a result of an observed increase in QT interval corrected for heart rate by Bazett's formula (QTcB) above the pre-specified discontinuation threshold of 30 ms relative to mean baseline value. In repeat ECG measures, this threshold was within normal intra-patient variation. At week 52, all patients, except one aged 5–<18 years, had a categorized absolute QTcB value <450 ms (Appendix Table G).

In patients aged 5–<18 years, age-related improvements were observed in ocular accommodation (mean [SD] accommodative error index: baseline 1.88 [2.44] diopters; week 52 1.24 [0.52] diopters) and cognitive function (Appendix Table H).

Discussion

The studies reported herein are the first long-term multicenter investigations to demonstrate efficacy and safety of solifenacin in pediatric patients with NDO. There was a significant increase in the primary endpoint of MCC at week 24 and improvements were noted in secondary urodynamic and diary endpoints over 52 weeks' treatment. Our results support those from a study in pediatric patients with NDO who were refractory to oxybutynin or tolterodine [17].

MCC was selected as the primary efficacy endpoint as it is the most reproducible urodynamic parameter and to allow comparison with previous

oxybutynin studies [22,23]. The observed increases in both our studies are considered to be clinically relevant and demonstrate that a larger volume of fluid can be accommodated in the bladder prior to reaching intravesical pressures associated with leakage or discomfort. Increases in MCC are accepted as indicating a lower risk of high intravesical pressure and the associated potential for renal damage [24]. While the magnitude of the increase in MCC at week 24 was smaller in patients aged 6 months–<5 years versus 5–<18 years, this is considered to be a reflection of the smaller bladder size in the younger group [25]. The mean increases in MCC expressed as a percentage of EBC, or relative to individual bladder capacity estimated from the MCV, were greater in patients aged 6 months–<5 years versus older patients, although significant improvements from baseline were observed for all patients. These analyses suggest that solifenacin is at least equally effective across the younger and older age groups and demonstrate the benefit of early treatment initiation with an optimal dose. Similar trends in MCC improvement were observed in oxybutynin-treated pediatric patients with NDO [22,26].

Bladder compliance is a calculated parameter that reflects the relationship between bladder volume and pressure [1]. Solifenacin treatment increased bladder compliance in both populations, and thereby, the ability of the bladder to accommodate larger volumes before a deleterious increase in bladder pressure develops. Bladder compliance increases with age: 10 ml/cm H_2O is considered normal for infants [27], >10 ml/cm H_2O for children [28], and >25 ml/cm H_2O for adolescents and adults [29], which explains the lower baseline compliance in our younger patients.

The decrease in the number of overactive detrusor contractions alongside an increase in median bladder volume until first detrusor contraction expressed as a percentage of EBC suggests that solifenacin is effective in preventing involuntary detrusor contractions in pediatric patients with NDO. This is a key treatment goal as a later onset of overactive contractions can lead to reductions in incontinence and reductions in the number of overactive contractions of the bladder wall, thereby indirectly decreasing the likelihood of upper urinary tract infection and subsequent renal injury.

Solifenacin treatment improved MCV, which is indicative of maximum bladder capacity under normal physiological conditions. In both age groups, the magnitude of the increase from baseline to week 24 in MCV was similar to the magnitude of change in MCC, demonstrating ‘real-world’ relevance of the urodynamic findings. Moreover, solifenacin reduced incontinence, an important secondary NDO treatment goal, which is consistent with the decrease in incidence of involuntary contractions and increase in MCC.

The observed findings in pediatric patients are consistent with those in adults with NDO. In the prospective, placebo-controlled SOlifenacin in NeurogenIC detrusor overactivity (SONIC) study, solifenacin treatment improved the mean changes from baseline in MCC and bladder volume at first contraction and at first leak, in patients aged 18–65 years with NDO due to multiple sclerosis or spinal cord injury [14]. Additionally, in a retrospective analysis of case histories and urodynamic data from 35 patients with spinal cord injury, solifenacin treatment significantly improved bladder capacity, detrusor compliance, and reflex volume [30].

All doses of solifenacin were well tolerated, and the safety profiles in both age groups were comparable. The overall incidences of drug-related TEAEs were low, including those of the typical antimuscarinic side effects of constipation and dry mouth, and CNS-related side effects. These observations are in accordance with other studies in which solifenacin has demonstrated the potential for improved tolerability versus oxybutynin, especially for dry mouth [14] and cognition [31] in adults and for facial flushing, dry mouth and cognition in children [8]; these adverse effects of oxybutynin, particularly those on cognition, may require close patient monitoring [8]. The potential for cognitive adverse effects are highlighted by the results of an *in vivo* study which indicated that oxybutynin displays higher muscarinic receptor occupancy in the brain and greater blood-brain barrier penetration than solifenacin [32].

Importantly, we observed no clinically relevant changes in blood pressure, heart rate, or ECG parameters. Treatment discontinuation by four patients who exceeded the pre-specified QTcB criteria was considered to be a consequence of random variation in repeat ECG measures and unlikely to be due to solifenacin treatment. There were no clinically relevant changes in laboratory parameters including markers of renal function, demonstrating that kidney function was protected during 52 weeks of solifenacin treatment.

In the present study, age-related improvements were observed in both ocular accommodation and cognitive function. The improvements in ocular accommodation were an unexpected finding given that anticholinergic drugs inhibit iris sphincter and ciliary muscle stimulation, which can lead to mydriasis and cycloplegia. The improvements in cognitive function were anticipated owing

to the rapid cognitive maturation that occurs during late childhood and adolescence.

A limitation of our studies is the open-label design, which may introduce bias through unblinding. Use of placebo was not feasible because it is considered unethical to withhold treatment from patients with NDO for more than a few weeks. The studies were designed to limit the number of pediatric patients exposed to treatment while being adequately powered to demonstrate a clinically meaningful change in the primary efficacy endpoint.

Conclusions

Solifenacin is effective and well tolerated in pediatric patients with NDO, aged 6 months–<18 years. With the advantage of a flexible dosing formulation and no adverse ophthalmologic or cognitive effects, these first, long-term studies of solifenacin for NDO in a pediatric population demonstrate that the therapeutic is a potential alternative to oxybutynin, the current standard of care, especially in children aged <5 years, where there were previously no other NDO pharmacotherapies. Indeed, in Europe, the data from the studies presented herein contributed towards the approval of solifenacin for NDO in patients aged 2–18 years.

Author statements

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Ethical approval

Both studies were approved by the Independent Ethics Committee/Institutional Review Board for each site.

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Data sharing statement

Researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com.

For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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Table 1 Baseline demographics (SAF).

Category	6 months–<5 years (*n* = 23)	5–<18 years (*n* = 76)
Sex, *n* (%)		
Male	9 (39.1)	37 (48.7)
Female	14 (60.9)	39 (51.3)
Ethnicity, *n* (%)		
Hispanic or Latino	2 (8.7)	11 (14.5)
Not Hispanic or Latino	21 (91.3)	65 (85.5)
Race, *n* (%)		
White	12 (52.2)	45 (59.2)
Black/African American	0	2 (2.6)
Asian	11 (47.8)	23 (30.3)
American Indian/Alaskan Native	0	1 (1.3)
Others	0	5 (6.6)
Mean age[a], months/years (SD)	35.3 months (12.7)	10.8 years (3.3)
Weight[a] (kg)	13.2 (2.9)	38.1 (15.5)
Height[a] (cm)	89.3 (9.2)	138 (16.3)
Mean BMI, kg/m^2	16.5 (2.2)	19.2 (4.7)
Medical condition, *n* (%)[b]		
Lipomeningocele	NR	7 (9.2)
Meningomyelocele	NR	26 (34.2)
Spina bifida	23 (100)[b]	9 (11.8)
Spinal deformity	NR	24 (31.6)
Other	NR	10 (13.2)
Wheelchair bound, *n* (%)	NR	33 (43.4)
Spina bifida closure surgery, *n* (%)	23 (100)	64 (84.2)

Previous antimuscarinic medication, *n* (%)	14 (60.9)[a,c]	73 (96.1)[a,d]
Oxybutynin	5 (21.7)	29 (38.2)
Propiverine	2 (8.7)	19 (25.0)
Solifenacin	7 (30.4)	24 (31.6)
Tolterodine	–	6 (7.9)
Reason for discontinuing previous antimuscarinic medication, *n* (%)	14 (60.9)[a]	73 (96.1)[a]
Washout for current study	13 (56.5)	11 (14.5)
Lack of efficacy	–	1 (1.3)
Unknown	1 (4.3)	61 (80.3)

[a] Measured at screening.

[b] Spina bifida diagnosis was not differentiated.

[c] Two further patients received antimuscarinic medication prior to screening.

[d] All patients included in the SAF had taken previous antimuscarinic medication. Three further patients received medication prior to screening.

BMI, body mass index; NR, not recorded; SAF, safety analysis set; SD, standard deviation.

Table 2 Incidence of drug-related TEAEs (SAF).

	Patients, *n* (%)	
	6 months–<5 years (*n* = 23)	5–<18 years (*n* = 76)
Overall	5 (21.7)	15 (19.7)
Constipation	3 (13.0)	6 (7.9)
Dry mouth	2 (8.7)	2 (2.6)
ECG QT prolonged	0	3 (3.9)
UTI	1 (4.3)[a]	1 (1.3)
Abdominal pain	0	1 (1.3)
Bacterial test positive	1 (4.3)[b]	0
Pharyngotonsillitis	0	1 (1.3)
Somnolence	0	1 (1.3)
Viral rash	0	1 (1.3)

[a] One patient experienced three TEAEs of *Escherichia* UTI, UTI bacterial, and UTI enterococcal.

[b] Reported as bacteria in urine. Positive bacterial test was considered by the investigator to be related to solifenacin.

ECG, electrocardiogram; SAF, safety analysis set; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.

Figure legends

Fig. 1 Study design.

[a] Included washout (five half-lives) and diary completion for the 3 days before visit 2 and all subsequent visits.

[b] Washout was for 14 days and diary completion occurred for the 7 days before visit 2 and all subsequent visits.

[c] For patients aged 6 months–<2 years, treatment began on the day of the baseline visit; for patients aged ≥2–<5 years and 5–<18 years, treatment began on the day after the baseline visit.

[d] If the optimal dose was determined in <12 weeks, the fixed-dose assessment period was extended to keep the entire treatment period at 52 weeks.

Fig. 2 MCC of patients aged 6 months–<5 years and 5–<18 years at baseline and week 24 (primary endpoint) and week 52 (secondary endpoint; FAS). Data were analyzed using a paired two-sided *t*-test at $\alpha = 0.05$ significance level.

CI, confidence interval; FAS, full analysis set; MCC, maximum cystometric capacity; SD, standard deviation.

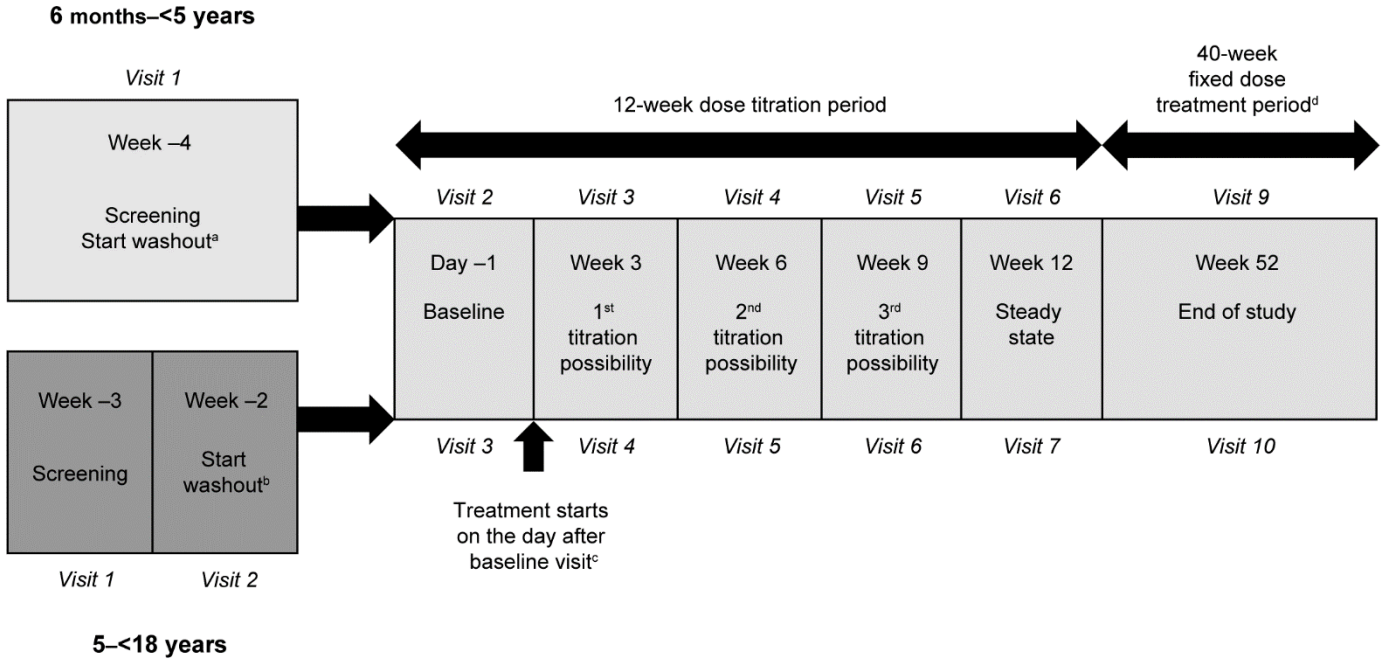

Fig. 1 Study design.

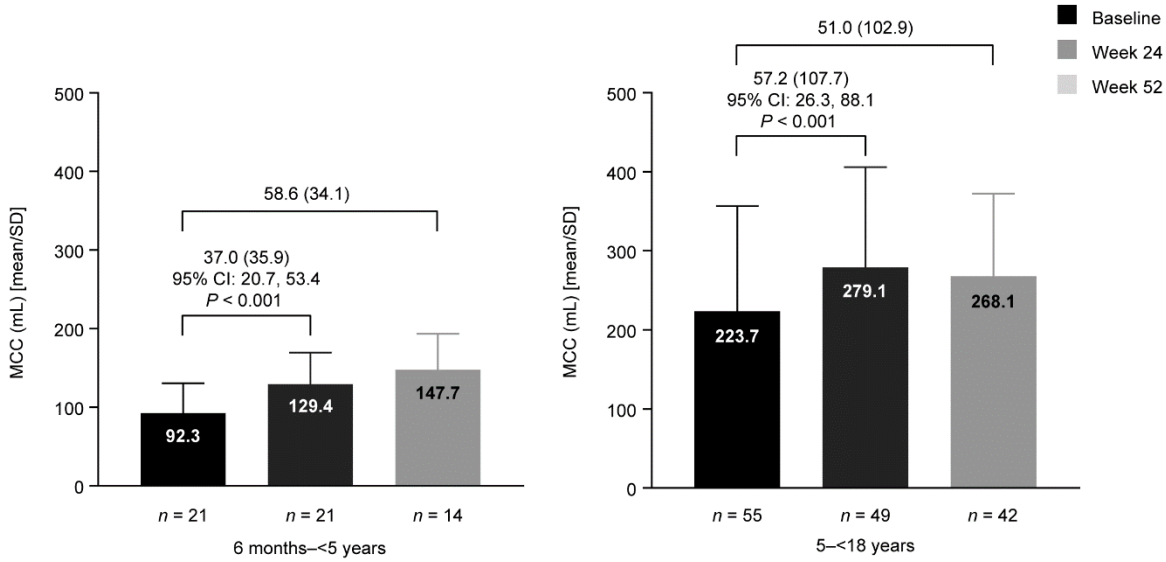

Fig. 2 MCC of patients aged 6 months–<5 years and 5–<18 years at baseline and week 24 (primary endpoint) and week 52 (secondary endpoint; FAS).

Appendices

Appendix A Planned sample size.

The planned sample size was approximately 24 patients aged 6 months–<5 years; ≥20 patients provided 59–84% power to detect a statistically significant difference from baseline to week 24 of between 52 ml and 70 ml in maximum cystometric capacity (MCC), with a standard deviation (SD) of 100 ml. Similarly, 50 patients aged 5–<18 years were planned to be enrolled. A total of 44 patients provided 90% power to detect a statistical significant difference from baseline to week 24 of ≥52 ml, with a SD not >103 ml [1,2].

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Appendix Table A Inclusion and exclusion criteria.

Inclusion criteria in patients aged 6 months–<5 years	Exclusion criteria in patients aged 6 months–<5 years
At screening	
• Male or female aged 6 months–<5 years • Minimum weight: 6 kg • Previous myelomeningocele • Documented diagnosis of NDO confirmed by urodynamic assessments at baseline • Previous history of DSD • Practicing CIC • Adjudged suitable for a regimen of four to six CICs per day fixed for the duration of the study • Able to swallow the study drug	

• Patient's parent(s)/legal representative(s) were able to comply with the study requirements and the concomitant medication restrictions • Written informed consent had to be obtained from the patient's parent(s)/legal guardian(s) prior to any study-related procedures • Patient's parent(s)/legal representative(s) agreed not to allow patient to participate in another interventional study while on treatment and throughout the pre-treatment period	
At screening or baseline	
	• Bladder capacity <25% of expected age-related capacity • Vesicoureteral reflux Grade 3 to 5[a]

	• Known genitourinary condition (other than NDO) that might have caused incontinence • Indwelling urinary catheter within 4 weeks prior to study visit • Undergone bladder augmentation surgery • Surgically-corrected underactive sphincter • Electrostimulation within 2 weeks prior to the visit • Received intravesical botulinum toxin within 9 months prior to screening • UTI confirmed by urinalysis (urine culture containing >100 000 cfu/ml) at baseline • Used prohibited medications • Kidney/bladder stones or other pathology causing urinary symptoms • Central or congenital nephrogenic diabetes insipidus

	• Bowel dysfunction, unless the condition was being actively managed • Fecal impaction • Severe gastrointestinal condition, partial/complete bowel obstruction, decreased motility, or at risk for gastric retention • History of glaucoma • Known or suspected hypersensitivity to solifenacin, any of the excipients used, or previous severe hypersensitivity to any drug • Malnutrition or severely overweight • QTcB >440 ms, a history of QTc prolongation, or at risk of QT prolongation • Severe renal impairment (GFR <30 ml/min)

	• AST or ALT ≥2 times the ULN, or total bilirubin ≥1.5 times the ULN • Any other clinically significant out-of-range urinalysis, biochemistry, or hematology results • Current or previous history of epilepsy • History or presence of any malignancy • Clinically significant or unstable medical condition, which precluded the patient's participation • Participated in another clinical trial and/or had taken an investigational drug within 30 days (or five half-lives of the drug, or the limit set by national law, whichever was longer) prior to the visit • Parent(s)/legal representative(s) of the patient was an employee of the Astellas Group, the CRO involved, or the investigator site that executed the study

	• Breast-fed by a woman taking any prohibited medication/fed with a milk product in which the presence of prohibited medication ingredients could not be excluded

Inclusion criteria in patients aged 5–<18 years	Exclusion criteria in patients aged 5–<18 years
At screening	
• Male or female aged 5–<18 years • Documented diagnosis of NDO • Patient and patient's parent(s)/legal guardian(s) were able to comply with the study requirements and the concomitant medication restrictions • Practicing CIC • Adjudged suitable for a regimen of four to six CICs per day fixed for the duration of the study • Treated with an antimuscarinic drug for ≥6 months • Weight was within normal percentiles for their age • Bowel dysfunction had to be actively managed in afflicted individuals	• Breastfeeding, pregnant, or intended to become pregnant • Known genitourinary condition (other than NDO) that might have caused incontinence • Undergone bladder augmentation surgery • Bladder capacity <25% of expected age-related capacity • Electrostimulation within 2 weeks prior to screening and at any time during the study • Vesicoureteral reflux Grade 3 to 5[a] • Kidney/bladder stones or other pathology causing urinary symptoms • Indwelling urinary catheter within 4 weeks prior to screening

• Able to swallow the study medication • Sexually active female patients of childbearing potential agreed to use a reliable form of birth control for the duration of the study and for ≥1 month afterwards. Sexually active male patients agreed to use a condom for the duration of the study and for ≥1 month afterwards • Written informed consent had to be obtained from the patient's parent(s)/legal representative(s) prior to any study-related procedures; assent (patient) where appropriate was given • Agreed not to participate in another interventional study while on treatment	• One of the following gastrointestinal problems: partial or complete bowel obstruction, decreased motility, or at risk of gastric retention • Existing fecal impaction • QTcB >440 ms, a history of QTc prolongation, or at risk of QT prolongation • History or presence of any malignancy within 5 years prior to screening; any relevant history or presence of malignancy related to urogenital tract • Clinically significant or unstable medical condition or disorder, which, in the opinion of the investigator, precluded the patient's participation • Central or congenital nephrogenic diabetes insipidus • Severe renal impairment (GFR <30 ml/min)

	• AST or ALT ≥2 times the ULN, or total bilirubin ≥1.5 times the ULN • Any other clinically significant out-of-range urinalysis, biochemistry, or hematology results • Known or suspected hypersensitivity to solifenacin (or other antimuscarinics), any of the excipients used, or previous severe hypersensitivity to any drug • Participated in another clinical trial and/or had taken an investigational product within 30 days (or five half-lives of the drug, or the limit set by national law, whichever was longer) prior to screening • Used prohibited medications and restricted medications, when the conditions for restricted medications were not met • Received intravesical botulinum toxin within 9 months prior to screening

	• Parent(s)/legal representative(s) of the patient was an employee of the Astellas Group, the CRO involved, or the investigator site that executed the study • History of glaucoma
At baseline	
• Diagnosis of NDO had to be confirmed by urodynamics demonstrating the presence of involuntary detrusor contractions involving a detrusor pressure increase >15 cmH_2O above baseline	• UTI confirmed by urinalysis (urine culture containing >100 000 cfu/ml) • Recurrent UTI between screening and baseline • DSD or surgically corrected underactive urethral sphincter and did not meet the urodynamic inclusion criteria for NDO

[a] Vesicoureteral reflux Grade 1 and 2 was not included in the exclusion criteria due to urodynamic filling. Ureters are low-resistance vessels and in patients with substantial ureteral reflux, not only the bladder but also the ureters are filled at cystometry. This results in a maximum infusion volume not representing maximum cystometric capacity.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CIC, clean intermittent catheterization; CRO, contract research organization; DSD, detrusor sphincter dyssynergia; GFR, glomerular filtration rate; NDO, neurogenic detrusor

overactivity; QTc, QT interval corrected for heart rate; QTcB, QT interval corrected for heart rate by Bazett's formula; ULN, upper limit of normal; UTI, urinary tract infection.

Appendix Table B Reasons for exclusion from FAS.

Reasons for exclusion	Patients, *n*	
	6 months–<5 years (*n* = 23)	5–<18 years (*n* = 76)
Overall	2[a]	21
Early withdrawal at baseline		
UTI	0	6
QTcB prolongation	1	7
Withdrawal by patient	0	1
First urodynamic assessment after solifenacin intake	0	3
Non-eligibility for urodynamic assessment		
No baseline urodynamic assessment	0	1
UTI during post-baseline assessment	0	1
Inconsistent filling rates between baseline and post-baseline urodynamic assessment	0	1
Unreliable baseline urodynamic trace because of abdominal pressure changes	0	1

[a] The reason for exclusion was unknown for one patient.

FAS, full analysis set; QTcB, QT interval corrected for heart rate by Bazett’s formula; UTI, urinary tract infection.

Appendix Table C Incidence of SAEs (SAF).

	Patients, *n*	
	6 months–<5 years (*n* = 23)	5–<18 years (*n* = 76)
Overall	3	7
Dengue fever	0	1
Hypertension	0	1
Megacolon	0	1
Orchitis	0	1
Pharyngitis	1	0
Spinal cord operation	0	1
Tachycardia	0	1
Teratoma	1	0
Tethered cord syndrome	0	1
UTI bacterial	0	1
UTI NOS	1	0
Vomiting	1	0

Patients may have experienced >1 SAE.

NOS, not otherwise specified; SAE, serious adverse event; SAF, safety analysis set; UTI, urinary tract infection.

Appendix Table D Vital signs (SAF).

	6 months–<5 years (*n* = 23)	5–<18 years (*n* = 76)
Mean systolic blood pressure, mmHg		
Baseline (SD)	97.1 (10.4)	108 (12.3)
Week 52 (SD)	102 (11.4)	108 (11.9)
Change from baseline (SD)	4.7 (10.2)	−0.0 (11.1)
Mean diastolic blood pressure, mmHg		
Baseline (SD)	63.1 (6.4)	69.1 (11.1)
Week 52 (SD)	64.9 (10.0)	67.1 (10.3)
Change from baseline (SD)	1.6 (8.2)	−1.7 (9.9)
Mean pulse rate, bpm		
Baseline (SD)	113 (17.4)	89.3 (18.0)
Week 52 (SD)	109 (14.0)	87.9 (14.3)
Change from baseline (SD)	−3.2 (11.6)	−2.2 (12.3)
Mean body temperature, °C		
Baseline (SD)	36.5 (0.3)	36.4 (0.4)
Week 52 (SD)	36.6 (0.3)	36.4 (0.4)
Change from baseline (SD)	0.1 (0.3)	0.0 (0.4)

SAF, safety analysis set; SD, standard deviation.

Appendix Table E 12-lead ECGs (SAF).

Criteria	6 months–<5 years (*n* = 23)	5–<18 years (*n* = 76)
PR duration (ms)		
Baseline, mean (SD)	125 (12.6)	135 (14.4)
Week 52, mean (SD)	126 (13.4)	140 (15.0)
Change from baseline, mean (SD)	0.7 (6.6)	3.5 (7.3)
RR duration (ms)		
Baseline, mean (SD)	560 (57.5)	711 (147)
Week 52, mean (SD)	561 (73.6)	735 (130)
Change from baseline, mean (SD)	−0.7 (61.4)	30.4 (106)
QRS duration (ms)		
Baseline, mean (SD)	76.8 (4.2)	84.1 (5.3)
Week 52, mean (SD)	76.5 (5.3)	84.9 (4.2)
Change from baseline, mean (SD)	0.0 (3.7)	0.8 (3.7)
QT duration		
Baseline, mean (SD)	312 (14.5)	350 (31.1)
Week 52, mean (SD)	315 (15.0)	356 (30.0)
Change from baseline, mean (SD)	3.3 (14.6)	7.9 (23.8)
QTcB (ms)		
Baseline, mean (SD)	419 (13.3)	419 (16.7)
Week 52, mean (SD)	422 (13.0)	418 (18.9)
Change from baseline, mean (SD)	4.7 (13.0)	0.3 (12.5)

QTcF (ms)		
Baseline, mean (SD)	380 (10.9)	394 (15.1)
Week 52, mean (SD)	383 (8.0)	395 (17.4)
Change from baseline, mean (SD)	4.2 (10.0)	3.2 (11.8)
Heart rate (beats/min)		
Baseline, mean (SD)	109 (10.9)	88.2 (17.4)
Week 52, mean (SD)	109 (13.4)	84.6 (16.2)
Change from baseline, mean (SD)	0.3 (11.9)	−3.94 (12.7)

The baseline value is the mean of the triplicate ECG measurements at visit 1 and visit 2 for patients aged 6 months–<5 years and visit 2 and visit 3 for patients aged 5–<18 years.

ECG, electrocardiogram; QTcB, QT interval corrected for heart rate by Bazett's formula; QTcF, QT interval corrected for heart rate by Fridericia's formula; SAF, safety analysis set; SD, standard deviation.

Appendix Table F Treatment discontinuation (SAF).

Parameter	Category	Patients, *n* (%)	
		6 months–<5 years (*n* = 23)	5–<18 years (*n* = 76)
Treatment discontinuation	Yes	2 (8.7)	18 (23.7)
	No	21 (91.3)	58 (76.3)
Primary reason for discontinuation	Registered but never received/dispensed study drug	0	0
	AE	0	4 (5.3)
	Lack of efficacy	1 (4.3)	0
	Protocol violation[a]	1 (4.3)	10 (13.2)
	Withdrawal by patient	0	4 (5.3)

[a] The baseline test results were only available a few days after baseline. These patients should not have started the study due to exclusion criteria violations (6 months–<5 years: one patient had an average QTcB >440 ms, a history of QTc prolongation, or was at risk of QT prolongation; 5–<18 years: six patients had UTIs at baseline and four patients had an average QTcB >440 ms, a history of QTc prolongation, or were at risk of QT prolongation).

AE, adverse event; QTc, QT interval corrected for heart rate; QTcB, QT interval corrected for heart rate by Bazett's formula; SAF, safety analysis set; UTI, urinary tract infection.

Appendix Table G Change from baseline in QTcB (SAF).

Criteria	6 months–<5 years (*n* = 23)	5–<18 years (*n* = 76)
Value at baseline, *n* (%)		
N	23	76
<450 ms	22 (95.7)	76 (100)
450–<480 ms	1 (4.3)	0
Value at week 52, *n* (%)		
N	20	57
<450 ms	20 (100.0)	56 (98.2)
450–<480 ms	0	1 (1.8)
Change from baseline to week 52, *n* (%)		
N	20	57
<0	9 (45.0)	29 (50.9)
0–<30 ms	9 (45.0)	27 (47.4)
30–<60 ms	2 (10.0)	1 (1.8)

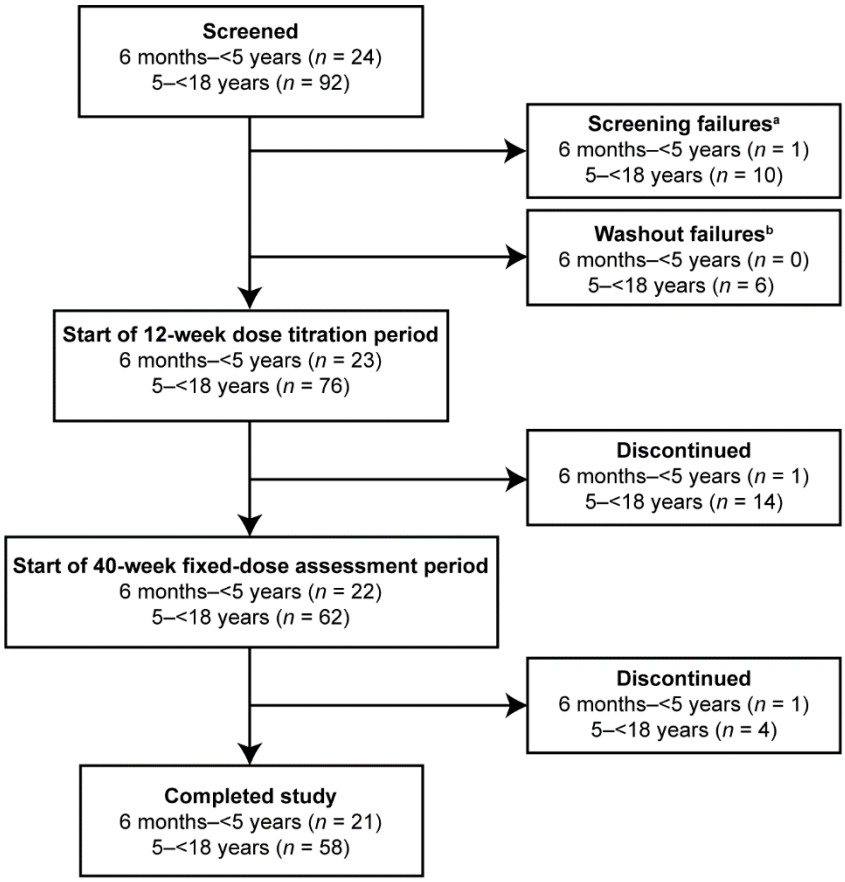
QTcB, QT interval corrected for heart rate by Bazett's formula; SAF, safety analysis set.

Appendix Table H Change from baseline in cognitive function (SAF).

Test[a]	Change from baseline in score			
	24 weeks		52 weeks	
	Score	*P*	Score	*P*
Detection test	−0.04	< 0.001	−0.05	< 0.001
Identification test	−0.03	0.012	−0.05	< 0.001
One card learning test	0.02	0.268	0.05	0.007
One back test	−0.03	0.005	−0.04	< 0.001

[a] Decrease from baseline indicates an improvement except for the one card learning test where an increase in score is indicative of improvement.

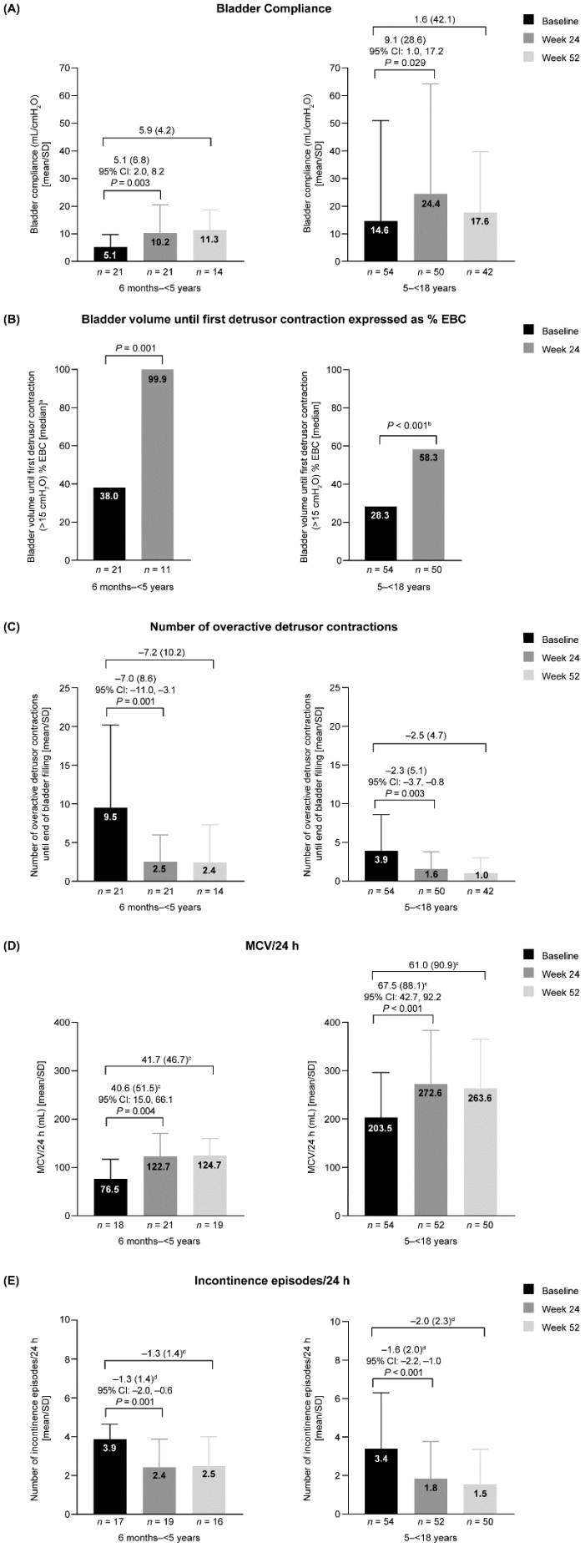
SAF, safety analysis set.



Appendix Fig. A Patient disposition.

[a] Any enrolled patient who discontinued the study at/prior to visit 2, or who entered the washout period, but subsequent results from visit 2 indicated that the patient was not eligible to enter the washout period and thereby discontinued the study.

[b] Any patient who was not a screening failure and who discontinued the study at/prior to visit 3, or who entered the treatment period but did not take any dose of solifenacin and discontinued the study because subsequent results from visit 3 indicated that the patient was not eligible to enter the treatment period.


(A)
Bladder Compliance
Baseline
Week 24
Week 52
Bladder compliance (mL/cmH2O) [mean/SD]
5.9 (4.2)
5.1 (6.8)
95% CI: 2.0, 8.2
P = 0.003
5.1
10.2
11.3
n = 21
n = 21
n = 14
6 months–<5 years
1.6 (42.1)
9.1 (28.6)
95% CI: 1.0, 17.2
P = 0.029
14.6
24.4
17.6
n = 54
n = 50
n = 42
5–<18 years
(B)
Bladder volume until first detrusor contraction expressed as % EBC
Baseline
Week 24
Bladder volume until first detrusor contraction (>15 cmH2O) % EBC [median]a
P = 0.001
38.0
99.9
n = 21
n = 11
6 months–<5 years
P < 0.001b
28.3
58.3
n = 54
n = 50
5–<18 years
(C)
Number of overactive detrusor contractions
Baseline
Week 24
Week 52
Number of overactive detrusor contractions until end of bladder filling [mean/SD]
−7.2 (10.2)
−7.0 (8.6)
95% CI: −11.0, −3.1
P = 0.001
9.5
2.5
2.4
n = 21
n = 21
n = 14
6 months–<5 years
−2.5 (4.7)
−2.3 (5.1)
95% CI: −3.7, −0.8
P = 0.003
3.9
1.6
1.0
n = 54
n = 50
n = 42
5–<18 years
(D)
MCV/24 h
Baseline
Week 24
Week 52
MCV/24 h (mL) [mean/SD]
41.7 (46.7)c
40.6 (51.5)c
95% CI: 15.0, 66.1
P = 0.004
76.5
122.7
124.7
n = 18
n = 21
n = 19
6 months–<5 years
61.0 (90.9)c
67.5 (88.1)c
95% CI: 42.7, 92.2
P < 0.001
203.5
272.6
263.6
n = 54
n = 52
n = 50
5–<18 years
(E)
Incontinence episodes/24 h
Baseline
Week 24
Week 52
Number of incontinence episodes/24 h [mean/SD]
−1.3 (1.4)e
−1.3 (1.4)d
95% CI: −2.0, −0.6
P = 0.001
3.9
2.4
2.5
n = 17
n = 19
n = 16
6 months–<5 years
−2.0 (2.3)d
−1.6 (2.0)d
95% CI: −2.2, −1.0
P < 0.001
3.4
1.8
1.5
n = 54
n = 52
n = 50
5–<18 years

Appendix Fig. B Secondary efficacy variables in patients aged 6 months–<5 years and 5–<18 years: (A) bladder compliance, (B) bladder volume until first detrusor contraction (>15 cmH_2O) as a percentage of EBC, (C) number of overactive detrusor contractions (>15 cmH_2O) until leakage or end of bladder filling, (D) MCV/24 h and (E) incontinence episodes/24 h (FAS).

Bladder compliance was calculated by dividing volume change by change in detrusor pressure [1]. If an overactive contraction was noted, the underlying basal detrusor pressure was used. Filling rates were defined as 5% of the patient's MCV (6 months–<2 years), 5% of the EBC (2–<5 years), or 30 ml/min (5–<18 years) except for patients with capacities of approximately 150 ml (15 ml/min). EBC was calculated using Hjälmås formula [2] (30 + [age in years x 30] [maximum 390 ml]).

Data were analyzed using a paired two-sided *t*-test at $\alpha = 0.05$ significance level.

[a] *Post hoc* analysis was performed to include patients who did not have detrusor contraction.

[b] Wilcoxon signed-rank test was used to analyze the statistical significance of the median change from baseline in bladder volume.

[c] Change in MCV from baseline to week 24 and week 52 was evaluated in 18 and 16 patients aged 6 months–<5 years, respectively; and 51 and 49 patients aged 5–<18 years, respectively.

[d] Change in incontinence episodes/24 h from baseline to week 24 and week 52 was evaluated in 17 and 14 patients aged 6 months–<5 years, respectively; and 51 and 49 patients aged 5–<18 years, respectively.

CI, confidence interval; EBC, expected bladder capacity; FAS, full analysis set; MCV, maximum catheterized volume; SD, standard deviation.

References

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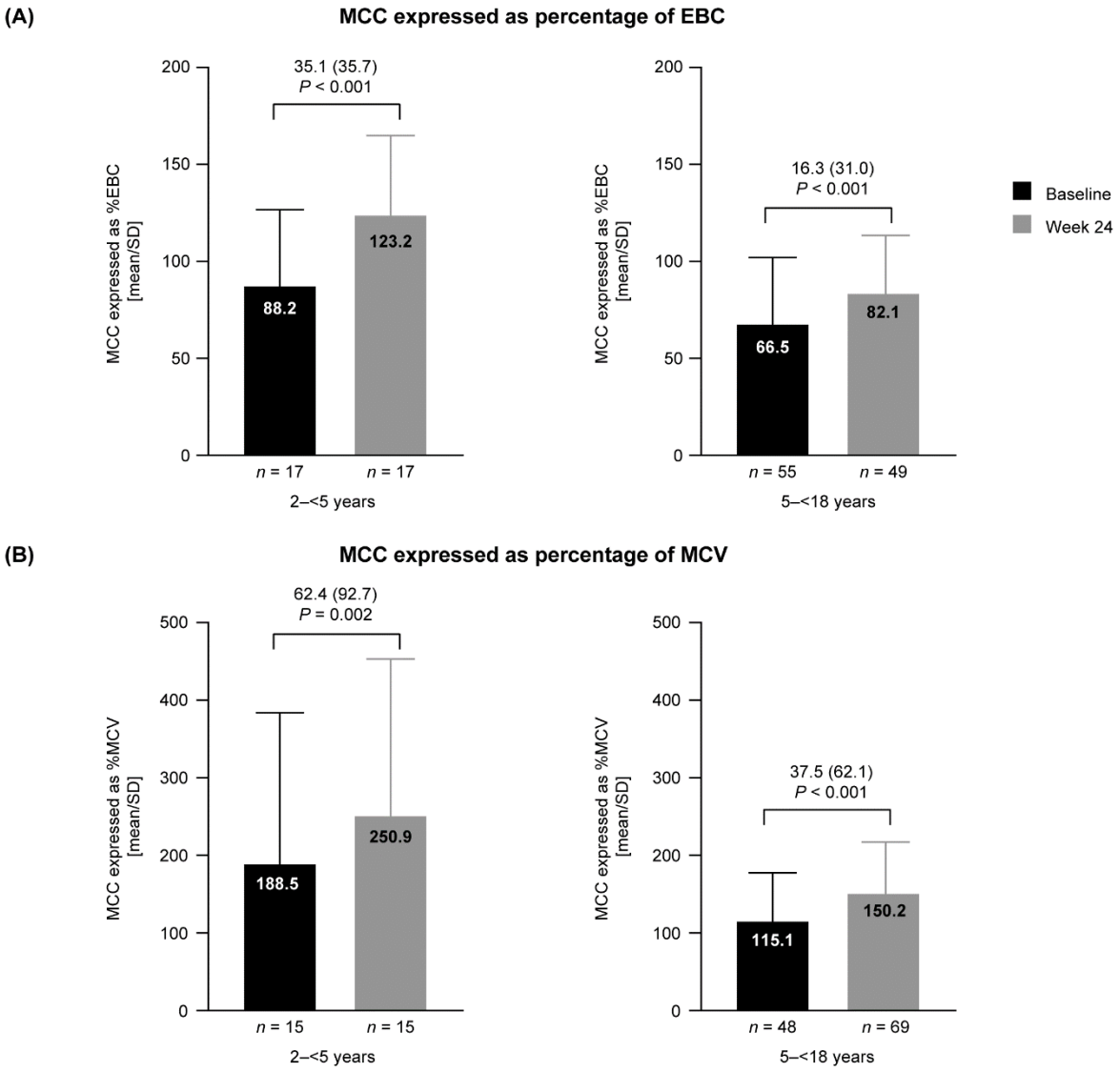

Appendix Fig. C MCC expressed as a percentage of (A) EBC and (B) MCV.

EBC, expected bladder capacity; MCC, maximum cystometric capacity; MCV, maximum catheterized volume; SD, standard deviation.