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Solifenacin in Children and Adolescents with Overactive Bladder: Results of a Phase 3 Randomised Clinical Trial

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Abstract

Background: Solifenacin, an effective, well-tolerated treatment for adult overactive bladder (OAB) symptoms, has not been evaluated in placebo-controlled paediatric clinical trials.
Objectives: To evaluate the efficacy and safety of once-daily oral solifenacin suspension in OAB patients aged 5–<12 yr (children) and 12–<18 yr (adolescents).
Design, setting, and participants: The study involved a 4-wk urotherapy run-in followed by 1:1 randomisation to 12-wk double-blind solifenacin or placebo treatment alongside urotherapy.
Intervention: Solifenacin paediatric equivalent doses (PEDs) of adult doses: 2.5 mg, 5 mg, 7.5 mg, and 10 mg. The starting dose was PED 5 mg; all patients were titrated to an optimum dose at 3-wk intervals over 9 wk, resulting in ≥3 wk at the optimum dose before end of treatment (EoT).
Outcome measurements and statistics: Superiority of solifenacin versus placebo in change from baseline to EoT for mean volume voided/micturition (MVV, primary endpoint); daytime maximum volume voided/micturition (DMaxVV); incontinence episodes (mean/24 h); mean number of incontinence-free days or nights/7 d; micturition frequency; and Micturition frequency adjusted for baseline total voided volume (VT_B) as an exploratory parameter). Efficacy parameters were analysed using analysis of covariance. Safety parameters (treatment-emergent adverse events, serious adverse events, laboratory variables, vital signs, electrocardiogram, postvoid residual volume) are summarised using descriptive statistics.
Results and limitations: In children, solifenacin was superior to placebo in terms of the change from baseline to EoT for MVV (solifenacin-placebo difference 12.1 ml, 95% confidence interval [CI] 0.2–24.0; $p = 0.046$), DMaxVV (difference in adjusted mean change from baseline for solifenacin–placebo 31.9 ml, 95% CI 4.3–59.5; $p = 0.024$), VT_B-adjusted micturition frequency ($p = 0.028$). Other endpoints were not significantly different. Solifenacin was well tolerated. For adolescents, it was not possible to draw firm efficacy conclusions because of the low numbers recruited.
Conclusions: Once-daily solifenacin oral suspension in children with OAB was superior to placebo for MVV (primary efficacy endpoint) and was well tolerated.
Patient summary: In this 12-wk study, a once-daily oral suspension of solifenacin in children aged 5–<12 yr with overactive bladder was superior to placebo in increasing mean volume voided/micturition, the primary efficacy variable in the study. Solifenacin was well tolerated, with a low incidence of dry mouth and constipation.
This study is registered at ClinicalTrials.gov as NCT01565707.

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1. Introduction

Overactive bladder (OAB) is a bothersome condition in the paediatric population, with limited treatment options. Urotherapy is the recommended first-line treatment [1]; when urotherapy alone is insufficient, adjunctive antimuscarinic therapy is recommended [2]. Oxybutynin is currently the only widely available antimuscarinic approved for paediatric OAB patients. Trospium is approved for OAB patients aged ≥12 yr and propiverine for children aged ≥5 yr (Germany, Czech Republic, and Slovakia only). In many children, intolerable side effects (eg, constipation, dry mouth, altered behaviour, headache, blurred vision, and flushed cheeks) result in early treatment discontinuation [3,4]. Furthermore, central nervous system side effects, including cognitive impairment, have been reported for oxybutynin [4–6]. Antimuscarinic dose flexibility in the paediatric population is problematic, although liquid oxybutynin is available in some countries. There is a need for new, effective, and well-tolerated paediatric OAB therapies with convenient, flexible dosing.

Solifenacin succinate (VESIcare®, Astellas Pharma, Leiden, The Netherlands) is a competitive muscarinic receptor antagonist approved worldwide at daily doses of 5 mg and 10 mg in tablet formulation for the treatment of urinary frequency, incontinence, or urgency associated with adult OAB, and has demonstrated good efficacy and tolerability in adult clinical trials [7–16]. Small studies without a placebo control suggest that solifenacin may be useful for paediatric OAB [17–20]. A once-daily oral suspension of solifenacin has been developed that allows greater dosing flexibility in all patients.

We describe efficacy and safety data for a phase 3 study in OAB patients aged 5–<18 yr receiving once-daily solifenacin oral suspension (the LION study).

2. Patients and methods

2.1. Study design

This phase 3, double-blind, randomised, placebo-controlled, sequential, dose-titration study was conducted in 16 countries worldwide from June 2012 to January 2014 in children aged 5–<12 yr and adolescents aged 12–<18 yr diagnosed with OAB according to the International Children's Continence Society criteria (urgency with/without incontinence or increased voiding frequency) [1] and who had four or more episodes of daytime incontinence during a 7-d prebaseline diary period.

Patients who satisfied the screening inclusion/exclusion criteria at visit 1 (Supplementary Table 1) underwent a 4-wk urotherapy run-in period (Supplementary material), including a timed schedule of seven voids/24 h. After 2 wk (visit 2), single-blind placebo treatment was combined with urotherapy (Fig. 1), after which (visit 3, baseline) patients who still met the inclusion/exclusion criteria were randomised 1:1 by country to receive double-blind solifenacin oral suspension or placebo once daily for 12 wk alongside urotherapy (Supplementary material). The solifenacin starting dose, based on the patient's weight at screening, aimed to deliver steady-state plasma drug exposure equivalent to that of the 5-mg tablet dose in adults (paediatric equivalent dose 5 mg, PED 5; Table 1). The solifenacin or placebo dose could be titrated up or down every 3 wk up to a maximum of three times (week 9) to a final dose of PED 2.5, PED 5, PED 7.5 or PED 10 (equivalent to 2.5, 5.0, 7.5 or 10.0 mg, respectively, in adults). Treatment was

Table 1 – Predicted paediatric equivalent doses and corresponding administration dose [a]

Weight range	Administration dose (mg) [b]			
	PED 2.5 or PCB	PED 5 or PCB	PED 7.5 or PCB	PED 10 or PCB
<14 kg	0.6	1.4	2.2	2.8
14–20 kg [a]	1	1.8	2.8	3.6
21–31 kg [a]	1.2	2.6	3.8	5.2
32–50 kg [a]	1.8	3.4	5.2	7
51–69 kg	2.2	4.6	6.8	9
>69 kg	2.4	5	7.4	10

PCB = placebo; PED = paediatric equivalent dose. Target exposure was derived from population PK studies in adult clinical trials

[a] In children who experienced an event that was considered possibly treatment-related and that was either bothersome or led to medical intervention, the dose could be titrated down to a minimum of PED 2.5. Dose titration was not required if patients remained incontinence-free, and, for those aged 12–<18 yr, if they also had no grade 3 urgencies on the Patient Perception of Intensity of Urgency Scale [17]. For any patient with incontinence or for patients aged 12–<18 yr free of incontinence but with grade 3 urgencies, the dose could be titrated up if the maximum voided volume was less than the age-related bladder capacity ([age + 1] × 30 ml). Titration could be undertaken every 3 wk up to a maximum of three times, or until the optimum dose was achieved.

[b] Aqueous suspension containing 1 mg/ml solifenacin succinate.

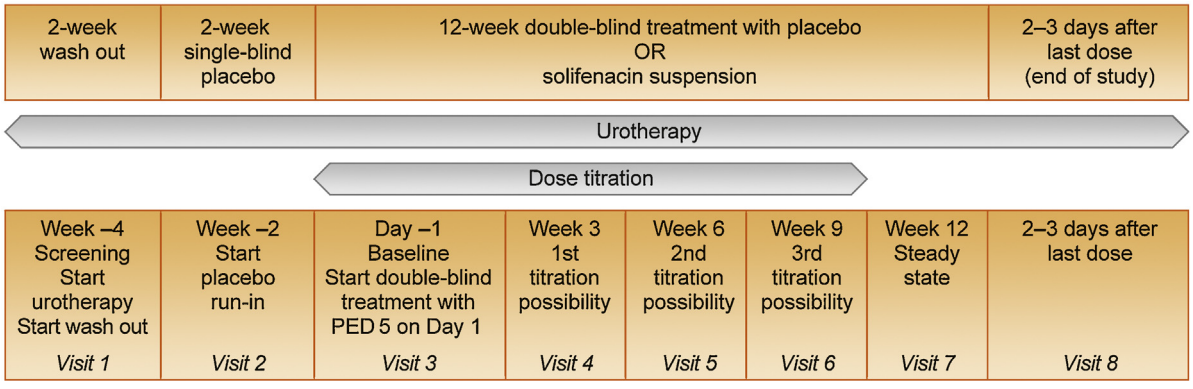

Fig. 1 – Study flow chart. PED = paediatric equivalent dose.

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