Efficacy of solifenacin, mirabegron and combination therapy in children with daytime urinary incontinence (BeDry): Protocol for a randomized single-blinded controlled trial

Ann-Kristine Mandøe Svendsen, Søren Hagstrøm, Kristina Nauheimer Thorsteinsson, Konstantinos Kamperis, Anne Estrup Olesen, Luise Borch

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Ann-Kristine Mandøe Svendsen[1, 2]; Søren Hagstrøm[3, 4*]; Kristina Nauheimer Thorsteinsson[3, 4*]; Konstantinos Kamperis[5*]; Anne Estrup Olesen[4, 6*]; Luise Borch[1, 2*]

[1] Department of Pediatrics and Adolescent Medicine, Gødstrup Hospital, Denmark Herning DK
[2] NIDO, Centre for Research and Education, Gødstrup Hospital Herning DK
[3] Department of Pediatrics and Adolescent Medicine, Aalborg University Hospital Aalborg DK
[4] Department of Clinical Medicine, Aalborg University Aalborg DK
[5] Department of Pediatrics and Adolescent Medicine, Aarhus University Hospital Aarhus DK
[6] Department of Clinical Pharmacology, Aalborg University Hospital Aalborg DK
[*] these authors contributed equally

Corresponding Author:
Ann-Kristine Mandøe Svendsen

Department of Pediatrics and Adolescent Medicine, Gødstrup Hospital, Denmark
Herning
DK

Abstract

Background: According to International Children's Continence Society (ICCS), first-line treatment of children with daytime urinary incontinence is standard urotherapy, eventually followed by pharmacotherapy of anticholinergics. The effect of medical treatment is sparsely investigated and primarily in non-randomized trials.

Objective: The primary objective is to evaluate if (1) combination therapy of solifenacin and mirabegron in low doses is superior to monotherapy of solifenacin in high dose and if (2) combination therapy of mirabegron and solifenacin in low doses is superior to monotherapy of mirabegron in high dose in treatment of daytime urinary incontinence among children aged 5 to 14 years who are none complete responders to respectively monotherapy of solifenacin in low dose or monotherapy of mirabegron in low dose.

The secondary objective is to evaluate the treatment response of combination therapy of solifenacin and mirabegron in low doses, monotherapy in high dose and monotherapy in low doses as supplementary comparisons. Additionally, the secondary objective is to evaluate side effects, safety, and tolerability of the medical treatment as well as the effect of treatment on well-being and quality of life.

Methods: Children aged 5-14 years diagnosed with daytime urinary incontinence refractory to standard urotherapy will be randomized to four treatment groups, randomization 1:1:1:1. Initially two groups will receive solifenacin 5 mg and two groups will receive mirabegron 25 mg. After 6 weeks, non-complete respondsers will receive add-on treatment according to their primary randomization group; group 1A will reviece solifenacin 5 mg and add-on solifenacin 5 mg, group 1B will receive solifenacin 5 mg and add-on mirabegron 25 mg, group 2A will receive mirabegron 25 mg and add-on mirabegron 25 mg, group 2B will receive mirabegron 25 mg and add-on solifenacin 5 mg. Total treatment period will be 18 weeks.
The primary endpoint measure is treatment response assessed by change from visit 2 to end of study, according to number of wet days pr. 7 days by DryPie.

Results: Participants will be included from June 2024 to December 2027.

Conclusions: The trial has the potential to optimize medical treatment of children with daytime urinary incontinence, to shorten the treatment period, diminish side effects and minimized unnecessary medical expenses. Clinical Trial: EU CT 2023-510187-13-00

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Title:
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ABSTRACT

Background

According to International Children's Continence Society (ICCS), first-line treatment of children with daytime urinary incontinence is standard urotherapy, eventually followed by pharmacotherapy of anticholinergics. The effect of medical treatment is sparsely investigated and primarily in nonrandomized trials.

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Children aged 5-14 years diagnosed with daytime urinary incontinence refractory to standard urotherapy will be randomized to four treatment groups, randomization 1:1:1:1. Initially two groups will receive solifenacin 5 mg and two groups will receive mirabegron 25 mg. After 6 weeks, noncomplete respondsers will receive add-on treatment according to their primary randomization group; group 1A will reviece solifenacin 5 mg and add-on solifenacin 5 mg, group 1B will receive solifenacin 5 mg and add-on mirabegron 25 mg, group 2A will receive mirabegron 25 mg and addon mirabegron 25 mg, group 2B will receive mirabegron 25 mg and add-on solifenacin 5 mg. Total treatment period will be 18 weeks.
The primary endpoint measure is treatment response assessed by change from visit 2 to end of study, according to number of wet days pr. 7 days by DryPie.

Results

Recruitment began ultimo June 2024 and will continue until 236 patients are included, which is expected by September 2026. As of primary February 2025, 58 participants are included.

Conclusion

The trial has the potential to optimize medical treatment of children with daytime urinary

incontinence, to shorten the treatment period, diminish side effects and minimized unnecessary medical expenses.

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Introduction

Background and rationale

Daytime urinary incontinence (DUI) is affecting up to 1 out of 5 children aged 5 to 7 years[1] [2] [3] [4], and 4.5% of children and adolescents aged 11-16 years[3] [4]. Urinary incontinence is most often a physically benign condition[2]. Nevertheless, it is associated with a considerable psychological burden, as it leads to poor self-esteem and quality of life among affected children, leading to psychological failure to thrive[5] [6].

The most common cause of DUI is an overactive bladder (OAB)[2] [7]. The International Children's Continence Society (ICCS) defines OAB as a condition with urinary urgency with or without DUI among children and adolescents without competitive pathology explaining the symptoms, such as

neurogenic detrusor overactivity or urinary tract infection[8].
Treatment often requires a multidisciplinary effort involving contributors in the healthcare system, at home and at day-care/school. First-line treatment of urinary incontinence is urotherapy, aiming at improving the bladder reservoir function and the voluntary bladder control[2]. If urotherapy is insufficient for achieving continence, second-line treatment in most clinical settings is adadition of pharmacological treatment aiming at suppressing bladder smooth muscle contraction[2].
Solifenacin and mirabegron act on the bladder through different mechanisms. Solifenacin is an antimuscarinic agent that selectively inhibits M2/M3 muscarinic receptors in the bladder [2]. Mirabegron is a β3-adrenergic receptor agonist that stimulates β3 receptors in the detrusor muscle. While solifenacin decreases bladder contractions by inhibiting parasympathetic activity, mirabegron promotes bladder relaxation through sympathetic stimulation [9].
In Denmark the current pharmacological therapy consists of an antimuscarinic as solifenacin, or a beta3-adrenoreceptor agonist as mirabegron. If monotherapy of solifenacin or mirabegron is without sufficient effect, the child is treated with a combination of solifenacin and mirabegron. According to expert opinions, the current pharmacological treatment strategy in Denmark typically follows this sequence: Initially, solifenacin is prescribed at 5 mg daily, with an increase to 10 mg depending on therapeutic response. If monotherapy in high dose proves insufficient, add-on therapy with mirabegron at 25 mg daily is introduced and may be increased to 50 mg depending on treatment effect. Occasionally mirabegron monotherapy is used as an alternative second step before combination therapy.
Solifenacin and mirabegron are widely used off-label in the pediatric population, and only a few studies dealt with the efficacy and tolerability of these agents[10] [11] [12] [13] [14]. Only one study has evaluated combination therapy[14].
Since the pharmacological approach is widely used off-label in pediatric departments, an evidencebased treatment approach of pharmacological therapy is highly needed. This study aims to evaluate the efficacy, safety and tolerability of solifenacin, mirabegron and combination of solifenacin and mirabegron in pediatric patients with DUI.

Objectives

We hypothesize that combination therapy with solifenacin 5 mg and mirabegron 25 mg is effective in reduction of DUI episodes over 18-week treatment period compared to baseline, and that combination therapy in low dose is superior to high dose of either solifenacin 10 mg or mirabegron 50 mg.
The primary objective is to evaluate the effect of high dose anticholinergic monotherapy (solifenacin 10 mg) compared to low dose combination therapy of anticholinergic and beta3adrenoreceptor agonist combination therapy (solifenacin 5 mg and mirabegron 25 mg), and high dose monotherapy beta3-adrenoreceptor agonist (mirabegron 50 mg) compared to low dose anticholinergic and beta3-adrenoreceptor agonist combination therapy of (solifenacin 5 mg and mirabegron 25 mg) for treatment of daytime urinary incontinence in children aged 5 to 14 years, who are non-complete responders to standard urotherapy and low dose anticholinergic or beta3adrenoreceptor agonist monotherapy.
The secondary objective is to evaluate the treatment response of combination therapy of solifenacin and mirabegron in low doses, monotherapy in high dose and monotherapy in low doses as supplementary comparisons. Additionally, the secondary objective is to evaluate side effects, safety, and tolerability of the medical treatment as well as the effect of treatment on well-being and quality of life.

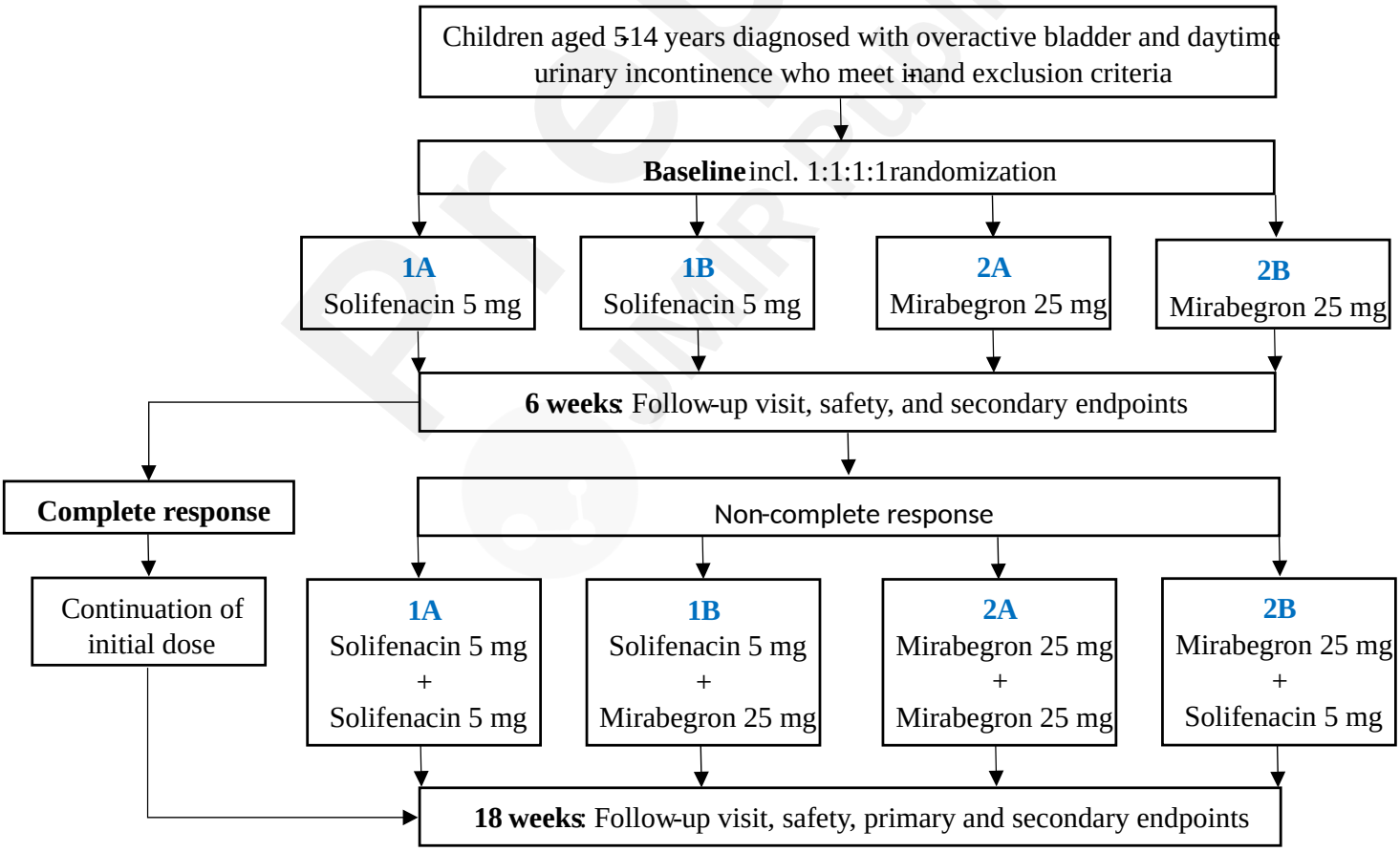
Methods

Study design

The BeDry study is designed as a multicenter, randomized, single-blind, controlled clinical trial. Included children will be randomized 1:1:1:1 to one of four treatment groups. The study duration for each participant will be 18 weeks and encompasses 3 visits to the outpatient clinic. See Figure 1 for an overview of the study design. Children aged 5 to 14 years are diagnosed with overactive bladder and DUI will be included if they meet criteria for inclusion.

Recruitment will take place from five outpatient clinics at pediatric departments in Denmark: Aarhus University Hospital, Aalborg University Hospital, Regional Hospital Kolding, Regional Hospital Esbjerg and Gødstrup Hospital.

Figure 1. Participant flow chart



Eligibility criteria

Inclusion and exclusion criteria for this study are provided in figure 2.

Figure 2. In- and exclusion criteria

Inclusion
1. The participants' custody holder(s) must voluntarily sign and date an informed consent prior to initiation of any study specific procedures. 2. Age 5 to 14 years (inclusive) at the time of inclusion. 3. OAB as per ICCS criteria 4. At least 2 DUI episodes per week 5. Inadequate effect of at least 4 weeks urotherapy (non-pharmacological treatment) 6. No previous treatment with solifenacin, mirabegron or bladder/sphincter botulinum toxin injections 7. No current constipation as per ROME IV criteria or fecal incontinence (laxative treatment is accepted) 8. Per investigator's judgment, the participant can swallow or can learn to swallow study medication
Exclusion
1. Inability of the patent(s) or legal guardian(s) to understand the Danish written and oral information 2. Known or suspected hypersensitivity to study medication 3. Any contraindication to the use of the study medication 4. Known urogenital anatomical abnormalities affecting lower urinary tract function 5. Known kidney or bladder stones 6. Known diabetes insipidus 7. Ongoing symptomatic urinary tract infection 8. Recurrent urinary tract infection or ongoing prophylactic antibiotic treatment 9. Known QTc prolongation, QTc >460 ms, or risk of QTc prolongation (hypokalaemia, exercise-induced syncope, or familial long QT syndrome) 10. Other significant ECG abnormalities 11. Know hypertension 12. ≤3 daily voiding, evaluated by 48-hour frequency-volume chart 13. Uroflowmetry suggestive of other pathology than OAB (staccato-shaped, interruptedshaped, or plateau-shaped curve) 14. Post-void residual >50 ml after double voiding

15. Dipstick haematuria (≥2+ erythrocytes) or macroscopic haematuria
16. Pregnancy or breastfeeding
17. Female subjects of childbearing potential
18. Ongoing constipation according to Rome IV-criteria which is intractable to medication or fecal incontinence
19. Inability to swallow study medication
20. Use of any medication during study period, except permitted medication

Intervention

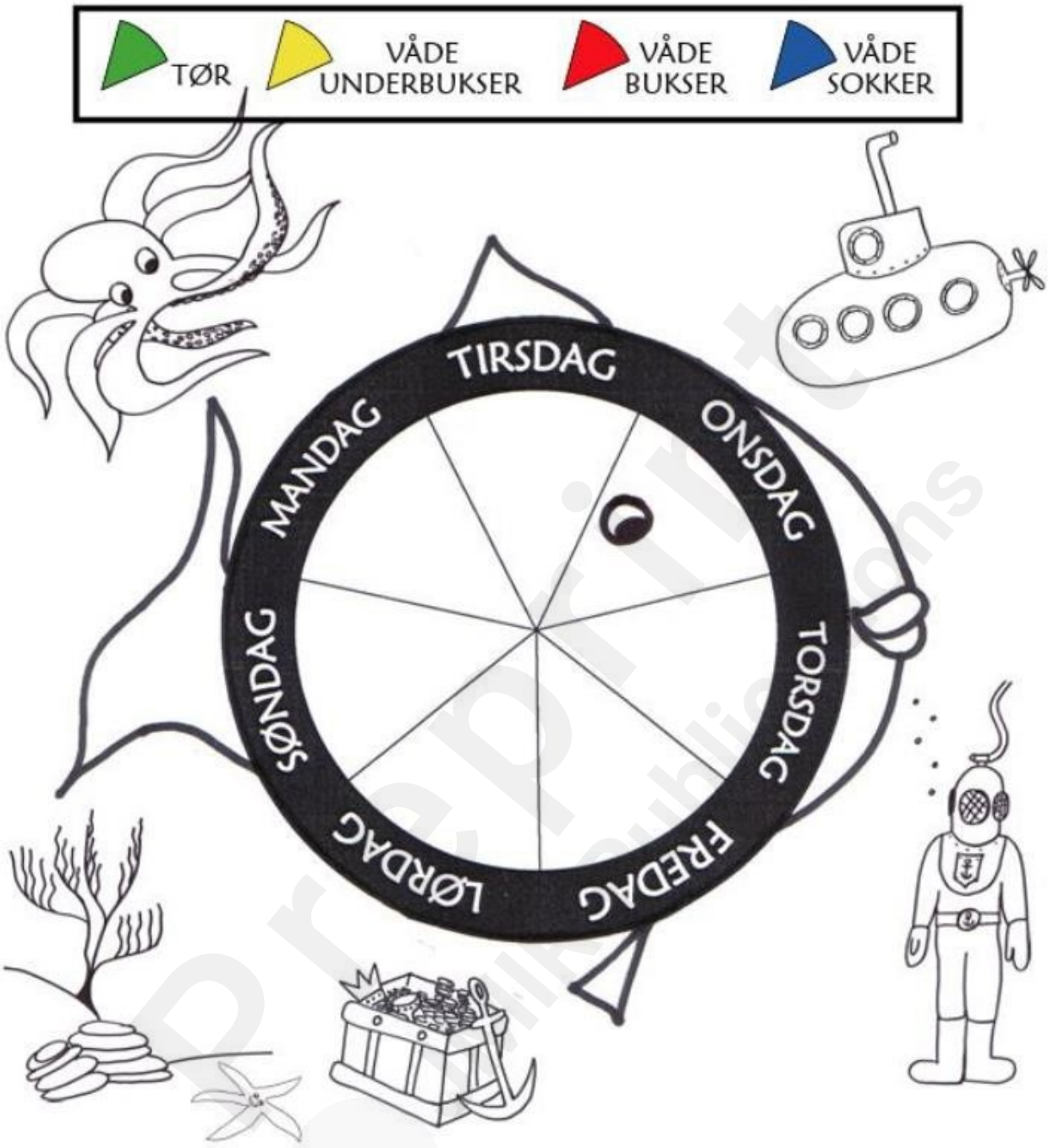
Eligible children will be randomized 1:1:1:1 to one of the following four treatment groups:

- 1A: Solifenacin 5 mg (and if non-complete response after 6 weeks add-on solifenacin 5 mg)
- 1B: Solifenacin 5 mg (and if non-complete response after 6 weeks add- on mirabegron 25 mg)
- 2A: Mirabegron 25 mg (and if non-complete response after 6 weeks add-on mirabegron 25 mg)
- 2B: Mirabegron 25 mg (and if non-complete response after 6 weeks add-on solifenacin 5 mg)

All participants will initially receive low dose monotherapy. Two groups will receive solifenacin 5 mg and two groups will receive mirabegron 25 mg. After 6 weeks the treatment outcome will be evaluated based on number of wet days per week assessed by DryPie[15] (see figure 3). Noncomplete respondsers will receive add-on treatment according to their primary randomization group; group 1A will reviece solifenacin 5 mg and add-on solifenacin 5 mg, group 1B will receive solifenacin 5 mg and add-on mirabegron 25 mg, group 2A will receive mirabegron 25 mg and addon mirabegron 25 mg, group 2B will receive mirabegron 25 mg and add-on solifenacin 5 mg. Participants with complete response prior 6 weeks will continue the initial low dose monotherapy for the rest of the study period. Total treatment period will be 18 weeks.

Figure 3 Danish translation of DryPie, develop by W. Bower[15].

Green: Dry. Yellow: Wet underpants. Red: Wet trousers. Blue: Wet socks. Monday, Tuesday, Wednesday, Thursday, Friday, Saturday, Sunday.


TØR
VÅDE UNDERBUKSER
VÅDE BUKSER
VÅDE SOKKER
TIRSDAG
ONSDAG
TORSDAG
FREDAG
LØRDAG
SØNDAG
MANDAG

Withdrawal of participants and criteria of discontinuation of study

A study participant should be withdrawn from the study, if at any time one of following criteria is met:

1. It is the wish of the participant (or their parents/legally acceptable representative) for any reason (withdrawal of informed consent)
2. The discretion of the investigator for safety or behavioural reasons.
3. Severe non-compliance to protocol as judged by the investigator.
4. The investigator judges it necessary due to medical reasons.
5. Female participants who become pregnant should immediately discontinue study drug administration and will be discontinued from the study (female participant with childbearing potential are excluded from the study).
6. The participant experiences adverse reactions, which either endanger the health of the participant, require emergency treatment, is incompatible with continuation of the study or is expected to influence the results of the study.
7. Participant with a condition and/or a situation that, in the investigator's opinion, may put the participant at significant risk, or may interfere significantly with the participants participation in the study will be discontinued from the study.
8. Participant with any other condition and/or situation, that in the investigator's opinion may be valid for discontinuation from the study.

Primary endpoint

The primary endpoint measure is treatment response assessed by change from visit 2 to end of study, according to number of wet days pr. 7 days by DryPie.

Secondary endpoints

Secondary outcome measures are change from baseline across the 18-week treatment period:

- Treatment response, according to number of wet days pr. 7 days by DryPie. - Change in incontinence severity score pr. 7 days assessed by Dry Pie
- Change in urge severity quantified by Bower VAS Urgency Scheme[15]
- Change in ml of maximum volume voided (MVV)
- Change in ml of age standardized MVV
- Change in ml average voided volume (AVV)
- Change in number of micturition frequency
- Change in total score of PinQ (Pediatric incontinence questionnaire)
- Change in total score of WHO-5

Safety outcomes

Safety outcome measures encompass:

- Adverse event (AE), serious adverse event (SAE) and Suspected Unexpected Serious Adverse Reaction (SUSAR) monitoring

- Identifications of electrocardiogram (ECG) abnormalities by electrocardiogram before entering the study and after 6 weeks
- Increase in blood pressure and pulse beyond the 95th percentile
- Change in ultrasonic assessed post-void residual urine (PVR), baseline to 18 weeks
- Identification of urinary tract infection by urine dipstick and verified by routine urine culture

Procedures during pharmacotherapy

The participant timeline is illustrated in figure 4.

Figure 4. Schedule of assessment

	Visit 1 Baseline	Visit 2	Visit 3 End of study or PD
Week (Day)	0	6 (42)	18 (126)
Visit scheduling window	-	± 5 days	± 5 days
Informed consent	X		
In- and exclusion criteria	X		
Background information incl. demographics	X		
Registration of concomitant	X	X	X

medication			
Urotherapy	X	X	X
Randomization	X		
Dispensation of study medication	X	X	
Compliance		X	X
Drug Accountability		X	X
Registration of side effects as reported in the product summary		X	X
Registration of AE/SAE/SUSAR		X	X
Clinical examination	X		
Weight and height	X		
Dry Pie	X	X	X
48-hour frequency-volume chart	X	X	X
Bower VAS Urgency	X	X	X
Uroflowmetry	X		X
Post-void residual urine	X	X	X
Blood pressure and pulse	X	X	X
Electrocardiogram	X	X	
Urine dipstick test	X	(X)	(X)
PinQ	X		X
WHO-5	X		X

Visit 1 (day 0/week 0)

Participants will enter the study after parents/parental custody holder(s) have signed the informed consent.

The participant and parents will be instructed in filling in a 48-hour frequency-volume chart (one filled out in the last 2 months prior to visit 1 is accepted) and a Dry Pie for one week prior to visit 1.

Background information (incl. age, gender, DUI history incl. urotherapy, any concomitant medication present and previously, any other diseases or psychiatric diagnosis) will be obtained.
A clinical examination including anthropometric measurements, measurement of blood pressure and pulse, an uroflowmetry (or one performed the last 6 months prior visit 1) with ultrasonic assessment of PVR (or one performed the last 2 months prior visit 1), a urine dipstick, and an electrocardiogram will be performed. Moreover, Bower VAS Urgency will be filled out.
Quality of life and well-being of the participating children will be assessed by the Pediatric Incontinence Questionnaire (PinQ) and WHO-5. The questionnaires will be filled out electronically at the outpatient clinic or at home with help from the parent(s)/parental custody holder(s).
Participants will be instructed in continuing urotherapy during the study.
The participant will be randomized 1:1:1:1 to one of the four treatment groups described above.
The participants will be unblinded and receive study medication according to their unique participant number. An unblinded study nurse can guide if necessary.

Visit 2 (day 42/week 6)

The participant will be instructed to bring a 48-hour frequency-volume chart and a Dry Pie for one week, filled in prior to visit 2. Moreover, Bower VAS Urgency will be filled out during the visit.

A clinical examination including measurement of blood pressure and pulse, ultrasonic assessment of PVR, safety electrocardiogram and a urine dipstick test (in case of symptoms of urinary tract infection) will be performed.
Registration of side effects as reported reference documents of side effects as reported in the product summaries, authorized in adults. Any AE, SAE or SUSAR will be registered and handled according to Good Clinical Practice.

The treatment outcome will be evaluated based on number of wet days per week assessed by DryPie. Based on the ICCS definitions of treatment outcome, the participants in group 1 (solifenacin 5 mg) and 2 (mirabegron 25 mg) will be treated as follows:

- Level 1: Complete response (100 % reduction in number of wet days) → maintain current treatment level
- Level 2: Not complete response (<100 % reduction in number of wet days) → 1A: Solifenacin 5 mg + Solifenacin 5 mg, 1B Solifenacin 5 mg + Mirabegron 25 mg, 2A Mirabegron 25 mg + Mirabegron 25 mg, 2B Mirabegron 25 mg + Solifenacin 5 mg

The dose titration will be notified in the electronic patient journal, and as the study is blinded by investigators it will only be noted whether the participant is treated with study medication level 1 or level 2.
An unblinded nurse will guide and answer questions to participants in case of dose titration. The compliance to the study medication will be evaluated by an unblinded project nurse at every site. Compliance will be evaluated by counting the remaining tablets in the container on every visit. Three categories will be used: ≥ 80%, 50-79%, or <50%.
The participant should contact the outpatient clinic by phone between visit 2 and visit 3 in case of any AE, SAE, SUSAR.
In case dose titration to level 2 results in increased PVR, symptoms of urinary tracts infections and positive urine dip stick, side effects or development of hypertension the investigator can adjust the dose to the initial dose (level 1).

Visit 3 (day 126/week 18)

The participant will be instructed to bring a 48-hour frequency-volume chart and a Dry Pie for one week, filled in prior visit 3. Moreover, Bower VAS Urgency will be filled out during the visit.
A clinical examination including measurement of blood pressure and pulse, and ultrasonic assessment of PVR will be performed. In case of symptoms of urinary tract infection, a urine dipstick test will be performed.
Registration of side effects as reported reference documents of side effects as reported in the product summaries. Any AE, SAE or SUSAR will be registered and handled according to Good Clinical Practice.

End of treatment quality of life will be evaluated by Pediatric Incontinence Questionnaire and WHO-5.
The compliance to the study medication will be evaluated by an unblinded project nurse at every site, by counting the remaining tablets in the container.
At the end of the study or in case of early discontinuation, the child continues at the outpatient clinic

at the respective study site to determine the future treatment. An unblinded medical doctor at the study site will decide the future treatment.

Randomization procedure

Randomization will be performed in the RedCap portal and will occur centrally. An electronic CRF (eCRF) will be built for the study data to be entered. The randomization will be performed in a separate module, and the randomisation list will be kept by the unblinded nurse at Department of Pediatric and Adolescent Medicine, Gødstrup Hospital until the end of study.
Following written informed consent randomization is stratified by a 1:1:1:1 allocation within each stratum using predefined block sizes for sites. Block randomization is by a computer-generated random number list. The investigators and all other medical staff are kept blinded to the allocation except for the unblinded study nurses. The unblinded study nurse at each study centre will have a unique account for the eCRF that allows randomization and seeing which product needs to be prepared for the study subject. The blinded study team will not be able to see the allocation in the eCRF. The participants will be unblinded and receive study medication according to their unique participant number.

Blinding and unblinding

The study is single-blinded, and the study subject will receive medication delivered from the study site. The investigator does not know which treatment the individual participant receives.
Participants will be informed that they are not allowed to reveal the blinded investigator the study medication, and an unblinded nurse will guide and answer questions to participants in case of dose titration. The children and their parents will be asked for possible side effects at every visit and will always be able to contact a medical doctor or an investigator when a side effect is suspected. The participant should contact the outpatient clinic by phone in between visit 2 and visit 3 in case of any AE, SAE, SUSAR. All participating children will be provided with a “trial card” on which the investigational product, the trial number and investigator’s name, and a 24-hours emergency contact number are stated. Unblinding is possible in case of a SAE or SUSAR. If an investigator needs to unblind a study subject due to a safety issue, the investigator will be able to do this in REDCap. Unblinding will be performed according to GCP guidelines. Any unblinding will be logged per user, with timestamp. The investigator will keep the rest of the study team and study subject blind, unless the nature of emergency requires that all parties should be informed. The sponsor will be notified of the unblinding.

Statistical analysis

The primary outcome will be analyzed as follows. First, the change from visit 2 across the 18-week pharmacological treatment period in number of wet days per week assessed by DryPie will be assessed, for all groups. Second, treatment response (either non-response or response) will be assessed, for all groups. Third, to analyze and compare the treatment groups, the Persons chi-square test will be used.

The secondary outcomes of treatment response across 18-week will be analyzed as follows. First, change from baseline across the 18-week pharmacological treatment period in number of wet days per week assessed by DryPie will be assessed, for all groups. Second, treatment response (either non-response or response) will be assessed, for all groups. Third, to analyze and compare the

treatment groups, the Persons chi-square test will be used.
Additionally secondary outcomes will be reported as follows. Continuous data will be reported as median with interquartile range for non-normal distributed data and as mean ± standard deviation for normally distributed data and the assumption of normally distributed data will be checked by QQ-plots. Categorical data will be presented as number (%).
Safety parameters (treatment-emergent adverse events, serious adverse events, vital signs, electrocardiogram, postvoid residual volume, urinary dipstick) will be summarized using descriptive statistics.

Sample size

The estimates for the sample size calculations are based on one placebo-controlled trial, prospective and retrospective studies[16], [17], [18], [19], [20]. We expect 15% of the children to have a complete response on treatment with low dose solifenacin 5 mg, and 15% of the children to have a complete response on treatment with low dose mirabegron 25 mg. Of the remaining children (100% -15% = 85%) who are non-complete responders to low dose monotherapy, we expect 20% to have complete response on solifenacin 10 mg, 20% to have complete response with mirabegron 50 mg and 50% to have complete response on combination therapy (solifenacin and mirabegron).

With the above-mentioned estimates, 32% (0.15 + 0,85 · 0.2 = 0.32) of the participants randomized to group 1A will have a complete response. The sample size calculation was based on solifenacin 10 mg versus combination therapy and mirabegron 50 mg versus combination therapy.

The estimated sample sizes for a two-sample proportions test were performed by Pearson’s chisquare test.

With a power of 80% and for obtaining a statistically significant (alfa 0.05) difference between solifenacin 10 mg and combination therapy of solifenacin 5 mg and mirabegron 25 mg and combination therapy of mirabegron 25 mg and solifenacin 5 mg, the sample size was calculated by two-sample proportions test.

alpha	power	N	N1	N2	delta	p1	p2
.05	.8	118	59	59	.255	.32	.575

To obtain a power of 80% and with two-sided statistical significance levels of 5%, the required sample size is 59 in each group (1A, 1B, 2A, 2B). The sample size included the expected children who will continue the initial dose. In total, the required sample size is 236 participants.

Ethics Approval

The study is authorized by the authorities The Danish Medicines Agency and The Danish Health Research Ethics Committee and registered at CTIS (EU CT 2023-510187-13-00).

Ethical considerations

All pharmacological side effects will be handled in accordance with the Danish legislation. No risk

or unknown side effects are expected to urotherapy, medical treatment or withdrawal. No risks are expected by clinical examination and paraclinical measurements.
The therapeutic potential for future patients justifies the project to be carried out. Participation in this study will not lead to any disadvantages for the patient in their treatment.
All pharmacological side effects will be handled in accordance with the Danish legislation. No risk or unknown side effects are expected to medical treatment or withdrawal. The therapeutic potential for future patients justifies the project to be carried out. Participation in this study will not lead to any disadvantages for the patient in their treatment.
The study will be conducted in accordance with the protocol, applicable regulatory requirements according to Good Clinical Practice and the ethical principles of the Declaration of Helsinki. Information regarding the participants is protected and anonymized according to the General Data Protection Regulation and the actual law.

Safety

Safety evaluations include AE, SAE and SUSAR monitoring, registration of side effects as reported in the product summary, blood pressure, pulse, ultrasonic assessed PVR and identification of urinary tract infection by urine dipstick and verified by routine urine cultivation and electrocardiogram. The listed safety parameters except electrocardiograms will be monitored at every visit during the study treatment administration, and urine dipstick will be performed a visit 2 and 3 if a participant reports symptoms of a urinary tract infection. Electrocardiograms will be monitored at baseline and at visit 2.
The children and their parents will be asked for possible side effects at every visit and will always be able to contact a medical doctor or an investigator when a side effect is suspected.
All participating children will be provided with a “trial card” on which the investigational product, the trial number and investigator’s name, and a 24-hours emergency contact number are stated.

Results

Recruitment began ultimo June 2024 and will continue until 236 patients are included, which is expected by September 2026. As of February 2025, 58 participants are included.

Discussion

Anticipated findings and importance of this research

Solifenacin is approved for treatment of neurogenic detrusor overactivity in children and adolescents ages 2-18 years. Though not approved for treatment of idiopathic OAB in children, solifenacin is widely used off-label. The efficacy of solifenacin was found superior to placebo in terms of average voided volume pr miction, daily maximum voided volume, and micturition frequency adjusted for total voided volumens[11]. The efficacy of solifenacin by decreasing number of incontinence episodes pr. day was demonstrated by non-placebo-controlled prospective studies[21] [22]. The safety and tolerability of solifenacin were found to be high, also by long-term use[12]. Predominantly, side effects as xerostomia, constipation, blurred vision, headache, and fatigue were reported [11] [21] [22]. A few participants experienced more severe side effects, encompassing QT prolongation, severe constipation, fecal incontinence, and aggressive behavior, some of which withdrew from the study due to the intolerable side effects and for safety reasons.

Mirabegron has been approved as an alternative to antimuscarinics in adults with OAB. In the pediatric population, mirabegron is used off-label, either as monotherapy or in combination with antimuscarinics[13] [14]. The efficacy of mirabegron compared to placebo has been elucidated among children[10]. Furthermore, the drug has high safety and tolerability in the pediatric population[23]. Reported side effects in prospective studies were blurred vision, constipation, abdominal cramps, and these were transient. No additional risk to studying subjects is anticipated with the use of solifenacin and mirabegron.
A favorable safety profile was observed. In adult population, the efficacy benefits of solifenacin and mirabegron outweigh the risks. This favorable benefit-risk ratio supports the further development of solifenacin and mirabegron in the treatment of the pediatric population with DUI.

With the current protocol, we aim to investigate if treatment with a combination of solifenacin and mirabegron in low dose is effective in reduction of DUI episodes over 18-week treatment period compared to baseline, and that combination therapy in low dose is superior to maximum dose of either solifenacin or mirabegron in children with non-complete response to urotherapy and low dose monotherapy of solifenacin or mirbegron.
The results from this study will ensure evidence-based knowledge about the off-label treatment approach. By optimizing the stepwise medical treatment approach, the treatment can be shortened, side effects can be diminished, and unnecessary medical expenses can be minimized for the individual families and society both nationally and internationally.
Compared to experience from daily practice, randomized controlled trials allow for the systematic evaluation of both the safety and efficacy of treatments. This is crucial in pediatrics, where considerations such as appropriate dosing, potential side effects, and long-term outcomes need to be carefully assessed to ensure the well-being of children receiving treatment.

Strengths and limitations

The strengths of our study are the randomized single-blinded, controlled design with and the multicenter inclusion at five pediatric departments in Denmark.
The investigators are blind, and participants know the treatment. This could cause a possible risk of affecting the final outcome of the study. Hence, no placebo effect is introduced. With single blinding, the investigators are not biased while treating the patients nor when interpretating data.
The study is embedded into daily clinical practice and reflects standard practice in many aspects other than randomization and collection of data. Usually, mirabegron is add-on pharmacotherapy if anticholinergics are not fully effective in treating DUI. The pragmatic design ensures timely inclusion of patients and reflects daily clinical practice where pharmacotherapy is initiated after inadequate effect of urotherapy.
The main limitation is compliance to the study medication over the 18 weeks. We aim to reduce this risk by early termination of children with severe compliance issues (as <50%) during the treatment period. Compliance to the study medication is determined by counting remaining tablets in the containers at each visit. This is done by an unblinded nurse.
The risk of unblinding blinded investigators is present, but we expect to reduce the risk by introducing unblinded study staff as project nurses as well as the participants and their parents are instructed to not inform the investigator about the medication.
Another limitation is the fixed dose of the combination therapy introducing a potential risk of undertreating the children allocated to this interventions group.

Conclusion

If the low dose of combination therapy is superior to high dose monotherapy, children with DUI will benefit significantly from the new treatment in terms of shorter treatment periods, fewer side effects and possibly a better quality of life.
The trial has the potential to optimize the medical treatment approach, to shorten the treatment period, diminish side effects and minimized unnecessary medical expenses. Due to predefined criteria for discontinuation of the allocated therapy, we expect the risk of treatment failure to be minimal. The results are expected to influence the treatment strategy of children with daytime urinary incontinence worldwide.

Registration

The trial is in general in accordance with the CONSORT checklist.
CTIS: EU CT 2023-510187-13-00.
ClinicalTrial.gov ID: NCT06551246.
The study is registered at the research inventory of the Regions of Denmark (1-16-02-210-24) and at Aarhus University (ARG-2024-731-23829).
The results will be submitted to CTIS within one year after the end of the trial. Moreover, data will be published in www.clinicaltrialsregister.eu .

Acknowledgements

Generative AI tools were not used for this study.
The study participants and their families will not be economically compensated for participating in the study; however, study medication costs will be covered throughout the entire study period.

Funding Statement

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None of the study personnel have any economic interests in the study.

Data Availability

The data sets generated during this study are planned to be available on reasonable request.

Conflicts of interest

Nothing to declare.

Author contributions

All authors contributed to conceptualization, methodology, writing reviewing and editing of the published work. The investigation process and project administration are planned to be performed

by SH, KK, LB and AS.

References

[1] L. V. Swithinbank, J. Heron, A. Von Gontard, and P. Abrams, “The natural history of daytime urinary incontinence in children: A large British cohort,” *Acta Paediatrica, International Journal of Paediatrics*, vol. 99, no. 7, pp. 1031–1036, 2010, doi: 10.1111/j.1651-2227.2010.01739.x.

[2] S. J. Chang, E. Van Laecke, and S. B. Bauer, “Treatment of Daytime Urinary Incontinence: A standardization document from the International Children’s Continence Society,” *Neurourol Urodyn.*, vol. 36, no. 1, pp. 43–50, 2017.

[3] T. C. Warner, U. Baandrup, R. Jacobsen, H. Bøggild, P. S. Aunsholt Østergaard, and S. Hagstrøm, “Prevalence of nocturia and fecal and urinary incontinence and the association to childhood obesity: a study of 6803 Danish school children,” *J Pediatr Urol*, vol. 15, no. 3, pp. 225.e1-225.e8, 2019, doi: 10.1016/j.jpurol.2019.02.004.

[4] E. Gür *et al.*, “Enuresis: Prevalence, risk factors and urinary pathology among school children in Istanbul, Turkey,” *Pediatrics International*, vol. 46, no. 1, pp. 58–63, 2004, doi: 10.1111/j.1442200X.2004.01824.x.

[5] W. F. Bower, “Self-reported effect of childhood incontinence on quality of life,” *Journal of Wound, Ostomy and Continence Nursing*, vol. 35, no. 6, pp. 617–621, 2008, doi: 10.1097/01.WON.0000341476.71685.78.

[6] B. A. Thibodeau, P. Metcalfe, P. Koop, and K. Moore, “Urinary incontinence and quality of life in children,” *J Pediatr Urol*, vol. 9, no. 1, pp. 78–83, 2013, doi: 10.1016/j.jpurol.2011.12.005.

[7] P. Hoebeke, E. Van Laecke, C. Van Camp, A. Raes, and J. Van De Walle, “One thousand videourodynamic studies in children with non-neurogenic bladder sphincter dysfunction,” *BJU Int*, vol. 87, no. 6, pp. 575–580, 2001, doi: 10.1046/j.1464-410X.2001.00083.x.

[8] P. F. Austin *et al.*, “The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the international children’s continence society,” *Journal of Urology*, vol. 191, no. 6, pp. 1863-1865.e13, 2014, doi: 10.1016/j.juro.2014.01.110.

[9] T. Takasu *et al.*, “Effect of (R)-2-(2-Aminothiazol-4-yl)-4′-{2-[(2-hydroxy-2phenylethyl)amino]ethyl} Acetanilide (YM178), a Novel Selective β3-Adrenoceptor Agonist, on Bladder Function,” *J Pharmacol Exp Ther*, vol. 321, no. 2, pp. 642–647, 2007, doi: 10.1124/jpet.106.115840.

[10] M. G. Soliman, S. El-Abd, O. M. El-Gamal, A. A. Raheem, A. R. Abou-Ramadan, and A. S. El-Abd, “Mirabegron versus Solifenacin in Children with Overactive Bladder: Prospective Randomized Single-Blind Controlled Trial,” *Urol Int*, vol. 105, no. 11–12, pp. 1011–1017, 2021, doi: 10.1159/000515992.

[11] D. Newgreen *et al.*, “Solifenacin in Children and Adolescents with Overactive Bladder: Results of a Phase 3 Randomised Clinical Trial,” *Eur Urol*, vol. 71, no. 3, pp. 483–490, 2017, doi: 10.1016/j.eururo.2016.08.061.

[12] D. Newgreen *et al.*, “Long-Term Safety and Efficacy of Solifenacin in Children and Adolescents with Overactive Bladder,” *Journal of Urology*, vol. 198, no. 4, pp. 928–936, 2017, doi: 10.1016/j.juro.2017.05.038.

[13] A. S. Blais, G. Nadeau, K. Moore, L. Genois, and S. Bolduc, “Prospective Pilot Study of Mirabegron in Pediatric Patients with Overactive Bladder,” *Eur Urol*, vol. 70, no. 1, pp. 9–13, 2016, doi: 10.1016/j.eururo.2016.02.007.

[14] F. Morin, A. S. Blais, G. Nadeau, K. Moore, L. Genois, and S. Bolduc, “Dual Therapy for Refractory Overactive Bladder in Children: A Prospective Open-Label Study,” *Journal of Urology*, vol. 197, no. 4, pp. 1158–1163, 2017, doi: 10.1016/j.juro.2016.11.101.

[15] W. F. Bower, K. H. Moore, and R. D. Adams, “A novel clinical evaluation of childhood incontinence and urinary urgency.,” *J Urol*, vol. 166, no. 6, pp. 2411–5, Dec. 2001.

[16] M. G. Soliman, S. El-Abd, O. M. El-Gamal, A. A. Raheem, A. R. Abou-Ramadan, and A. S. El-Abd, “Mirabegron versus Solifenacin in Children with Overactive Bladder: Prospective Randomized Single-Blind Controlled Trial,” *Urol Int*, vol. 105, no. 11–12, pp. 1011–1017, 2021, doi: 10.1159/000515992.

[17] D. Newgreen *et al.*, “Solifenacin in Children and Adolescents with Overactive Bladder: Results of a Phase 3 Randomised Clinical Trial,” *Eur Urol*, vol. 71, no. 3, pp. 483–490, 2017, doi: 10.1016/j.eururo.2016.08.061.

[18] D. Newgreen *et al.*, “Long-Term Safety and Efficacy of Solifenacin in Children and Adolescents with Overactive Bladder,” *Journal of Urology*, vol. 198, no. 4, pp. 928–936, 2017, doi: 10.1016/j.juro.2017.05.038.

[19] F. Morin, A. S. Blais, G. Nadeau, K. Moore, L. Genois, and S. Bolduc, “Dual Therapy for Refractory Overactive Bladder in Children: A Prospective Open-Label Study,” *Journal of Urology*, vol. 197, no. 4, pp. 1158–1163, 2017, doi: 10.1016/j.juro.2016.11.101.

[20] S. Fryer *et al.*, “Effectiveness and tolerability of mirabegron in children with overactive bladder:
A retrospective pilot study,” *J Pediatr Surg*, vol. 55, no. 2, pp. 316–318, 2020, doi: 10.1016/j.jpedsurg.2019.10.044.

[21] G. Nadeau *et al.*, “Long-term use of solifenacin in pediatric patients with overactive bladder: Extension of a prospective open-label study,” *Canadian Urological Association Journal*, vol. 8, no. 3–4, pp. 118–123, 2014, doi: 10.5489/cuaj.1356.

[22] S. D. Lee, J. M. Chung, D. Il Kang, D. S. Ryu, W. Y. Cho, and S. Park, “Efficacy and

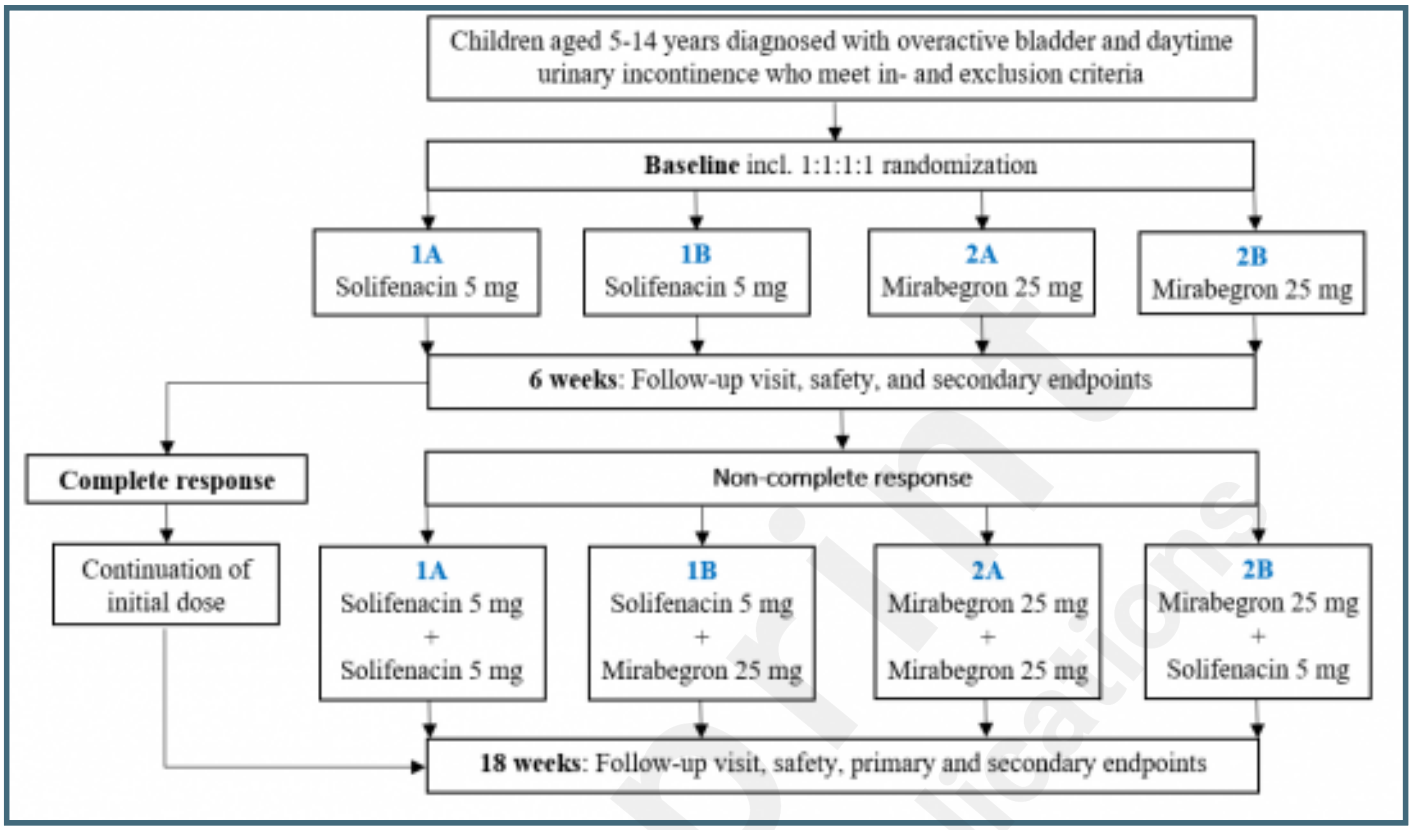
tolerability of solifenacin 5 mg fixed dose in Korean children with newly diagnosed idiopathic overactive bladder: A multicenter prospective study," *J Korean Med Sci*, vol. 32, no. 2, pp. 329–334, 2017, doi: 10.3346/jkms.2017.32.2.329.

[23] S. Rittig *et al.*, "The pharmacokinetics, safety, and tolerability of mirabegron in children and adolescents with neurogenic detrusor overactivity or idiopathic overactive bladder and development of a population pharmacokinetic model–based pediatric dose estimation," *J Pediatr Urol*, vol. 16, no. 1, pp. 31.e1-31.e10, 2020, doi: 10.1016/j.jpurol.2019.10.009.

Supplementary Files

Figures

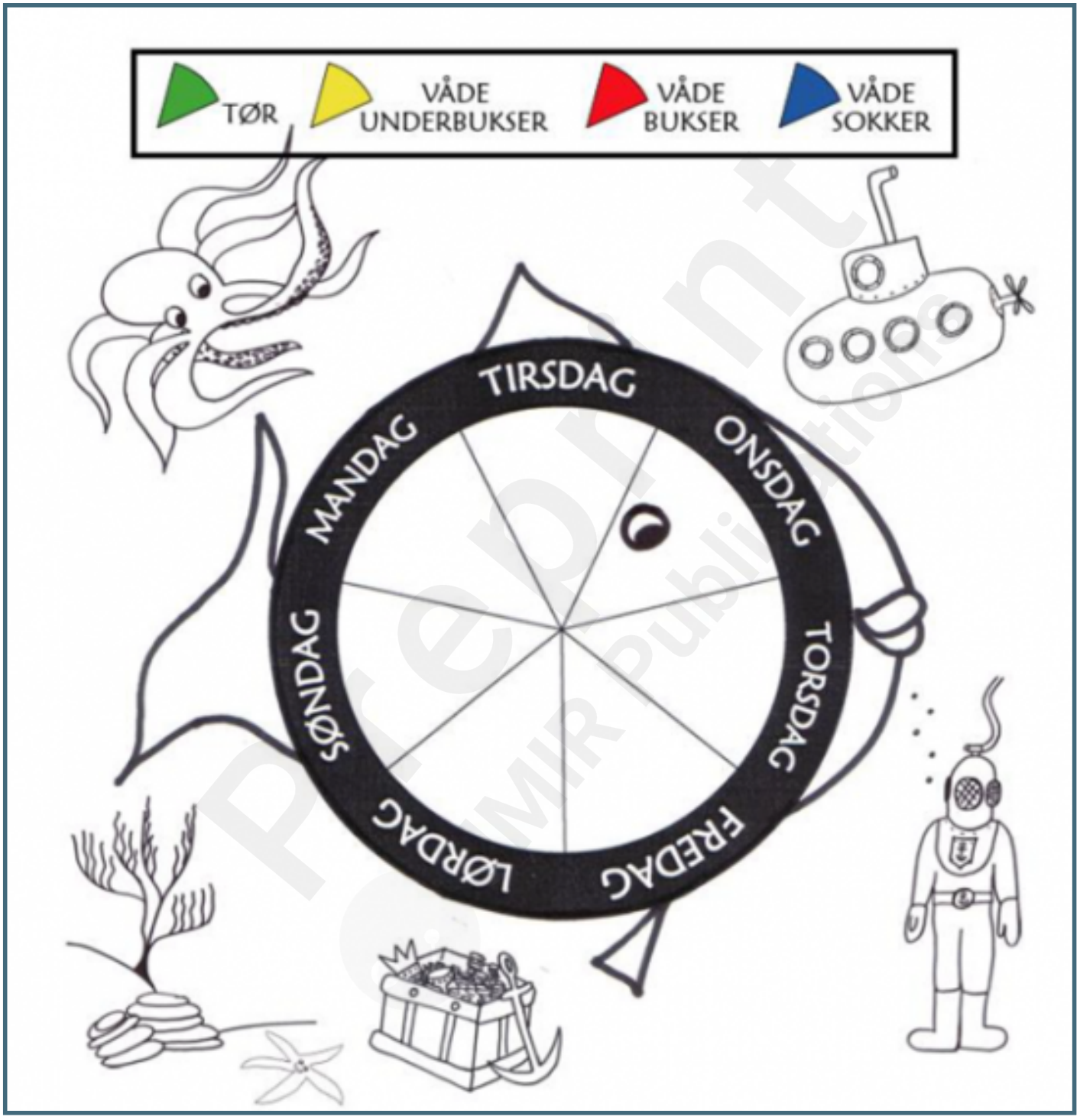
Participant flow chart.



In- and exclusion criteria.

Inclusion
1. The participants' custody holder(s) must voluntarily sign and date an informed consent prior to initiation of any study specific procedures.
2. Age 5 to 14 years (inclusive) at the time of inclusion.
3. OAB as per ICCS criteria
4. At least 2 DUI episodes per week
5. Inadequate effect of at least 4 weeks urotherapy (non-pharmacological treatment)
6. No previous treatment with solifenacin, mirabegron or bladder/sphincter botulinum toxin injections
7. No current constipation as per ROME IV criteria or fecal incontinence (laxative treatment is accepted)
8. Per investigator's judgment, the participant can swallow or can learn to swallow study medication
Exclusion
1. Inability of the patent(s) or legal guardian(s) to understand the Danish written and oral information
2. Known or suspected hypersensitivity to study medication
3. Any contraindication to the use of the study medication
4. Known urogenital anatomical abnormalities affecting lower urinary tract function
5. Known kidney or bladder stones
6. Known diabetes insipidus
7. Ongoing symptomatic urinary tract infection
8. Recurrent urinary tract infection or ongoing prophylactic antibiotic treatment
9. Known QTc prolongation, QTc >460 ms, or risk of QTc prolongation (hypokalaemia, exercise-induced syncope, or familial long QT syndrome)
10. Other significant ECG abnormalities
11. Know hypertension
12. ≤3 daily voiding, evaluated by 48-hour frequency-volume chart
13. Uroflowmetry suggestive of other pathology than OAB (staccato-shaped, interrupted-shaped, or plateau-shaped curve)
14. Post-void residual >50 ml after double voiding
15. Dipstick haematuria (≥2+ erythrocytes) or macroscopic haematuria
16. Pregnancy or breastfeeding
17. Female subjects of childbearing potential
18. Ongoing constipation according to Rome IV-criteria which is intractable to medication or fecal incontinence
19. Inability to swallow study medication
20. Use of any medication during study period, except permitted medication

Danish translation of DryPie, develop by W. Bower[15]. Green: Dry. Yellow: Wet underpants. Red: Wet trousers. Blue: Wet socks. Monday, Tuesday, Wednesday, Thursday, Friday, Saturday, Sunday.



Schedule of assessment.

	Visit 1 Baseline	Visit 2	Visit 3 End of study or PD
Week (Day)	0	6 (42)	18 (126)
Visit scheduling window	-	± 5 days	± 5 days
Informed consent	X		
In- and exclusion criteria	X		
Background information incl. demographics	X		
Registration of concomitant medication	X	X	X
Urotherapy	X	X	X
Randomization	X		
Dispensation of study medication	X	X	
Compliance		X	X
Drug Accountability		X	X
Registration of side effects as reported in the product summary		X	X
Registration of AE/SAE/SUSAR		X	X
Clinical examination	X		
Weight and height	X		
Dry Pie	X	X	X
48-hour frequency-volume chart	X	X	X
Bower VAS Urgency	X	X	X
Uroflowmetry	X		X
Post-void residual urine	X	X	X
Blood pressure and pulse	X	X	X
Electrocardiogram	X	X	
Urine dipstick test	X	(X)	(X)
PinQ	X		X
WHO-5	X		X

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