Clinical trial results:
Monocentric, open-label, phase III study that compares the efficiency and tolerance between intravesical oxybutynin and oral fesoterodine in children (5-16y) with neurogenic detrusor overactivity.

Summary

EudraCT number	2012-005295-33
Trial protocol	BE
Global end of trial date	01 July 2013

Results information

Result version number	v1 (current)
This version publication date	23 February 2023
First version publication date	23 February 2023
Summary attachment (see zip file)	Publication 22MAY2019 (S54913_PUBLICATIE_spina fesoteridine Bogaert urologia internationalis_22MAY2019.pdf)

Trial information

Trial identification

Sponsor protocol code	S54913

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UZ Leuven- Department of Urology
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Guy Bogaert, UZ Leuven-Department of Urology, +32 16346930, guy.bogaert@uzleuven.be
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2013
Global end of trial reached?	Yes
Global end of trial date	01 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Efficiency and tolerance of fesoterodine in comparison with intravesical oxybutynin +/- tolterodine in children with neurogenic detrusor overactivity.

Protection of trial subjects:

The Clinical Trial Center of UZ Leuven, the Medical Ethics Committee and the Federal Agency for Medicines and Health Products approved this study. The children needed to be older than 4 years of age because they had to be able to swallow an entire tablet, so that the prolonged release formula could work. Based on previous studies with tolterodine, which has the same active metabolite as fesoterodine, and the results of the pharmacokinetic behaviour of fesoterodine in a study with paediatric subjects, we calculated that a maximal dose of fesoterodine of 0.2 mg/kg/24 h would be safe. The child’s body weight had to be at least 20 kg because fesoterodine is available in 4 and 8 mg slow release tablets.

Background therapy:

A low-pressure bladder in children with neuropathic bladder dysfunction can be achieved using anticholinergic medication. Due to the significant side effects of oral oxybutynin, our patients are treated with daily intravesical oxybutynin instillations. Newer oral anticholinergic medication, such as fesoterodine, claim to have fewer side effects in a once daily formulation. Because once-daily oral intake is
easier than performing twice-daily intravesical instillations, we studied the effects of switching from intravesical oxybutynin to oral fesoterodine and compared the clinical response, urodynamic parameters and side effects.

Evidence for comparator:

Anticholinergic medication lowers the frequency of involuntary bladder contractions, can lower the intravesical pressure, prevents the development of a hypertrophic bladder and augments the bladder capacity. However, anticholinergics cause side effects due to concomitant suppression of the muscarinic receptors in the rest of the body. The oldest and most well-known anticholinergic used to suppress detrusor overactivity is oxybutynin, a mild muscarinic-3 receptor selective antagonist. It is registered for the use in children and adults with neuropathic and non-neuropathic bladder disturbances.

Actual start date of recruitment	03 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	10
Adolescents (12-17 years)	10
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty children with a body weight of at least 20 kg were enrolled and all completed the study. All children had NDO and sphincter overactivity proved by a UDS for which they performed CIC (4–6 times a day) and used intravesical oxybutynin. Out of 20 children, 12 (60%) took concom prophylactic AB. Monocentric, open-label, pilot study with 1 arm.

Pre-assignment

Screening details:

Children with NDO and sphincter overactivity (DSD) proved by a urodynamic study (UDS) performing daily CIC taking intravesical oxybutynin hydrochloride (0.3–0.6 mg/kg/24 h divided over 2–3 instillations a day) were included. The children needed to be older than 4 years of age because they had to be able to swallow an entire tablet.

Pre-assignment period milestones

Number of subjects started	20
Intermediate milestone: Number of subjects	Part 1: 20
Intermediate milestone: Number of subjects	Part 2: 20
Intermediate milestone: Number of subjects	Part 3: 20
Number of subjects completed	20

Period 1

Period 1 title	Part 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A, as it's an academic, monocentric, open-label, pilot study with 1 study-arm.

Arms

Arm title	Intravesical oxybutynin instillation

Arm description:

During the first 2 patient contacts in part 1, the current urinary tract status was collected while on intravesical oxybutynin treatment by filling out 2 voiding diaries and urodynamics.

Arm type	Intravesical oxybutynin
Investigational medicinal product name	Oxybutynin Hydrochloride
Investigational medicinal product code	SUB03581MIG
Other name	1508-65-2
Pharmaceutical forms	Intravesical solution
Routes of administration	Intravesical use

Dosage and administration details:

40g oxybutynin hydrochloride is solved into 40 liters of physiological solution, it is filtrated, then 5ml solution is put in an ampule. (0.3–0.6 mg/kg/24 h divided over 2–3 instillations
a day)

Number of subjects in period 1	Intravesical oxybutynin instillation
Started	20
Completed	20

Period 2

Period 2 title	Part 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A, as it's an academic, monocentric, open-label, pilot study with 1 study-arm.

Arms

Arm title	Stop oxybutynin

Arm description:

In the second part of the study, intravesical oxybutynin instillations were stopped for 4 days as a washout of the medication. During this washout, the child and parents were asked to fill a third voiding diary.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Stop oxybutynin
Started	20
Completed	20

Period 3

Period 3 title	Part 3
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A, as it's an academic, monocentric, open-label, pilot study with 1 study-arm.

Arms

Arm title	Oral Fesoterodine

Arm description:

The third part of the study consisted of 40 days of oral fesoterodine administration, a slow release tablet every morning, instead of intravesical oxybutynin, and the CIC was continued. Children with a body weight 20–40 kg took 4 mg per day, children with a body weight of more than 40 kg a day took 8 mg per day. They had to contain their normal life style but had to avoid grapefruit because this fruit interferes with the metabolism of fesoterodine.

Arm type	Experimental
Investigational medicinal product name	Fesoterodine
Investigational medicinal product code	G04BD11
Other name	SUB25383
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Based on previous studies with tolterodine, which has the same active metabolite as fesoterodine, and the results of the pharmacokinetic behaviour of fesoterodine in a study with paediatric subjects, we calculated that a maximal dose of fesoterodine of 0.2 mg/kg/24 h would be safe. The child's body weight had to be at least 20 kg because fesoterodine is available in 4 and 8 mg slow release tablets, taken orally. Children with a body weight 20–40 kg took 4 mg per day, children with a body weight of more than 40 kg a day took 8 mg per day.

Number of subjects in period 3	Oral Fesoterodine
Started	20
Completed	20

Baseline characteristics

Reporting groups	
Reporting group title	Part 1

Reporting group description: -

Reporting group values	Part 1	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Twenty children (11 girls, 9 boys, 4–17 years) with neuropathic bladder dysfunction who perform clean intermittent catheterization and use intravesical oxybutynin instillations twice daily were included in this prospective study.			
Units: years			
median	13		
full range (min-max)	4 to 17	-	
Gender categorical			
Twenty children (11 girls, 9 boys, 4–17 years) with neuropathic bladder dysfunction who perform clean intermittent catheterization and use intravesical oxybutynin instillations twice daily were included in this prospective study.			
Units: Subjects			
Female	11	11	
Male	9	9	
Neurogenic detrusor overactivity (NDO)			
Neurogenic detrusor overactivity (NDO) is seen in children with congenital neuropathic bladder disturbance like spinal dysraphism. In the long term, secondary pathological-anatomical changes can occur with consequent vesico-ureteral reflux, hydronephrosis, an increased risk of urinary tract infections, renal damage and renal insufficiency. 58% of untreated patients develop renal damage after 3 years. The primary treatment goal in this patient group is to keep the intravesical detrusor pressure low from birth in order to preserve kidney function.			
Units: Subjects			
Spina bifida	15	15	
Tethered cord	2	2	
Caudal regression syndrome	1	1	
Transverse myelitis	1	1	
Traumatic spinal cord injury	1	1	
Number of patients applying CIC			
The primary treatment goal in this patient group is to keep the intravesical detrusor pressure low from birth in order to preserve kidney function. This can be achieved by frequent emptying of the bladder by clean intermittent catheterization (CIC) in combination with anticholinergic medication. All children had NDO and sphincter overactivity proved by a UDS for which they performed CIC (4–6			

times a day) and used intravesical oxybutynin.			
Units: Subjects			
Clean intermittent catheterization	20	20	
Number of patients applying intravesical oxybutynin at start			
Due to the significant side effects of oral oxybutynin, our patients are treated with daily intravesical oxybutynin instillations. Twenty children with neuropathic bladder dysfunction who perform CIC catheterization and use intravesical oxybutynin instillations twice daily were included in this prospective study.			
Units: Subjects			
Intravesical oxybutynin	20	20	

Subject analysis sets

Subject analysis set title	Patient Characteristics
Subject analysis set type	Full analysis

Subject analysis set description:

Twenty children with a body weight of at least 20 kg were enrolled and all completed the study. All children had NDO and sphincter overactivity proved by a UDS for which they performed CIC (4–6 times a day) and used intravesical oxybutynin. Out of 20 children, 12 (60%) took concomitant prophylactic antibiotics (nitrofurantoin) of whom 1 patient (5%) used erythromycin for acne, which was stopped at informed consent because it could interact with the metabolism of fesoterodine.

Reporting group values	Patient Characteristics		
Number of subjects	20		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Twenty children (11 girls, 9 boys, 4–17 years) with neuropathic bladder dysfunction who perform clean intermittent catheterization and use intravesical oxybutynin instillations twice daily were included in this prospective study.			
Units: years median full range (min-max)	 13 4 to 17		
Gender categorical			
Twenty children (11 girls, 9 boys, 4–17 years) with neuropathic bladder dysfunction who perform clean intermittent catheterization and use intravesical oxybutynin instillations twice daily were included in this prospective study.			
Units: Subjects			
Female Male	11 9		
Neurogenic detrusor overactivity (NDO)			
Neurogenic detrusor overactivity (NDO) is seen in children with congenital neuropathic bladder disturbance like spinal dysraphism. In the long term, secondary pathological-anatomical changes can occur with consequent vesico-ureteral reflux, hydronephrosis, an increased risk of urinary tract			

infections, renal damage and renal insufficiency. 58% of untreated patients develop renal damage after 3 years. The primary treatment goal in this patient group is to keep the intravesical detrusor pressure low from birth in order to preserve kidney function.			
Units: Subjects			
Spina bifida	15		
Tethered cord	1		
Caudal regression syndrome	1		
Transverse myelitis	1		
Traumatic spinal cord injury	1		
Number of patients applying CIC			
The primary treatment goal in this patient group is to keep the intravesical detrusor pressure low from birth in order to preserve kidney function. This can be achieved by frequent emptying of the bladder by clean intermittent catheterization (CIC) in combination with anticholinergic medication. All children had NDO and sphincter overactivity proved by a UDS for which they performed CIC (4–6 times a day) and used intravesical oxybutynin.			
Units: Subjects			
Clean intermittent catheterization	20		
Number of patients applying intravesical oxybutynin at start			
Due to the significant side effects of oral oxybutynin, our patients are treated with daily intravesical oxybutynin instillations. Twenty children with neuropathic bladder dysfunction who perform CIC catheterization and use intravesical oxybutynin instillations twice daily were included in this prospective study.			
Units: Subjects			
Intravesical oxybutynin	20		

End points

End points reporting groups

Reporting group title	Intravesical oxybutynin instillation

Reporting group description:

During the first 2 patient contacts in part 1, the current urinary tract status was collected while on intravesical oxybutynin treatment by filling out 2 voiding diaries and urodynamics.

Reporting group title	Stop oxybutynin

Reporting group description:

In the second part of the study, intravesical oxybutynin instillations were stopped for 4 days as a washout of the medication. During this washout, the child and parents were asked to fill a third voiding diary.

Reporting group title	Oral Fesoterodine

Reporting group description:

The third part of the study consisted of 40 days of oral fesoterodine administration, a slow release tablet every morning, instead of intravesical oxybutynin, and the CIC was continued. Children with a body weight 20–40 kg took 4 mg per day, children with a body weight of more than 40 kg a day took 8 mg per day. They had to contain their normal life style but had to avoid grapefruit because this fruit interferes with the metabolism of fesoterodine.

Subject analysis set title	Patient Characteristics
Subject analysis set type	Full analysis

Subject analysis set description:

Twenty children with a body weight of at least 20 kg were enrolled and all completed the study. All children had NDO and sphincter overactivity proved by a UDS for which they performed CIC (4–6 times a day) and used intravesical oxybutynin. Out of 20 children, 12 (60%) took concomitant prophylactic antibiotics (nitrofurantoin) of whom 1 patient (5%) used erythromycin for acne, which was stopped at informed consent because it could interact with the metabolism of fesoterodine.

Primary: Maximum tolerable cystometric capacity

End point title	Maximum tolerable cystometric capacity[1]

End point description:

The primary efficacy variable, change from baseline in mean maximum cystometric capacity was 18.4 mL, which did not represent a significant increase (Wilcoxonmatched pairs test, p = 0.196). Maximum tolerable cystometric capacity until voiding, until leaking and at 40cmH2O.

End point type	Primary

End point timeframe:

Week 1 and 7 before and after admission of fesoterodine.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The included population is too small for statistical analysis; to obtain significant results re the efficacy, more pts should be included. We anticipated including 20 children as an initial pilot study to study the trend of efficiency, safety and tolerance rather than a formal statistical analysis. Results are given in %, average and range; no formal statistical testing of these results was performed. Shapiro Wilk test was performed to identify between parametric and non-parametric distribution.

End point values	Intravesical oxybutynin instillation	Oral Fesoterodine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: in mililitres				
arithmetic mean (standard error)	353.4 (± 0.196)	371.8 (± 0.196)		

Attachments (see zip file)	Table 2/S54913_PUBLICATIE_spina fesoteridine Bogaert

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary efficacy variables

End point title	Secondary efficacy variables

End point description:

Secondary variables were other UDS parameters like detrusor pressure at maximum cystometric capacity in cm H20. In case of involuntary loss of urine, the UDS parameters detrusor leak point pressure in cm H20 as well as the filling volume of the bladder during urine loss in mLs was assessed. The voiding diary parameters that were analyzed were the average catheterized urine volume in mLs, the percentage of pads that were dry during 3 days and the average incontinence volume per day in grams.

End point type	Secondary

End point timeframe:

During intravesical oxybutynin administration (Baseline) and after 40 days of fesoterodine oral administration.

End point values	Intravesical oxybutynin instillation	Oral Fesoterodine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: cm H2O				
median (standard error)				
Maximum detrusor pressure (UDS)	28.2 (± 0.563)	30.6 (± 0.563)		
Bladder filling volume during urine loss (UDS)	217.9 (± 0.038)	353.4 (± 0.038)		
Detrusor leak point pressure (UDS)	18.8 (± 0.674)	22.0 (± 0.674)		
Catheterized urine volume (bladder diary)	147.5 (± 0.247)	139.5 (± 0.247)		
Volume urine incontinence per day (bladder diary)	121.0 (± 0.657)	132.9 (± 0.657)		
Dry pads during 3 days (bladder diary)	53.3 (± 0.215)	45.1 (± 0.215)		

Attachments (see zip file)	Table 2/S54913_PUBLICATIE_spina fesoteridine Bogaert

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study duration was 12 weeks, starting from ICF signing. Written ICF was obtained from at least one of the parents and from the children themselves if they were older than 12 years old. In those 12w, pt contacts were done, either clinic visit by phone.

Adverse event reporting additional description:

Safety+tolerability of fesoterodine were compared with those of intravesical oxybutynin based on data of anamnesis during 3 clinical contacts and 4 phone calls, vital signs (BP, HR, temperature and weight), clinical examination, behavioural checklists, lab evaluations (blood, urine). We specifically asked for the development of poss side effects.

Assessment type	Systematic

Dictionary used

Dictionary name	unknown
Dictionary version	1

Reporting groups

Reporting group title	All enrollend subjects

Reporting group description:

Safety and tolerability of fesoterodine were compared with those of intravesical oxybutynin based on data of anamnesis during 3 clinical contacts and 4 telephone interviews, vital signs (blood pressure, heart rate, axillary temperature and body weight), clinical examination, behavioural checklists, laboratory evaluations like blood and urine samples.
There were no remarkable differences seen between the vital functions and clinical examination during both treatments.

Serious adverse events	All enrollend subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All enrollend subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 20 (40.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrointestinal disorders			

Dry mouth	Additional description: Light-moderate dry mouth		
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Nausea	Additional description: Nausea and hot flushes		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Psychiatric disorders			
Behaviour disorder	Additional description: Behavioral changes (reversible)		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Appetite disorder	Additional description: Increased appetite		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The results of this study have to be interpreted with their limitations. The included population is too small for statistical analysis; moreover, in order to obtain significant results about the efficacy, more patients should be included.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31117096