Clinical trial results:
12-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy, pharmacodynamic and safety of two doses of alfuzosin (0.1 mg/kg/day; 0.2 mg/kg/day) in the treatment of children and adolescents 2 – 16 years of age with elevated detrusor leak point pressure of neuropathic etiology followed by a 40-week open-label extension

Summary

EudraCT number	2004-002397-38
Trial protocol	FR PT DE ES PL EE SK BG
Global end of trial date	09 December 2009

Results information

Result version number	v2 (current)
This version publication date	01 April 2016
First version publication date	06 December 2014
Version creation reason	• Correction of full data set Minor correction to non-serious adverse events data (number of occurrences)

Trial information

Trial identification

Sponsor protocol code	EFC5722

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00549939
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin , France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 January 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 December 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Alfuzosin in comparison to Placebo on the detrusor Leak Point Pressure (LPP) in children and adolescents 2-16 years of age with elevated detrusor LPP of neuropathic etiology and detrusor LPP greater than or equal to (≥) 40 centimeter of water (cm H2O).

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 October 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	Slovakia: 14
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	Serbia: 17
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	Russian Federation: 19
Country: Number of subjects enrolled	India: 20
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Malaysia: 3

Country: Number of subjects enrolled	Germany: 5
Worldwide total number of subjects	172
EEA total number of subjects	81

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)	127
Adolescents (12-17 years)	45
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 55 sites in 18 countries. A total of 261 subjects were screened between September 2007 and November 2008.

Pre-assignment

Screening details:

172/261 subjects were randomized in the 12-week double blind phase.
89/261 subjects were not randomized for the following reasons:
- Adverse event (1 subject*),
- Inclusion/Exclusion criteria not met (69 subjects*),
- Subject's request (11 subjects*),
- Other (13 subjects*).

'*' Subjects could have several reasons.

Period 1

Period 1 title	12-week efficacy phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Subjects were randomized to either Alfuzosin 0.1 milligram per kilogram per Day (mg/kg/Day) or matching placebo 0.1 mg/kg/Day or Alfuzosin 0.2 mg/kg/Day or matching placebo 0.2 mg/kg/Day. Each placebo treatment matched the active drug treatment (tablet or solution) and was indistinguishable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo - 12 weeks

Arm description:

Placebo (for Alfuzosin 0.1 mg/kg/Day) or placebo (for Alfuzosin 0.2 mg/kg/Day) for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Either solution or tablet formulation depending on age;
The daily dose with solution was divided in 3 doses given at breakfast, lunch and dinner.
The daily dose with tablets was divided in 2 doses given at breakfast and dinner.

Arm title	Alfuzosin 0.1 mg/kg/Day - 12 weeks

Arm description:

Alfuzosin 0.1 mg/kg/Day for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Alfuzosin
Investigational medicinal product code	SL770499
Other name	
Pharmaceutical forms	Tablet, Oral solution
Routes of administration	Oral use

Dosage and administration details:

Either solution or tablet formulation depending on age;

The daily dose with solution was divided in 3 doses given at breakfast, lunch and dinner.
The daily dose with tablet was divided in 2 doses given at breakfast and dinner.

Arm title	Alfuzosin 0.2 mg/kg/Day - 12 weeks

Arm description:

Alfuzosin, 0.2 mg/kg/Day for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Alfuzosin
Investigational medicinal product code	SL770499
Other name	
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Either solution or tablet formulation depending on age;
The daily dose with solution was divided in 3 doses given at breakfast, lunch and dinner.
The daily dose with tablet was divided in 2 doses given at breakfast and dinner.

Number of subjects in period 1	Placebo - 12 weeks	Alfuzosin 0.1 mg/kg/Day - 12 weeks	Alfuzosin 0.2 mg/kg/Day - 12 weeks
Started	57	57	58
Treated	57	57	58
Completed	56	55	56
Not completed	1	2	2
Adverse Event	1	1	2
'Too many blood draws '	-	1	-

Period 2

Period 2 title	40-week safety extension phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Alfuzosin 0.1 mg/kg/Day - 40 weeks extension

Arm description:

Alfuzosin 0.1 mg/kg/Day for 40 additional weeks open-label to subjects on Alfuzosin, 0.1 mg/kg/Day or on Placebo (for Alfuzosin, 0.1 mg/kg/Day) during the efficacy phase.

Arm type	Experimental

Investigational medicinal product name	Alfuzosin
Investigational medicinal product code	SL770499
Other name	
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Same dosage and administration details as for the period 1.

Arm title	Alfuzosin 0.2 mg/kg/Day - 40 weeks extension

Arm description:

Alfuzosin 0.2 mg/kg/Day for 40 additional weeks open-label to subjects on Alfuzosin, 0.2 mg/kg/Day or on Placebo (for Alfuzosin, 0.2 mg/kg/Day) during the efficacy phase

Arm type	Experimental
Investigational medicinal product name	Alfuzosin
Investigational medicinal product code	SL770499
Other name	
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Same dosage and administration details as for the period 1.

Number of subjects in period 2[1]	Alfuzosin 0.1 mg/kg/Day - 40 weeks extension	Alfuzosin 0.2 mg/kg/Day - 40 weeks extension
Started	80	83
Completed	75	78
Not completed	5	5
Adverse Event	2	1
Other	1	4
Protocol Violation	1	-
Lack of efficacy	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects who completed the 12-week double-blind period had the possibility to continue in the 40-week open-label extension period or to stop.
-54/56 subjects in the placebo group switched to Alfuzosin 0.1 mg/kg/Day (26 subjects) or 0.2 mg/kg/Day (28 subjects) according to initial randomization;
-54/55 subjects in the Alfuzosin 0.1 mg/kg/Day continued;
- 55/56 subjects in the Alfuzosin 0.2 mg/kg/Day continued.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo - 12 weeks
Reporting group description:	
Placebo (for Alfuzosin 0.1 mg/kg/Day) or placebo (for Alfuzosin 0.2 mg/kg/Day) for 12 weeks.	
Reporting group title	Alfuzosin 0.1 mg/kg/Day - 12 weeks
Reporting group description:	
Alfuzosin 0.1 mg/kg/Day for 12 weeks.	
Reporting group title	Alfuzosin 0.2 mg/kg/Day - 12 weeks
Reporting group description:	
Alfuzosin, 0.2 mg/kg/Day for 12 weeks.	

Reporting group values	Placebo - 12 weeks	Alfuzosin 0.1 mg/kg/Day - 12 weeks	Alfuzosin 0.2 mg/kg/Day - 12 weeks
Number of subjects	57	57	58
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			
Not recorded			
Age continuous			
Units: years			
arithmetic mean	8.3	7.9	8.7
standard deviation	± 4.4	± 3.9	± 3.9
Gender categorical			
Units: Subjects			
Female	28	27	30
Male	29	30	28
Urinary Tract Infection (UTI) history in the last 3 months			
Units: Subjects			
No UTI episode	48	50	40
One UTI episode	8	5	16
Two UTI episodes	1	2	2
Study drug formulation			
Units: Subjects			
Solution (2-7 years)	28	28	28
Solution (8-16 years)	8	10	9
Tablets (8-16 years)	21	19	21

Reporting group values	Total		
Number of subjects	172		
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		
Not recorded	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	85		
Male	87		
Urinary Tract Infection (UTI) history in the last 3 months Units: Subjects			
No UTI episode	138		
One UTI episode	29		
Two UTI episodes	5		
Study drug formulation Units: Subjects			
Solution (2-7 years)	84		
Solution (8-16 years)	27		
Tablets (8-16 years)	61		

End points

End points reporting groups

Reporting group title	Placebo - 12 weeks
Reporting group description:	
Placebo (for Alfuzosin 0.1 mg/kg/Day) or placebo (for Alfuzosin 0.2 mg/kg/Day) for 12 weeks.	
Reporting group title	Alfuzosin 0.1 mg/kg/Day - 12 weeks
Reporting group description:	
Alfuzosin 0.1 mg/kg/Day for 12 weeks.	
Reporting group title	Alfuzosin 0.2 mg/kg/Day - 12 weeks
Reporting group description:	
Alfuzosin, 0.2 mg/kg/Day for 12 weeks.	
Reporting group title	Alfuzosin 0.1 mg/kg/Day - 40 weeks extension
Reporting group description:	
Alfuzosin 0.1 mg/kg/Day for 40 additional weeks open-label to subjects on Alfuzosin, 0.1 mg/kg/Day or on Placebo (for Alfuzosin, 0.1 mg/kg/Day) during the efficacy phase.	
Reporting group title	Alfuzosin 0.2 mg/kg/Day - 40 weeks extension
Reporting group description:	
Alfuzosin 0.2 mg/kg/Day for 40 additional weeks open-label to subjects on Alfuzosin, 0.2 mg/kg/Day or on Placebo (for Alfuzosin, 0.2 mg/kg/Day) during the efficacy phase	
Subject analysis set title	Subjects Exposed to Alfuzosin 0.1 mg/kg/Day
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least one dose of Alfuzosin 0.1 mg/kg/Day during the overall study period (efficacy phase and/or safety extension phase) and regardless of the amount of treatment received.	
Subject analysis set title	Subjects Exposed to Alfuzosin 0.2 mg/kg/Day
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least one dose of Alfuzosin 0.2 mg/kg/Day during the overall study period (efficacy phase and/or safety extension phase) and regardless of the amount of treatment received.	

Primary: Number of Subjects With Detrusor LPP Less Than (<) 40 cm H2O at 12 Weeks

End point title	Number of Subjects With Detrusor LPP Less Than (<) 40 cm H2O at 12 Weeks

End point description:

Detrusor LPP was measured by cystometry. For each measure, 2 or 3 cystometries were carried out depending on the difference between the 2 first LPP values (if the difference >=20 cm H2O, a third cystometry was done). The lowest value was retained. Investigators reading was then consolidated by the review of all cystometry data by 2 external "Expert Reviewers", who were blinded for the study treatment.

The analysis was performed on consolidated investigators data (that is, endorsed by the Investigator taking into account reviewers opinion).
The Intent-to-treat (ITT) population was used for the analysis. All randomized subjects were included in the analysis in the treatment group to which they were allocated as per randomization.

End point type	Primary

End point timeframe:

12 weeks (double blind treatment period)

End point values	Placebo - 12 weeks	Alfuzosin 0.1 mg/kg/Day - 12 weeks	Alfuzosin 0.2 mg/kg/Day - 12 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	57	58	
Units: subject				
< 40 cmH2O ("Success")	23	23	28	
≥ 40 cmH2O or missing ("Failure")	34	34	30	

Statistical analyses

Statistical analysis title	Alfuzosin 0.1 mg/kg/Day vs. Placebo
Comparison groups	Placebo - 12 weeks v Alfuzosin 0.1 mg/kg/Day - 12 weeks
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [1]
Method	Fisher exact

Notes:

[1] - P-value was adjusted for multiplicity using the Hochberg procedure. The a priori threshold for statistical significance was 0.05.

Statistical analysis title	Alfuzosin 0.2 mg/kg/Day vs. Placebo
Comparison groups	Placebo - 12 weeks v Alfuzosin 0.2 mg/kg/Day - 12 weeks
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91 [2]
Method	Fisher exact

Notes:

[2] - P-value was adjusted for multiplicity using the Hochberg procedure. The a priori threshold for statistical significance was 0.05.

Secondary: Detrusor LPP at Baseline and 12 Weeks

End point title	Detrusor LPP at Baseline and 12 Weeks

End point description:

Detrusor LPP was assessed at baseline and 12 weeks as described for the primary outcome measure. The analysis was performed on the ITT population excluding the subjects who didn't have baseline and/or post-baseline LPP values. Subjects were included in the treatment group to which they were allocated as per randomization.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo - 12 weeks	Alfuzosin 0.1 mg/kg/Day - 12 weeks	Alfuzosin 0.2 mg/kg/Day - 12 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	53	56	
Units: cmH2O				
arithmetic mean (standard deviation)				
Baseline	54.2 (± 12.6)	53.3 (± 13.4)	50.9 (± 10)	
12 Weeks	48.2 (± 23.4)	41.6 (± 18.2)	39.4 (± 19.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Detrusor LPP at 12 Weeks

End point title	Absolute Change in Detrusor LPP at 12 Weeks

End point description:

Absolute change = Detrusor LPP at 12 weeks - Detrusor LPP at baseline.
LS Means were estimated using a 3-way analysis of covariance (ANCOVA) with treatment group (alfuzosin 0.1 mg/kg/day, alfuzosin 0.2 mg/kg/day or placebo), age/formulation group (2-7 years of age on solution, 8-16 years of age on solution or 8-16 years of age on tablets) and anticholinergic/antimuscarinic use (yes or no) as fixed effects, and centered baseline detrusor LPP as covariate. The analysis was performed on the ITT population excluding the subjects who didn't have baseline and/or post-baseline value).

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo - 12 weeks	Alfuzosin 0.1 mg/kg/Day - 12 weeks	Alfuzosin 0.2 mg/kg/Day - 12 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	53	56	
Units: cm H2O				
least squares mean (standard error)	-5.4 (± 2.8)	-11.7 (± 2.8)	-12.5 (± 2.8)	

Statistical analyses

Statistical analysis title	Alfuzosin 0.1 mg/kg/Day vs. Placebo
Comparison groups	Alfuzosin 0.1 mg/kg/Day - 12 weeks v Placebo - 12 weeks

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.104 [4]
Method	ANCOVA
Parameter estimate	LS Mean difference versus Placebo
Point estimate	-6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.72
upper limit	1.29
Variability estimate	Standard error of the mean
Dispersion value	3.8

Notes:

[3] - Change in detrusor LPP was analyzed using a three-way analysis of covariance (ANCOVA) including 3 variables as fixed effects:
- Treatment group (alfuzosin 0.1 mg/kg/day, alfuzosin 0.2 mg/kg/day or placebo),
- Age/formulation group (2-7 years of age on solution, 8-16 years of age on solution or 8-16 years of age on tablets),
- Anticholinergic/antimuscarinic use (yes or no),
and using centered baseline detrusor LPP as covariate.

[4] - P-value was adjusted for multiplicity using the Hochberg procedure.
The a priori threshold for statistical significance was 0.05.

Statistical analysis title	Alfuzosin 0.2 mg/kg/Day vs. Placebo
Comparison groups	Placebo - 12 weeks v Alfuzosin 0.2 mg/kg/Day - 12 weeks
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.104 [5]
Method	ANCOVA
Parameter estimate	LS Mean difference versus Placebo
Point estimate	-7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.51
upper limit	0.39
Variability estimate	Standard error of the mean
Dispersion value	3.77

Notes:

[5] - P-value was adjusted for multiplicity using the Hochberg procedure. The a priori threshold for statistical significance was 0.05.

Secondary: Relative Change in Detrusor LPP at 12 Weeks

End point title	Relative Change in Detrusor LPP at 12 Weeks

End point description:

Relative change = 100 * (Detrusor LPP at 12 weeks - Detrusor LPP at baseline) / Detrusor LPP at baseline.
LS Means were estimated using the same ANCOVA model as for Absolute Change in Detrusor LPP.
The analysis was performed on the ITT population excluding the subjects who didn't have baseline and/or post-baseline value.

End point type	Secondary

End point timeframe:
Baseline and 12 weeks

End point values	Placebo - 12 weeks	Alfuzosin 0.1 mg/kg/Day - 12 weeks	Alfuzosin 0.2 mg/kg/Day - 12 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	53	56	
Units: percentage of cmH2O				
least squares mean (standard error)	-9.2 (± 5.53)	-20.6 (± 5.56)	-23.5 (± 5.51)	

Statistical analyses

Statistical analysis title	Alfuzosin 0.1 mg/kg/Day vs. Placebo
Comparison groups	Placebo - 12 weeks v Alfuzosin 0.1 mg/kg/Day - 12 weeks
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.1338 [7]
Method	ANCOVA
Parameter estimate	LS Mean difference versus Placebo
Point estimate	-11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.27
upper limit	3.53
Variability estimate	Standard error of the mean
Dispersion value	7.54

Notes:

[6] - Change in detrusor LPP was analyzed using a three-way analysis of covariance (ANCOVA) including 3 variables as fixed effects:

- Treatment group (alfuzosin 0.1 mg/kg/day, alfuzosin 0.2 mg/kg/day or placebo),
- Age/formulation group (2-7 years of age on solution, 8-16 years of age on solution or 8-16 years of age on tablets),
- Anticholinergic/antimuscarinic use (yes or no),

and using centered baseline detrusor LPP as covariate.

[7] - P-values was adjusted for multiplicity using the Hochberg procedure. The a priori threshold for statistical significance was 0.05.

Statistical analysis title	Alfuzosin 0.2 mg/kg/Day vs. Placebo
Comparison groups	Placebo - 12 weeks v Alfuzosin 0.2 mg/kg/Day - 12 weeks
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1152 [8]
Method	ANCOVA
Parameter estimate	LS Mean difference versus Placebo
Point estimate	-14.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.1
upper limit	0.47
Variability estimate	Standard error of the mean
Dispersion value	7.48

Notes:

[8] - P-value was adjusted for multiplicity using the Hochberg procedure. The a priori threshold for statistical significance was 0.05.

Secondary: Detrusor Compliance at Baseline and at 12 Weeks

End point title	Detrusor Compliance at Baseline and at 12 Weeks

End point description:

Detrusor compliance is defined as the relationship between change in detrusor volume and change in detrusor pressure.

It was calculated by dividing the volume change (ΔV) by the change in detrusor pressure (Δpdet) during that change in detrusor volume at leak point (C= ΔV/Δpdet).
The analysis was performed on the ITT population excluding the subjects who didn't have baseline and/or post baseline detrusor compliance values. Subjects were included in the treatment group to which they were allocated as per randomization.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo - 12 weeks	Alfuzosin 0.1 mg/kg/Day - 12 weeks	Alfuzosin 0.2 mg/kg/Day - 12 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	55	
Units: mL/cmH20				
arithmetic mean (standard deviation)				
Baseline	3.4 (± 2.8)	3.4 (± 2.8)	3.3 (± 2.5)	
12 weeks	4.8 (± 5)	5.3 (± 4.9)	5.8 (± 5.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Change in Detrusor Compliance at 12 Weeks

End point title	Relative Change in Detrusor Compliance at 12 Weeks

End point description:

Relative change = 100 * (Detrusor compliance at 12 weeks - Detrusor compliance at baseline) / Detrusor compliance at baseline

LS means were estimated using a 3-way analysis of covariance (ANCOVA) including treatment group (alfuzosin 0.1 mg/kg/day, alfuzosin 0.2 mg/kg/day or placebo), age/formulation group (2-7 years of age on solution, 8-16 years of age on solution or 8-16 years of age on tablets), anticholinergic/antimuscarinic use (yes or no) as fixed effects and centered baseline detrusor compliance as covariate.

The analysis was performed on the ITT population excluding the subjects who didn't have baseline and/or post-baseline value.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo - 12 weeks	Alfuzosin 0.1 mg/kg/Day - 12 weeks	Alfuzosin 0.2 mg/kg/Day - 12 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	55	
Units: percentage of mL/cmH2O				
least squares mean (standard error)	113.6 (± 35.26)	126.6 (± 35.76)	98.6 (± 35.24)	

Statistical analyses

Statistical analysis title	Alfuzosin 0.1 mg/kg/Day vs. Placebo

Statistical analysis description:

Change in detrusor compliance was analyzed using a three-way analysis of covariance (ANCOVA) including 3 variables as fixed effects:

- Treatment group (alfuzosin 0.1 mg/kg/day, alfuzosin 0.2 mg/kg/day or placebo),
- Age/formulation group (2-7 years of age on solution, 8-16 years of age on solution or 8-16 years of age on tablets),
- Anticholinergic/antimuscarinic use (yes or no),

and using centered baseline detrusor compliance as covariate.

Comparison groups	Alfuzosin 0.1 mg/kg/Day - 12 weeks v Placebo - 12 weeks
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7889 [9]
Method	ANCOVA

Notes:

[9] - P-value was adjusted for multiplicity using the Hochberg procedure. The a priori threshold for statistical significance was 0.05.

Statistical analysis title	Alfuzosin 0.2 mg/kg/Day vs. Placebo
Comparison groups	Placebo - 12 weeks v Alfuzosin 0.2 mg/kg/Day - 12 weeks
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7889 [10]
Method	ANCOVA

Notes:

[10] - P-value was adjusted for multiplicity using the Hochberg procedure. The a priori threshold for statistical significance was 0.05.

Secondary: Number of Subjects With Symptomatic UTI Episodes During the First 12 Weeks

End point title	Number of Subjects With Symptomatic UTI Episodes During the First 12 Weeks

End point description:

When a subject presented with symptoms such as pain, fever or hematuria (discretion of the Investigator), an urinalysis was performed including a dipstick and a quantitative urine culture.

A symptomatic UTI was defined as the presence of symptoms and a positive culture with > 100 000 Colony Forming Units (CFUs) with a single organism.

End point type	Secondary

End point timeframe:

12 weeks (double blind treatment period)

End point values	Placebo - 12 weeks	Alfuzosin 0.1 mg/kg/Day - 12 weeks	Alfuzosin 0.2 mg/kg/Day - 12 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	57	58	
Units: subjects				
No symptomatic UTI	50	53	51	
One symptomatic UTI	5	3	6	
Two symptomatic UTI	2	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Symptomatic UTI Episodes During the Overall Study Period

End point title	Number of Subjects With Symptomatic UTI Episodes During the Overall Study Period

End point description:

The analysis was performed on the safety population (that is, all subjects who received at least one dose of Alfuzosin regardless of the amount of treatment received). It included 3 + 3 subjects treated during the 1st treatment period only, 26 + 28 subjects treated during the 2nd treatment period only and 54 + 55 subjects treated during both periods.

End point type	Secondary

End point timeframe:

52 weeks (12 plus 40 weeks)

End point values	Subjects Exposed to Alfuzosin 0.1 mg/kg/Day	Subjects Exposed to Alfuzosin 0.2 mg/kg/Day		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	86		
Units: Subjects				
No symptomatic UTI	66	70		
One symptomatic UTI	12	13		

Two symptomatic UTI	3	0		
Three symptomatic UTI	1	1		
Four symptomatic UTI	1	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 52) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are treatment-emergent AEs that is AEs that developed/worsened during the 'on treatment period' (time from first dose of alfuzosin [study Day 1 for subjects who took alfuzosin during the double-blind phase and Week 12 for subjects who took placebo during the double-blind phase] to last dose of alfuzosin plus 48 hours [5 half lives]).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Alfuzosin 0.1 mg/kg/Day

Reporting group description:

Alfuzosin 0.1 mg/kg/Day tablet or solution orally for 52 weeks.

Reporting group title	Alfuzosin 0.2 mg/kg/Day

Reporting group description:

Alfuzosin 0.2 mg/kg/Day tablet or solution orally for 52 weeks.

Serious adverse events	Alfuzosin 0.1 mg/kg/Day	Alfuzosin 0.2 mg/kg/Day	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 83 (12.05%)	7 / 86 (8.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 83 (1.20%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	0 / 83 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventriculoperitoneal Shunt Malfunction			

subjects affected / exposed	1 / 83 (1.20%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Arnold-Chiari Malformation			
subjects affected / exposed	1 / 83 (1.20%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	2 / 83 (2.41%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tethered Cord Syndrome			
subjects affected / exposed	1 / 83 (1.20%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory Failure			
subjects affected / exposed	1 / 83 (1.20%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar Hypertrophy			
subjects affected / exposed	1 / 83 (1.20%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus Ulcer			
subjects affected / exposed	0 / 83 (0.00%)	2 / 86 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Impairment			

subjects affected / exposed	1 / 83 (1.20%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral Haemorrhage			
subjects affected / exposed	1 / 83 (1.20%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lobar Pneumonia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 83 (1.20%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	1 / 83 (1.20%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Alfuzosin 0.1 mg/kg/Day	Alfuzosin 0.2 mg/kg/Day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 83 (44.58%)	43 / 86 (50.00%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 83 (8.43%)	10 / 86 (11.63%)	
occurrences (all)	9	13	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 83 (9.64%)	10 / 86 (11.63%)	
occurrences (all)	14	13	
Vomiting			
subjects affected / exposed	4 / 83 (4.82%)	6 / 86 (6.98%)	
occurrences (all)	6	6	
Infections and infestations			
Cystitis			
subjects affected / exposed	5 / 83 (6.02%)	9 / 86 (10.47%)	
occurrences (all)	5	18	
Nasopharyngitis			
subjects affected / exposed	6 / 83 (7.23%)	12 / 86 (13.95%)	
occurrences (all)	8	17	
Pharyngitis			
subjects affected / exposed	8 / 83 (9.64%)	5 / 86 (5.81%)	
occurrences (all)	12	7	
Respiratory Tract Infection			
subjects affected / exposed	7 / 83 (8.43%)	5 / 86 (5.81%)	
occurrences (all)	9	8	
Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 83 (4.82%)	5 / 86 (5.81%)	
occurrences (all)	6	10	
Urinary Tract Infection			
subjects affected / exposed	9 / 83 (10.84%)	6 / 86 (6.98%)	
occurrences (all)	14	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2007	Modification of several aspects of the original protocol in order to define an exclusion criterion related to the study drug more precisely, to provide more details on the formulations used in the study, to change the PK sampling schedule, to better characterize the assessment of vital signs, and to revise the time window for cystometry.
06 October 2008	Modifications of the PK sampling schedule for subjects randomized after 31 August 2008, revision of the temporary treatment discontinuation procedure and characterization of the collection of laboratory results in more detail.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported