Clinical trial results:
12-week, Multicenter, Open-label, Non-comparative Study to Investigate Pharmacodynamic and Safety of Alfuzosin 0.2 mg/kg/Day in the Treatment of Children and Adolescents 2 - 16 Years of Age With Hydronephrosis Associated With Elevated Detrusor Leak Point Pressure of Neuropathic Etiology Followed by a 40-week Open-label Extension

Summary

EudraCT number	2007-000983-26
Trial protocol	PL EE BG SK ES
Global end of trial date	09 October 2009

Results information

Result version number	v1
This version publication date	01 April 2016
First version publication date	06 December 2014

Trial information

Trial identification

Sponsor protocol code	EFC6269

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00576823
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 & developpement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & developpement, 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	10 November 2009
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

Primary objective was to determine efficacy of Alfuzosin in the treatment of children and adolescents 2-16 years of age with newly diagnosed or progressive hydronephrosis due to elevated detrusor Leak Point Pressure (LPP) of neuropathic etiology.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Subjects continued their standard treatment including clean intermittent catheterization and anticholinergic/antimuscarinic agents. Antibiotics, over the counter analgesics, vitamins, dietary measures and/or laxatives were permitted if indicated.

Evidence for comparator:

NA

Actual start date of recruitment	06 March 2008
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	Slovakia: 2
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	India: 3
Worldwide total number of subjects	25
EEA total number of subjects	10

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)	21
Adolescents (12-17 years)	4
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 19 sites in 12 countries. A total of 43 subjects were screened between December 2007 and September 2008.

Pre-assignment

Screening details:

18/43 screened subjects were not included: Inclusion/Exclusion criteria not respected (16), Subject's request (1), Other (2).
Subjects could have several reasons for not being included. Eligible subjects received alfuzosin 0.2 mg/kg/day. Formulation/frequency assigned by Interactive Voice Response System as per age group,ability to swallow tablet.

Period 1

Period 1 title	12-week Efficacy Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Alfuzosin Solution 12 weeks - 2-7 Years

Arm description:

Alfuzosin solution for 12 weeks to children 2-7 years of age.

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

Dosage and administration details:

Alfuzosin solution 0.066 milligram per kilogram (mg/kg) three times daily (0.2 mg/kg/Day) administered orally for 12 weeks.

Arm title	Alfuzosin Solution 12 weeks - 8-16 Years

Arm description:

Alfuzosin solution 12 weeks to children and adolescents 8-16 years of age who were not able to swallow the tablets or preferred to take the solution or had a body weight less than (<) 30 kilogram (kg).

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

Dosage and administration details:

Alfuzosin solution 0.066 mg/kg three times daily (0.2 mg/kg/Day) administered orally for 12 weeks.

Arm title	Alfuzosin Tablet 12 weeks - 8-16 Years

Arm description:

Alfuzosin tablet for 12 weeks to children and adolescents 8-16 years of age who were able to swallow the tablets and had a body weight greater than or equal to (>=) 30 kg.

Arm type	Experimental

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

Dosage and administration details:

Alfuzosin tablet 0.1 mg/kg two times daily (0.2 mg/kg/Day) administered for 12 weeks.

Number of subjects in period 1	Alfuzosin Solution 12 weeks - 2-7 Years	Alfuzosin Solution 12 weeks - 8-16 Years	Alfuzosin Tablet 12 weeks - 8-16 Years
Started	12	6	7
Completed	11	6	7
Not completed	1	0	0
Parent's schedule issue	1	-	-

Period 2

Period 2 title	40-week Safety Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Alfuzosin Solution 40 weeks - 2-7 Years

Arm description:

Alfuzosin solution for additional 40 weeks to children 2-7 years of age.

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

Dosage and administration details:

Alfuzosin solution 0.066 mg/kg three times daily (0.2 mg/kg/Day) administered orally for 40 weeks.

Arm title	Alfuzosin Solution 40 weeks - 8-16 Years

Arm description:

Alfuzosin solution for additional 40 weeks to children and adolescents 8-16 years of age who were not able to swallow the tablets or preferred to take the solution or had a body weight <30 kg.

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

Dosage and administration details:

Alfuzosin solution 0.066 mg/kg three times daily (0.2 mg/kg/Day) administered orally for 40 weeks.

Arm title	Alfuzosin Tablet - 8-16 Years - 40 weeks

Arm description:

Alfuzosin tablet for additional 40 weeks to children and adolescents 8-16 years of age who were able to swallow the tablets and had a body weight >=30 kg.

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

Dosage and administration details:

Alfuzosin tablet 0.1 mg/kg two times daily (0.2 mg/kg/Day) administered for 40 weeks.

Number of subjects in period 2[1]	Alfuzosin Solution 40 weeks - 2-7 Years	Alfuzosin Solution 40 weeks - 8-16 Years	Alfuzosin Tablet - 8-16 Years - 40 weeks
Started	11	6	6
Completed	10	6	6
Not completed	1	0	0
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: One subject in the Alfuzosin Tablet 12 weeks - 8-16 Years arm refused to continue in the extension phase.

Baseline characteristics

Reporting groups	
Reporting group title	Alfuzosin Solution 12 weeks - 2-7 Years
Reporting group description:	
Alfuzosin solution for 12 weeks to children 2-7 years of age.	
Reporting group title	Alfuzosin Solution 12 weeks - 8-16 Years
Reporting group description:	
Alfuzosin solution 12 weeks to children and adolescents 8-16 years of age who were not able to swallow the tablets or preferred to take the solution or had a body weight less than (<) 30 kilogram (kg).	
Reporting group title	Alfuzosin Tablet 12 weeks - 8-16 Years
Reporting group description:	
Alfuzosin tablet for 12 weeks to children and adolescents 8-16 years of age who were able to swallow the tablets and had a body weight greater than or equal to (>=) 30 kg.	

Reporting group values	Alfuzosin Solution 12 weeks - 2-7 Years	Alfuzosin Solution 12 weeks - 8-16 Years	Alfuzosin Tablet 12 weeks - 8-16 Years
Number of subjects	12	6	7
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 Units: years			
arithmetic mean	4.3	10	11.2
standard deviation	± 1.5	± 1.7	± 2.3
Gender categorical Units: Subjects			
Female	7	4	5
Male	5	2	2
Type of hydronephrosis Units: Subjects			
Bilateral hydronephrosis (both kidneys affected)	11	4	5
Unilateral hydronephrosis (one kidney affected)	1	2	2
Urinary Tract Infection (UTI) history within the last 3 months Units: Subjects			
No UTI episode	9	4	6
One UTI episode	2	2	1
Two UTI episodes	1	0	0

Grade of hydronephrosis - Left kidney			
Hydronephrosis was investigated by ultrasound of the kidneys, and graded using the Society of Fetal Urology (SFU) classification (5-point ordinal scale grading hydronephrosis from 0 [No hydronephrosis] to 4 [worst condition]).			
Units: grade			
median	2	1.5	2
full range (min-max)	1 to 3	1 to 3	1 to 3
Grade of hydronephrosis - Right kidney			
Units: grade			
median	1	2	1
full range (min-max)	0 to 3	0 to 3	0 to 3
Duration of diagnosis for hydronephrosis			
Units: years			
arithmetic mean	1.83	5.45	3.35
standard deviation	± 2.3	± 4.2	± 3.05

Reporting group values	Total		
Number of subjects	25		
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			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	16		
Male	9		
Type of hydronephrosis			
Units: Subjects			
Bilateral hydronephrosis (both kidneys affected)	20		
Unilateral hydronephrosis (one kidney affected)	5		
Urinary Tract Infection (UTI) history within the last 3 months			
Units: Subjects			
No UTI episode	19		
One UTI episode	5		
Two UTI episodes	1		

Grade of hydronephrosis - Left kidney			
Hydronephrosis was investigated by ultrasound of the kidneys, and graded using the Society of Fetal Urology (SFU) classification (5-point ordinal scale grading hydronephrosis from 0 [No hydronephrosis] to 4 [worst condition]).			
Units: grade median full range (min-max)	- 		
Grade of hydronephrosis - Right kidney Units: grade median full range (min-max)	- 		
Duration of diagnosis for hydronephrosis Units: years arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	Alfuzosin Solution 12 weeks - 2-7 Years

Reporting group description:

Alfuzosin solution for 12 weeks to children 2-7 years of age.

Reporting group title	Alfuzosin Solution 12 weeks - 8-16 Years

Reporting group description:

Alfuzosin solution 12 weeks to children and adolescents 8-16 years of age who were not able to swallow the tablets or preferred to take the solution or had a body weight less than (<) 30 kilogram (kg).

Reporting group title	Alfuzosin Tablet 12 weeks - 8-16 Years

Reporting group description:

Alfuzosin tablet for 12 weeks to children and adolescents 8-16 years of age who were able to swallow the tablets and had a body weight greater than or equal to (>=) 30 kg.

Reporting group title	Alfuzosin Solution 40 weeks - 2-7 Years

Reporting group description:

Alfuzosin solution for additional 40 weeks to children 2-7 years of age.

Reporting group title	Alfuzosin Solution 40 weeks - 8-16 Years

Reporting group description:

Alfuzosin solution for additional 40 weeks to children and adolescents 8-16 years of age who were not able to swallow the tablets or preferred to take the solution or had a body weight <30 kg.

Reporting group title	Alfuzosin Tablet - 8-16 Years - 40 weeks

Reporting group description:

Alfuzosin tablet for additional 40 weeks to children and adolescents 8-16 years of age who were able to swallow the tablets and had a body weight >=30 kg.

Subject analysis set title	2-7 Years Subjects Exposed to Alfuzosin Solution
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects, 2-7 years of age, 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) regardless of the amount of treatment received.

Subject analysis set title	8-16 Years Subjects Exposed to Alfuzosin Solution
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects, 8-16 years of age, who received at least one dose of Alfuzosin solution 0.2 mg/kg/Day during the overall study period (efficacy phase and/or safety extension phase) regardless of the amount of treatment received.

Subject analysis set title	8-16 Years Subjects Exposed to Alfuzosin Tablet
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects, 8-16 years of age, who received at least one dose of Alfuzosin tablet 0.2 mg/kg/Day during the overall study period (efficacy phase and/or safety extension phase) regardless of the amount of treatment received.

Primary: Number of Subjects With a Decrease From Baseline >= 1 in the Society of Fetal Urology (SFU) Grade of Hydronephrosis

End point title	Number of Subjects With a Decrease From Baseline >= 1 in the Society of Fetal Urology (SFU) Grade of Hydronephrosis[1]

End point description:

Hydronephrosis was investigated by ultrasound and graded using SFU classification at each time point.

'Complete response' was assessed when bilateral hydronephrosis at baseline and grade decrease from baseline >=1 for both kidneys, or, unilateral hydronephrosis at baseline and grade decrease from baseline >=1 for the affected kidney without worsening of the other kidney.

'Partial response' was assessed when bilateral hydronephrosis at baseline and grade decrease from

baseline >=1 for one kidney without worsening of the other kidney.

The analysis was performed on the intent-to-treat (ITT) population (that is, all included subjects who received at least one dose of Alfuzosin) excluding the subjects who didn't have baseline SFU grade. Subjects without post-baseline SFU grade before Week 12 were included as non-responders.

End point type	Primary

End point timeframe:

baseline and 12 weeks (efficacy study phase)

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: This was an exploratory, open label, non-comparative trial. Analysis were purely descriptive.

End point values	Alfuzosin Solution 12 weeks - 2-7 Years	Alfuzosin Solution 12 weeks - 8-16 Years	Alfuzosin Tablet 12 weeks - 8-16 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	6	7	
Units: subjects				
Complete response	2	5	3	
- Bilateral hydronephrosis	1	3	1	
- Unilateral hydronephrosis	1	2	2	
Partial response	3	0	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Symptomatic Urinary Tract Infection (UTI) Episodes

End point title	Number of Subjects With Symptomatic Urinary Tract Infection (UTI) Episodes

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.

The analysis was performed on the ITT population (that is, all included subjects who received at least one dose of Alfuzosin).

End point type	Secondary

End point timeframe:

12 weeks (efficacy study phase)

End point values	Alfuzosin Solution 12 weeks - 2-7 Years	Alfuzosin Solution 12 weeks - 8-16 Years	Alfuzosin Tablet 12 weeks - 8-16 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	6	7	
Units: subject				
No symptomatic UTI	11	5	7	
One symptomatic UTI	0	1	0	
Two symptomatic UTI	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Symptomatic Urinary Tract Infection (UTI) Episodes

End point title	Number of Subjects With Symptomatic Urinary Tract Infection (UTI) Episodes

End point description:

The analysis was performed on the exposed population (that is, all subjects who received at least one dose of Alfuzosin regardless of the amount of treatment received).

End point type	Secondary

End point timeframe:

52 weeks (efficacy and extension study phases)

End point values	2-7 Years Subjects Exposed to Alfuzosin Solution	8-16 Years Subjects Exposed to Alfuzosin Solution	8-16 Years Subjects Exposed to Alfuzosin Tablet	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	6	7	
Units: subjects				
No symptomatic UTI	8	5	5	
One symptomatic UTI	2	0	2	
Two symptomatic UTI	2	0	0	
Three symptomatic UTI	0	1	0	

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 (52 weeks) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Treatment-emergent AEs are reported that is AEs that developed/worsened during on treatment period (time from 1st dose of drug up to 48 h [5 half lives] after last dose of drug of 12-week efficacy phase and up to time before 1st administration of extension phase for subjects continuing in the extension or after last dose of drug [for whole study]).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Afluzosin Solution - 2-7 years

Reporting group description:

All subjects, 2-7 years of age, 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) regardless of the amount of treatment received.

Reporting group title	Afluzosin Tablets - 8-16 years

Reporting group description:

All subjects, 8-16 years of age, who received at least one dose of Alfuzosin tablet 0.2 mg/kg/Day during the overall study period (efficacy phase and/or safety extension phase) regardless of the amount of treatment received.

Reporting group title	Afluzosin Solution - 8-16 years

Reporting group description:

All subjects, 8-16 years of age, who received at least one dose of Alfuzosin solution 0.2 mg/kg/Day during the overall study period (efficacy phase and/or safety extension phase) regardless of the amount of treatment received.

Serious adverse events	Afluzosin Solution - 2-7 years	Afluzosin Tablets - 8-16 years	Afluzosin Solution - 8-16 years
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	0 / 7 (0.00%)	2 / 6 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Femur Fracture			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric Injury			

subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus Urinary			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Impairment			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pyelonephritis			

subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Afluzosin Solution - 2-7 years	Afluzosin Tablets - 8-16 years	Afluzosin Solution - 8-16 years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 12 (75.00%)	5 / 7 (71.43%)	5 / 6 (83.33%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Forearm Fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Iatrogenic Injury			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Limb Injury			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Urethral Injury			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Oedema Peripheral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 7 (0.00%)	2 / 6 (33.33%)
occurrences (all)	2	0	2
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dry Mouth			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Vaginal Discharge			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory Disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis Allergic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Conjunctivitis Infective			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cystitis			
subjects affected / exposed	3 / 12 (25.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Ear Infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal Infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal Viral Infection			

subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	3 / 12 (25.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	1
Pharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pyelonephritis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 12 (16.67%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Urinary Tract Infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Viral Infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Viral Pharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Viral Rhinitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Viral Upper Respiratory Tract			

Infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2008	Several aspects of original protocol were modified in order to change the grading of hydronephrosis in the inclusion criteria (Grade 3 hydronephrosis was added), to clarify the grading of the Vesicoureteral Reflux (VUR) and grading of ureteral dilatation, to better characterize the assessment of vital signs, and to modify the schedule of the collection of pharmacokinetic samples and the schedule of the ultrasound assessments.
17 July 2008	Additional ultrasound assessments were scheduled and provided further clarification on the grading of the VUR and grading of ureteral dilatation. A detailed Investigator instruction letter for VUR grading was also provided to the sites.
06 October 2008	The temporary treatment discontinuation procedure was revised and characterized the collection of laboratory results in more detail. In addition, a few minor editorial changes were made to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported