



Clinical trial results:

A Multi-center, Open-label, Extension Study to Evaluate the Long-term Efficacy and Safety of Oral Tolvaptan Tablet Regimens in Subjects with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Summary

EudraCT number	2010-018401-10
Trial protocol	DE FR GB BE IT NL
Global end of trial date	29 February 2016

Results information

Result version number	v1 (current)
This version publication date	17 March 2017
First version publication date	17 March 2017

Trial information

Trial identification

Sponsor protocol code	156-08-271
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01214421
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, MD 20850
Public contact	Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp
Scientific contact	Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp

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	29 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 February 2016
Global end of trial reached?	Yes
Global end of trial date	29 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this ongoing open-label trial was to demonstrate whether tolvaptan modifies ADPKD progression as measured by changes in endpoints of total kidney volume (TKV) and renal function (eGFR CKD-EPI) measured from baseline in TEMPO 3:4 to Month 24 in TEMPO 4:4. Disease modification was evidenced further by the non-inferiority of endpoint progression slope during this trial for those receiving early-treatment with tolvaptan, as compared to those with delayed-treatment, ie, whose initial treatment was with placebo in Trial 2006-002768-24.

Protection of trial subjects:

This trial is being conducted under the investigational new drug exemption of the US FDA, 21 CFR Part 312. It is being performed in compliance with Good Clinical Practice, the sponsor's standard operating procedures, and ethical principles for the protection of human research subjects that have their origins in the Declaration of Helsinki. Consistent with ethical principles for the protection of human research subjects, no study procedures were performed on study candidates until written consent had been obtained from them. The informed consent form, protocol, and amendments for this study were submitted to and approved by the institutional review board (IRB) or ethics committee (EC) at each respective study center.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 May 2010
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	Argentina: 35
Country: Number of subjects enrolled	Australia: 43
Country: Number of subjects enrolled	Belgium: 55
Country: Number of subjects enrolled	Canada: 40
Country: Number of subjects enrolled	France: 66
Country: Number of subjects enrolled	Germany: 124
Country: Number of subjects enrolled	Italy: 45
Country: Number of subjects enrolled	Netherlands: 69
Country: Number of subjects enrolled	Poland: 71
Country: Number of subjects enrolled	Romania: 19
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	United Kingdom: 57
Country: Number of subjects enrolled	United States: 446

Worldwide total number of subjects	1083
EEA total number of subjects	506

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1083
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 1083 participants at 106 trial sites in 13 countries.

Pre-assignment

Screening details:

All subjects who completed a tolvaptan autosomal dominant polycystic kidney disease (ADPKD) or renal impairment trial were eligible to be screened for this study. The prespecified analyses were only for those that rolled over (transition time 13-829 days) from TEMPO 3:4 to month 24 in TEMPO 4:4.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label trial; blinding procedures were not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Trial 2006-002768-24 Prior Tolvaptan

Arm description:

Participants received a daily split-dose of tolvaptan titrated to the maximally tolerated dose, starting daily tolvaptan dose of 45mg/15mg titrated to 60mg/30mg, then 90mg/30mg based on tolerability were given orally twice daily until last participant originating from trial 2006-002768-24 who was eligible for efficacy analysis completed the Month 24 visit.

Arm type	Experimental
Investigational medicinal product name	Tolvaptan
Investigational medicinal product code	OPC-41061
Other name	OPC-156
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Daily split-dose of tolvaptan titrated to the maximally tolerated dose. Starting daily tolvaptan dose of 45mg/15mg titrated to 60mg/30mg, then 90mg/30mg based on tolerability.

Arm title	Trial 2006-002768-24 Prior Placebo
------------------	------------------------------------

Arm description:

Participants received placebo in previous trial 2006-002768-24 were enrolled in this study.

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

Dosage and administration details:

Participants received placebo in previous trial 2006-002768-24 were enrolled in this study.

Arm title	Other Trials Prior Tolvaptan
------------------	------------------------------

Arm description:

Participants received a daily split-dose of tolvaptan titrated to the maximally tolerated dose, starting daily tolvaptan dose of 45mg/15mg titrated to 60mg/30mg, then 90mg/30mg based on tolerability were given orally twice daily until last participant originating from other trials who was eligible for efficacy analysis completed the Month 24 visit.

Arm type	Experimental
Investigational medicinal product name	Tolvaptan
Investigational medicinal product code	OPC-41061
Other name	OPC-156
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Daily split-dose of tolvaptan titrated to the maximally tolerated dose. Starting daily tolvaptan dose of 45mg/15mg titrated to 60mg/30mg, then 90mg/30mg based on tolerability.

Arm title	Other Trials Prior Placebo
------------------	----------------------------

Arm description:

Participants received placebo in other previous trials were enrolled in this study.

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

Dosage and administration details:

Participants received placebo in other previous trials were enrolled in this study.

Number of subjects in period 1	Trial 2006-002768-24 Prior Tolvaptan	Trial 2006-002768-24 Prior Placebo	Other Trials Prior Tolvaptan
Started	557	314	181
Completed	507	256	143
Not completed	50	58	38
Physician decision	2	-	4
Consent withdrawn by subject	21	18	11
Adverse event, non-fatal	16	35	14
Withdrawal Criteria Met	3	-	2
Lost to follow-up	7	3	7
Sponsor discontinued study	1	2	-

Number of subjects in period 1	Other Trials Prior Placebo
Started	31
Completed	22
Not completed	9
Physician decision	-
Consent withdrawn by subject	2
Adverse event, non-fatal	3
Withdrawal Criteria Met	1
Lost to follow-up	3
Sponsor discontinued study	-

Baseline characteristics

Reporting groups

Reporting group title	Trial 2006-002768-24 Prior Tolvaptan
Reporting group description: Participants received a daily split-dose of tolvaptan titrated to the maximally tolerated dose, starting daily tolvaptan dose of 45mg/15mg titrated to 60mg/30mg, then 90mg/30mg based on tolerability were given orally twice daily until last participant originating from trial 2006-002768-24 who was eligible for efficacy analysis completed the Month 24 visit.	
Reporting group title	Trial 2006-002768-24 Prior Placebo
Reporting group description: Participants received placebo in previous trial 2006-002768-24 were enrolled in this study.	
Reporting group title	Other Trials Prior Tolvaptan
Reporting group description: Participants received a daily split-dose of tolvaptan titrated to the maximally tolerated dose, starting daily tolvaptan dose of 45mg/15mg titrated to 60mg/30mg, then 90mg/30mg based on tolerability were given orally twice daily until last participant originating from other trials who was eligible for efficacy analysis completed the Month 24 visit.	
Reporting group title	Other Trials Prior Placebo
Reporting group description: Participants received placebo in other previous trials were enrolled in this study.	

Reporting group values	Trial 2006-002768-24 Prior Tolvaptan	Trial 2006-002768-24 Prior Placebo	Other Trials Prior Tolvaptan
Number of subjects	557	314	181
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	557	314	181
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	42.2	42.5	40
standard deviation	± 6.9	± 7.2	± 10.1
Gender categorical			
Units: Subjects			
Female	254	156	91
Male	303	158	90

Reporting group values	Other Trials Prior Placebo	Total	
Number of subjects	31	1083	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	31	1083	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	35.6		
standard deviation	± 8.7	-	
Gender categorical Units: Subjects			
Female	15	516	
Male	16	567	

End points

End points reporting groups

Reporting group title	Trial 2006-002768-24 Prior Tolvaptan
Reporting group description: Participants received a daily split-dose of tolvaptan titrated to the maximally tolerated dose, starting daily tolvaptan dose of 45mg/15mg titrated to 60mg/30mg, then 90mg/30mg based on tolerability were given orally twice daily until last participant originating from trial 2006-002768-24 who was eligible for efficacy analysis completed the Month 24 visit.	
Reporting group title	Trial 2006-002768-24 Prior Placebo
Reporting group description: Participants received placebo in previous trial 2006-002768-24 were enrolled in this study.	
Reporting group title	Other Trials Prior Tolvaptan
Reporting group description: Participants received a daily split-dose of tolvaptan titrated to the maximally tolerated dose, starting daily tolvaptan dose of 45mg/15mg titrated to 60mg/30mg, then 90mg/30mg based on tolerability were given orally twice daily until last participant originating from other trials who was eligible for efficacy analysis completed the Month 24 visit.	
Reporting group title	Other Trials Prior Placebo
Reporting group description: Participants received placebo in other previous trials were enrolled in this study.	
Subject analysis set title	Early treated
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants were randomized to tolvaptan and placebo in trial 2006-002768-24.	
Subject analysis set title	Delayed treated
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants were enrolled and treated to tolvaptan and placebo in trial 2010-018401-10.	
Primary: Percent Change in Total Kidney Volume (TKV)	
End point title	Percent Change in Total Kidney Volume (TKV)
End point description: For participants continuing from protocol 2006-002768-24: change from trial 2006-002768-24 baseline TKV at month 24 of trial 2010-018401-10 comparing early-treated (those previously treated with tolvaptan) to delayed-treated (those previously treated with placebo).	
End point type	Primary
End point timeframe: 5+ years	

End point values	Early treated	Delayed treated		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	505	267		
Units: percent change from baseline				
arithmetic mean (standard deviation)	28.66 (± 26.14)	30.58 (± 27.21)		

Statistical analyses

Statistical analysis title	Treatment comparisons
Statistical analysis description:	
Derived from a MMRM analysis of the percent change from baseline in total kidney volume with fixed factors of treatment, visit, treatment visit interaction, hypertensive status, renal volume status and creatinine clearance status at baseline, region, baseline value, and baseline visit interaction as covariates, and with an unstructured variance covariance matrix.	
Comparison groups	Delayed treated v Early treated
Number of subjects included in analysis	772
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.358
Method	Mixed models analysis
Parameter estimate	Ratio of geometric means (final values)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.02

Secondary: Change in Estimated Glomerular Filtration Rate (eGFR)

End point title	Change in Estimated Glomerular Filtration Rate (eGFR)
End point description:	
For participants randomized to tolvaptan and placebo in trial 2006-002768-24 and enrolled and treated in trial 2010-018401-10 as early-treated and delayed-treated groups: change from trial 2006-002768-24 baseline eGFR at month 24 of trial 2010-018401-10.	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Early treated	Delayed treated		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	503	264		
Units: ml/min/1.73m ²				
least squares mean (standard deviation)	-16.77 (± 13.16)	-19.92 (± 16.4)		

Statistical analyses

Statistical analysis title	Treatment comparisons
Statistical analysis description:	
Derived from a mixed model repeated measures (MMRM) analysis with fixed factors of treatment, visit, treatment visit interaction, hypertensive status, renal volume status and creatinine clearance status at baseline, region, baseline value, and baseline visit interaction as covariates, and with a heterogeneous	

toeplitz variance covariance matrix.

Comparison groups	Delayed treated v Early treated
Number of subjects included in analysis	767
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	LS mean difference (final values)
Point estimate	3.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.462
upper limit	4.836

Secondary: Slope of TKV

End point title	Slope of TKV
End point description: For participants randomized to tolvaptan and placebo in trial 2006-002768-24 and enrolled and treated in trial 2010-018401-10 as early treated and delayed treatment groups: annual growth of TKV (slope) measured from TEMPO 4:4 baseline up to Month 24.	
End point type	Secondary
End point timeframe: 24 months	

End point values	Early treated	Delayed treated		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	509	268		
Units: %/Yr				
number (not applicable)	6.164	4.96		

Statistical analyses

Statistical analysis title	Treatment comparisons
Statistical analysis description: Derived from testing interaction of time and treatment using linear mixed model in which intercept and time are treated as random effects.	
Comparison groups	Early treated v Delayed treated

Number of subjects included in analysis	777
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0462
Method	Mixed models analysis
Parameter estimate	Ratio of geometric means (final values)
Point estimate	1.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.023

Secondary: Slope of eGFR (CKD-EPI)

End point title	Slope of eGFR (CKD-EPI)
End point description:	
For participants randomized to tolvaptan and placebo in trial 2006-002768-24 and enrolled and treated in trial 2010-018401-10 as early treated and delayed treatment groups: annual change in eGFR (slope) from 4:4 baseline up to Month 24.	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Early treated	Delayed treated		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	549	304		
Units: ml/min/1.73m ² /year				
number (not applicable)	-3.255	-3.142		

Statistical analyses

Statistical analysis title	Treatment comparisons
Statistical analysis description:	
Derived from testing interaction of time and treatment using linear mixed model in which intercept and time are treated as random effects.	
Comparison groups	Early treated v Delayed treated
Number of subjects included in analysis	853
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7259
Method	Mixed models analysis
Parameter estimate	Ratio of geometric means (final values)
Point estimate	-0.113

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.746
upper limit	0.52

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) and serious adverse events (SAEs) were reported from the signing of the informed consent form until the end of the study regardless of whether the subjects were on or off active study medication (approximately 5 years).

Adverse event reporting additional description:

The AEs were continued to be captured even when the study medication was discontinued for various participants. All subjects who died during the trial were in the rollover 251 tolvaptan treatment group. None of the 5 subjects with TEAEs that led to death were taking IMP at the time of death.

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	18.0
--------------------	------

Reporting groups

Reporting group title	Trial 2006-002768-24 Prior Tolvaptan
-----------------------	--------------------------------------

Reporting group description:

Participants received a daily split-dose of tolvaptan titrated to the maximally tolerated dose, starting daily tolvaptan dose of 45mg/15mg titrated to 60mg/30mg, then 90mg/30mg based on tolerability were given orally twice daily until last participant originating from trial 2006-002768-24 who was eligible for efficacy analysis completed the Month 24 visit.

Reporting group title	Trial 2006-002768-24 Prior Placebo
-----------------------	------------------------------------

Reporting group description:

Participants received placebo in previous trial 2006-002768-24 were enrolled in this study.

Reporting group title	Other Trials Prior Tolvaptan
-----------------------	------------------------------

Reporting group description:

Participants received a daily split-dose of tolvaptan titrated to the maximally tolerated dose, starting daily tolvaptan dose of 45mg/15mg titrated to 60mg/30mg, then 90mg/30mg based on tolerability were given orally twice daily until last participant originating from other trials who was eligible for efficacy analysis completed the Month 24 visit.

Reporting group title	Other Trials Prior Placebo
-----------------------	----------------------------

Reporting group description:

Participants received placebo in other previous trials were enrolled in this study.

Serious adverse events	Trial 2006-002768-24 Prior Tolvaptan	Trial 2006-002768-24 Prior Placebo	Other Trials Prior Tolvaptan
Total subjects affected by serious adverse events			
subjects affected / exposed	143 / 557 (25.67%)	79 / 314 (25.16%)	34 / 181 (18.78%)
number of deaths (all causes)	5	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	2 / 557 (0.36%)	0 / 314 (0.00%)	0 / 181 (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
Breast Cancer			

subjects affected / exposed	2 / 557 (0.36%)	0 / 314 (0.00%)	0 / 181 (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
Cervix Cancer Metastatic			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Cholesterin Granuloma Of Middle Ear			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Endometrial Cancer			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Stromal Tumour			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Intraductal Proliferative Breast Lesion			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Malignant Melanoma			
subjects affected / exposed	2 / 557 (0.36%)	0 / 314 (0.00%)	0 / 181 (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
Plasma Cell Myeloma			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Testis Cancer			

subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Leiomyoma			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aneurysm			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Aortic Dissection			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Arterial Stenosis			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Deep Vein Thrombosis			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Venous Disease			

subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian Vein Thrombosis			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Pregnancy, puerperium and perinatal conditions			
Ectopic Pregnancy			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gestational Hypertension			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Peripheral Swelling			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic Inflammatory Response Syndrome			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergy To Arthropod Sting			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atopy			

subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Drug Hypersensitivity			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Reproductive system and breast disorders			
Breast Discomfort			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Breast Haematoma			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Endometriosis			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postmenopausal Haemorrhage			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Prostatitis			

subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Lung Injury			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Nasal Septum Deviation			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Oropharyngeal Pain			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal Oedema			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Pulmonary Embolism			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Major Depression			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Suicide Attempt			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 557 (0.36%)	3 / 314 (0.96%)	5 / 181 (2.76%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	3 / 181 (1.66%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Bilirubin Increased			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Creatinine Increased			

subjects affected / exposed	6 / 557 (1.08%)	6 / 314 (1.91%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 6	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 557 (0.00%)	3 / 314 (0.96%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glomerular Filtration Rate Decreased			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Haemoglobin Decreased			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver Function Test Abnormal			
subjects affected / exposed	1 / 557 (0.18%)	2 / 314 (0.64%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Smear Cervix Abnormal			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Transaminases Increased			

subjects affected / exposed	3 / 557 (0.54%)	2 / 314 (0.64%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasopressin Challenge Test Abnormal			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White Blood Cell Count Increased			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Expired Product Administered			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Fall			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur Fracture			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot Fracture			

subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gun Shot Wound			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Incisional Hernia			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Joint Dislocation			
subjects affected / exposed	2 / 557 (0.36%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	2 / 557 (0.36%)	0 / 314 (0.00%)	0 / 181 (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
Ligament Rupture			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Ligament Sprain			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Limb Injury			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus Injury			

subjects affected / exposed	2 / 557 (0.36%)	0 / 314 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Haematoma			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shunt Occlusion			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon Rupture			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital Cystic Kidney Disease			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Cardiac disorders			
Accelerated Idioventricular Rhythm			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Coronary Syndrome			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Angina Pectoris			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	2 / 557 (0.36%)	2 / 314 (0.64%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	2 / 557 (0.36%)	0 / 314 (0.00%)	0 / 181 (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
Cardiac Arrest			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	3 / 557 (0.54%)	0 / 314 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Ischaemia			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Pericarditis			

subjects affected / exposed	2 / 557 (0.36%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prinzmetal Angina			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Arrhythmia			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Tachycardia			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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			
Amnesia			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid Artery Aneurysm			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Carotid Artery Dissection			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Cerebral Atrophy			

subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular Accident			
subjects affected / exposed	1 / 557 (0.18%)	3 / 314 (0.96%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Essential Tremor			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial Aneurysm			
subjects affected / exposed	3 / 557 (0.54%)	3 / 314 (0.96%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Radiculopathy			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Occipital Neuralgia			

subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Polyneuropathy			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Subarachnoid Haemorrhage			
subjects affected / exposed	2 / 557 (0.36%)	0 / 314 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	2 / 557 (0.36%)	0 / 314 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 557 (0.36%)	1 / 314 (0.32%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Retinal Detachment			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Hernia			
subjects affected / exposed	1 / 557 (0.18%)	2 / 314 (0.64%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	1 / 557 (0.18%)	2 / 314 (0.64%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Lower			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Abdominal Pain Upper			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis Erosive			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Gastroesophageal Reflux Disease			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Ileus Paralytic			

subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Inguinal Hernia			
subjects affected / exposed	5 / 557 (0.90%)	3 / 314 (0.96%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Fistula			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Polyp			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Localised Intraabdominal Fluid Collection			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Oesophagitis			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Acute			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Necrotising			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Umbilical Hernia			

subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary Dyskinesia			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Cholecystitis			
subjects affected / exposed	0 / 557 (0.00%)	2 / 314 (0.64%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Acute			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-Induced Liver Injury			
subjects affected / exposed	0 / 557 (0.00%)	2 / 314 (0.64%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic Hepatic Cyst			

subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Hepatic Cyst			
subjects affected / exposed	4 / 557 (0.72%)	0 / 314 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Failure			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Hepatic Pain			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Hepatocellular Injury			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal Hypertension			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	2 / 557 (0.36%)	0 / 314 (0.00%)	0 / 181 (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
Eczema			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hidradenitis			

subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Urticaria			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	2 / 557 (0.36%)	3 / 314 (0.96%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus Ureteric			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus Urinary			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Chronic Kidney Disease			
subjects affected / exposed	5 / 557 (0.90%)	2 / 314 (0.64%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Cyst			

subjects affected / exposed	2 / 557 (0.36%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Cyst Haemorrhage			
subjects affected / exposed	6 / 557 (1.08%)	4 / 314 (1.27%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 7	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Cyst Ruptured			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure			
subjects affected / exposed	2 / 557 (0.36%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Haemorrhage			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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	6 / 557 (1.08%)	3 / 314 (0.96%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 7	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Pain			
subjects affected / exposed	1 / 557 (0.18%)	2 / 314 (0.64%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Incontinence			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urine Flow Decreased			

subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Hypothyroidism			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Bursitis			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondropathy			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Flank Pain			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Foot Deformity			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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

Intervertebral Disc Protrusion			
subjects affected / exposed	2 / 557 (0.36%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loose Body In Joint			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Pain In Extremity			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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			
Abdominal Abscess			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Appendicitis			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Bronchopulmonary Aspergillosis			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter Site Infection			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicitis			

subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Sinusitis			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Clostridium Difficile Infection			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Diarrhoea Infectious			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Diverticulitis			
subjects affected / exposed	2 / 557 (0.36%)	1 / 314 (0.32%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis Viral			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital Herpes			

subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Kidney Infection			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar Pneumonia			
subjects affected / exposed	2 / 557 (0.36%)	0 / 314 (0.00%)	0 / 181 (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
Mastitis			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Pharyngitis Streptococcal			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Pulmonary Tuberculosis			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Pyelonephritis			
subjects affected / exposed	6 / 557 (1.08%)	1 / 314 (0.32%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Cyst Infection			

subjects affected / exposed	9 / 557 (1.62%)	3 / 314 (0.96%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 10	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 557 (0.54%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 557 (0.00%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteritis			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	4 / 557 (0.72%)	1 / 314 (0.32%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 557 (0.18%)	1 / 314 (0.32%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral Pericarditis			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Wound Infection			

subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 557 (0.00%)	0 / 314 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 557 (0.18%)	0 / 314 (0.00%)	0 / 181 (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

Serious adverse events	Other Trials Prior Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 31 (16.13%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast Cancer			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervix Cancer Metastatic			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholesterin Granuloma Of Middle Ear			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial Cancer			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Stromal Tumour			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intraductal Proliferative Breast Lesion			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant Melanoma			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Plasma Cell Myeloma			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Testis Cancer			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine Leiomyoma			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aneurysm			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic Dissection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arterial Stenosis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep Vein Thrombosis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral Venous Disease			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subclavian Vein Thrombosis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Ectopic Pregnancy			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gestational Hypertension			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Peripheral Swelling			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Systemic Inflammatory Response Syndrome			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergy To Arthropod Sting			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atopy			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug Hypersensitivity			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Breast Discomfort			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast Haematoma			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometriosis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Menorrhagia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metrorrhagia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postmenopausal Haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostatitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute Lung Injury			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nasal Septum Deviation			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oropharyngeal Pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pharyngeal Oedema			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary Embolism			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Major Depression			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide Attempt			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			

Alanine Aminotransferase Increased				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate Aminotransferase Increased				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood Alkaline Phosphatase Increased				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood Bilirubin Increased				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood Creatine Phosphokinase Increased				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood Creatinine Increased				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood Lactate Dehydrogenase Increased				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gamma-Glutamyltransferase Increased				

subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Glomerular Filtration Rate Decreased				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoglobin Decreased				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic Enzyme Increased				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver Function Test Abnormal				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Smear Cervix Abnormal				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transaminases Increased				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vasopressin Challenge Test Abnormal				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
White Blood Cell Count Increased				

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Expired Product Administered			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femur Fracture			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Foot Fracture			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gun Shot Wound			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Incisional Hernia			

subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint Dislocation				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laceration				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament Rupture				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament Sprain				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Limb Injury				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meniscus Injury				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal Haematoma				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Shunt Occlusion				

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tendon Rupture			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Congenital Cystic Kidney Disease			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Accelerated Idioventricular Rhythm			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute Coronary Syndrome			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute Myocardial Infarction			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina Pectoris			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial Fibrillation			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Bradycardia				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac Arrest				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary Artery Disease				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial Infarction				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial Ischaemia				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prinzmetal Angina				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus Arrhythmia				

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ataxia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Carotid Artery Aneurysm			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Carotid Artery Dissection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral Atrophy			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular Accident			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			

subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Essential Tremor				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intracranial Aneurysm				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic Stroke				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar Radiculopathy				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Occipital Neuralgia				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Polyneuropathy				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subarachnoid Haemorrhage				

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient Ischaemic Attack			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal Detachment			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Hernia			

subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal Pain				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal Pain Lower				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal Pain Upper				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis Erosive				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal Reflux Disease				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus Paralytic				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal Hernia				

subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal Fistula				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large Intestine Polyp				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Localised Intraabdominal Fluid Collection				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis Acute				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis Necrotising				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Umbilical Hernia				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Biliary Dyskinesia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis Acute			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug-Induced Liver Injury			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic Hepatic Cyst			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic Cyst			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic Failure			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic Pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatocellular Injury			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Portal Hypertension			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eczema			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hidradenitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urticaria			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Calculus Ureteric			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Calculus Urinary			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic Kidney Disease			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephropathy			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Cyst			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Cyst Haemorrhage			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Cyst Ruptured			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Failure			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Impairment			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary Incontinence			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urine Flow Decreased			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Goitre			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypothyroidism			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bursitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chondropathy			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Flank Pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Foot Deformity			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Loose Body In Joint			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain In Extremity			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal Abscess			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchopulmonary Aspergillosis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Catheter Site Infection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervicitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic Sinusitis			

subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium Difficile Colitis				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium Difficile Infection				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea Infectious				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis Viral				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Genital Herpes				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Kidney Infection				

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lobar Pneumonia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mastitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pharyngitis Streptococcal			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary Tuberculosis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Cyst Infection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ureteritis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral Pericarditis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound Infection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Gout			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Trial 2006-002768-24 Prior Tolvaptan	Trial 2006-002768-24 Prior Placebo	Other Trials Prior Tolvaptan
Total subjects affected by non-serious adverse events			
subjects affected / exposed	528 / 557 (94.79%)	310 / 314 (98.73%)	175 / 181 (96.69%)
Investigations			
Aspartate Aminotransferase Increased			
subjects affected / exposed	19 / 557 (3.41%)	5 / 314 (1.59%)	7 / 181 (3.87%)
occurrences (all)	25	7	7
Blood Creatinine Increased			
subjects affected / exposed	96 / 557 (17.24%)	39 / 314 (12.42%)	20 / 181 (11.05%)
occurrences (all)	113	49	25
Vascular disorders			
Hypertension			
subjects affected / exposed	160 / 557 (28.73%)	82 / 314 (26.11%)	42 / 181 (23.20%)
occurrences (all)	195	108	45
Nervous system disorders			
Dizziness			
subjects affected / exposed	30 / 557 (5.39%)	36 / 314 (11.46%)	13 / 181 (7.18%)
occurrences (all)	35	48	15
Headache			
subjects affected / exposed	75 / 557 (13.46%)	56 / 314 (17.83%)	20 / 181 (11.05%)
occurrences (all)	152	90	23
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	35 / 557 (6.28%)	20 / 314 (6.37%)	13 / 181 (7.18%)
occurrences (all)	39	25	13
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	53 / 557 (9.52%)	54 / 314 (17.20%)	32 / 181 (17.68%)
occurrences (all)	66	71	41
Oedema Peripheral			
subjects affected / exposed	51 / 557 (9.16%)	32 / 314 (10.19%)	9 / 181 (4.97%)
occurrences (all)	67	41	11
Thirst			
subjects affected / exposed	261 / 557 (46.86%)	161 / 314 (51.27%)	80 / 181 (44.20%)
occurrences (all)	291	196	99
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	37 / 557 (6.64%)	15 / 314 (4.78%)	13 / 181 (7.18%)
occurrences (all)	43	17	14
Abdominal Pain Upper			
subjects affected / exposed	23 / 557 (4.13%)	16 / 314 (5.10%)	4 / 181 (2.21%)
occurrences (all)	30	20	4
Constipation			
subjects affected / exposed	23 / 557 (4.13%)	25 / 314 (7.96%)	8 / 181 (4.42%)
occurrences (all)	25	27	10
Diarrhoea			
subjects affected / exposed	60 / 557 (10.77%)	30 / 314 (9.55%)	13 / 181 (7.18%)
occurrences (all)	78	38	14
Dry Mouth			
subjects affected / exposed	45 / 557 (8.08%)	44 / 314 (14.01%)	25 / 181 (13.81%)
occurrences (all)	54	59	30
Dyspepsia			
subjects affected / exposed	29 / 557 (5.21%)	15 / 314 (4.78%)	8 / 181 (4.42%)
occurrences (all)	29	17	8
Gastrooesophageal Reflux Disease			
subjects affected / exposed	24 / 557 (4.31%)	11 / 314 (3.50%)	10 / 181 (5.52%)
occurrences (all)	26	12	10
Nausea			
subjects affected / exposed	42 / 557 (7.54%)	32 / 314 (10.19%)	22 / 181 (12.15%)
occurrences (all)	60	39	28
Vomiting			

subjects affected / exposed occurrences (all)	32 / 557 (5.75%) 42	15 / 314 (4.78%) 15	9 / 181 (4.97%) 14
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	42 / 557 (7.54%) 51	23 / 314 (7.32%) 25	10 / 181 (5.52%) 10
Skin and subcutaneous tissue disorders Dry Skin subjects affected / exposed occurrences (all)	7 / 557 (1.26%) 7	12 / 314 (3.82%) 12	7 / 181 (3.87%) 7
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) Nocturia subjects affected / exposed occurrences (all) Pollakiuria subjects affected / exposed occurrences (all) Polyuria subjects affected / exposed occurrences (all) Renal Cyst Ruptured subjects affected / exposed occurrences (all) Renal Pain subjects affected / exposed occurrences (all)	47 / 557 (8.44%) 68 145 / 557 (26.03%) 156 30 / 557 (5.39%) 32 231 / 557 (41.47%) 264 3 / 557 (0.54%) 3 147 / 557 (26.39%) 260	36 / 314 (11.46%) 49 111 / 314 (35.35%) 137 24 / 314 (7.64%) 29 175 / 314 (55.73%) 215 2 / 314 (0.64%) 2 90 / 314 (28.66%) 179	13 / 181 (7.18%) 23 94 / 181 (51.93%) 113 20 / 181 (11.05%) 26 111 / 181 (61.33%) 128 2 / 181 (1.10%) 2 43 / 181 (23.76%) 78
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back Pain subjects affected / exposed occurrences (all)	57 / 557 (10.23%) 84 60 / 557 (10.77%) 77	16 / 314 (5.10%) 23 40 / 314 (12.74%) 59	13 / 181 (7.18%) 14 15 / 181 (8.29%) 18

Muscle Spasms subjects affected / exposed occurrences (all)	28 / 557 (5.03%) 35	18 / 314 (5.73%) 20	5 / 181 (2.76%) 5
Pain In Extremity subjects affected / exposed occurrences (all)	38 / 557 (6.82%) 42	11 / 314 (3.50%) 11	7 / 181 (3.87%) 7
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	30 / 557 (5.39%) 37	17 / 314 (5.41%) 23	4 / 181 (2.21%) 4
Gastroenteritis subjects affected / exposed occurrences (all)	31 / 557 (5.57%) 37	20 / 314 (6.37%) 22	9 / 181 (4.97%) 11
Gastroenteritis Viral subjects affected / exposed occurrences (all)	12 / 557 (2.15%) 16	7 / 314 (2.23%) 10	6 / 181 (3.31%) 7
Influenza subjects affected / exposed occurrences (all)	42 / 557 (7.54%) 48	25 / 314 (7.96%) 30	18 / 181 (9.94%) 21
Nasopharyngitis subjects affected / exposed occurrences (all)	83 / 557 (14.90%) 130	55 / 314 (17.52%) 90	18 / 181 (9.94%) 28
Sinusitis subjects affected / exposed occurrences (all)	40 / 557 (7.18%) 48	19 / 314 (6.05%) 27	13 / 181 (7.18%) 20
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	61 / 557 (10.95%) 110	35 / 314 (11.15%) 52	28 / 181 (15.47%) 44
Urinary Tract Infection subjects affected / exposed occurrences (all)	61 / 557 (10.95%) 89	33 / 314 (10.51%) 51	16 / 181 (8.84%) 27
Metabolism and nutrition disorders			
Decreased Appetite subjects affected / exposed occurrences (all)	5 / 557 (0.90%) 5	13 / 314 (4.14%) 13	12 / 181 (6.63%) 12
Gout			

subjects affected / exposed	35 / 557 (6.28%)	9 / 314 (2.87%)	6 / 181 (3.31%)
occurrences (all)	54	12	7
Hyperuricaemia			
subjects affected / exposed	37 / 557 (6.64%)	15 / 314 (4.78%)	2 / 181 (1.10%)
occurrences (all)	43	18	2
Polydipsia			
subjects affected / exposed	62 / 557 (11.13%)	51 / 314 (16.24%)	38 / 181 (20.99%)
occurrences (all)	66	57	39
Vitamin D Deficiency			
subjects affected / exposed	34 / 557 (6.10%)	16 / 314 (5.10%)	13 / 181 (7.18%)
occurrences (all)	36	16	14

Non-serious adverse events	Other Trials Prior Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 31 (93.55%)		
Investigations			
Aspartate Aminotransferase Increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Blood Creatinine Increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Oedema Peripheral			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Thirst			
subjects affected / exposed	13 / 31 (41.94%)		
occurrences (all)	21		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Abdominal Pain Upper			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Dry Mouth			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	5		
Dyspepsia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Nausea			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 31 (6.45%)</p> <p>3</p> <p>2 / 31 (6.45%)</p> <p>2</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 31 (0.00%)</p> <p>0</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Dry Skin</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 31 (9.68%)</p> <p>3</p>		
<p>Renal and urinary disorders</p> <p>Haematuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nocturia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pollakiuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Polyuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Renal Cyst Ruptured</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Renal Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 31 (12.90%)</p> <p>6</p> <p>17 / 31 (54.84%)</p> <p>21</p> <p>4 / 31 (12.90%)</p> <p>4</p> <p>22 / 31 (70.97%)</p> <p>30</p> <p>3 / 31 (9.68%)</p> <p>3</p> <p>7 / 31 (22.58%)</p> <p>12</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 31 (3.23%)</p> <p>1</p>		

Back Pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Muscle Spasms			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Pain In Extremity			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Gastroenteritis Viral			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Sinusitis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Urinary Tract Infection			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Metabolism and nutrition disorders			

Decreased Appetite			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Gout			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Hyperuricaemia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Polydipsia			
subjects affected / exposed	6 / 31 (19.35%)		
occurrences (all)	6		
Vitamin D Deficiency			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2011	Amendment 1 (dated 02 Jun 2011) added safety laboratory tests at 3-month intervals between the 6-month scheduled visits, added guidance to investigators regarding the work up of potential Hy's criteria cases, and revised the statistical approach to the disease modification analysis. Additional changes were made that did not have a major impact on trial conduct. Minor procedural changes included a modification of titration instructions to allow all participants to titrate to the highest dose tolerated regardless of previous trial dosing; the addition of eGFR calculation by CKD-EPI equation; extension of trial enrollment at the sponsor's discretion; change to entry criteria to allow participants who were unable to complete prior trials due to exceptional circumstances making them eligible for enrollment beginning in January 2012, with permission of the sponsor and approval of the medical monitor (these participants had to complete enrollment by May 2012); change to entry criteria to extend the timing of screening eGFR; and combining of the entry exclusion criterion regarding marketed therapies affecting PKD cysts with the efficacy exclusion criterion of medications or illnesses likely to confound endpoint assessments.
19 February 2013	Amendment 2 (dated 19 Feb 2013) clarified that hepatitis testing at screening was optional and that participants who chose to undergo hepatitis testing might receive appropriate pre- and post-screening counseling as per local requirements and best practices. It also clarified procedures for the inclusion and ongoing care of participants with eGFR < 30 mL/min/1.73m ² (by MDRD). It also specified the SAEs that were considered related to the underlying ADPKD being studied in the trial and, therefore, might not be reported to regulatory authorities as expedited reports. Amendment 2 also added the option to include the following evaluations to the protocol-specified chemistry panel if clinically indicated and approved by the medical monitor: serum calcium, phosphorous, parathyroid hormone, vitamin D, and bicarbonate levels. It also added serum laboratory tests at 1-month (\pm 1 week) intervals up to Month 18 between the scheduled 6-month visits rather than at 3-month intervals and reporting of product quality complaints. It clarified that sites would receive only the TKV assessment following each MRI evaluation, and trial participation options after participants discontinued tolvaptan. The exploratory endpoints of progressing hypertension and worsening albuminuria were removed.
11 March 2014	Amendment 3 (dated 11 Mar 2014) incorporated provisions for participants who terminated from this trial early to continue on tolvaptan treatment (under this protocol) until a subsequent trial was ready to screen and enroll participants. The exact dates for trial completion varied among sites, according to the approval dates of the individual country IRB/IECs for sites, but the trial was expected to be completed by 31 Dec 2014. Safety information for the overall program was updated, specifically the possible clinical importance of elevated hepatic transaminase levels as early indicators of hepatic toxicity. Amendment 3 also provided additional information on DNA genotyping, clarified information on the need for an MRI 24 months on treatment, and established a lower titrated dose, on a case-by-case basis, with prior consultation and approval of the medical monitor. Administrative Change 1 (dated 01 May 2014) was made primarily to restore the list of Institutions Concerned with the Trial (contained in Appendix 2 of the protocol), plus 2 additional institutions, as the former was accidentally deleted from the existing, approved amendment during the development of Amendment 3. Names of sponsor personnel listed in protocol Appendix 1 were updated to clearly depict administrative changes, and minor editorial changes were also made.

Notes:

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 trial did not meet its primary endpoint as both groups showed similar decreases in the rate of TKV growth due in part to unforeseen limitations in the trial design. However, early-treatment resulted in cumulative improvements in renal function.
--

Notes: