



## Clinical trial results: Optimal Treatment of Drug Resistant Hypertension Summary

EudraCT number	2008-007149-30
Trial protocol	GB
Global end of trial date	26 June 2015

### Results information

Result version number	v1 (current)
This version publication date	21 February 2020
First version publication date	21 February 2020
Summary attachment (see zip file)	Pathway 2 Publication (Pathway 2 Publication.pdf)

### Trial information

#### Trial identification

Sponsor protocol code	Pathway 2
-----------------------	-----------

#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02369081
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust & the University of Cambridge
Sponsor organisation address	R&D Department, Addenbrooke's Hospital, Hills Road, Cambridge, United Kingdom, CB2 0QQ
Public contact	Morris J Brown, William Harvey Research Institute, Queen Mary University of London, morris.brown@qmul.ac.uk
Scientific contact	Morris J Brown, William Harvey Research Institute, Queen Mary University of London, morris.brown@qmul.ac.uk

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	04 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 June 2015
Global end of trial reached?	Yes
Global end of trial date	26 June 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to test our primary hypothesis which states that the commonest cause of resistant hypertension is excessive sodium retention, and that further diuretic therapy, i.e. spironolactone will be superior to other potential "add-on drugs" for people with inadequate blood pressure control despite treatment with three drugs, i.e. Ace Inhibitors, Calcium Channel Blockers and Diuretics (A+C+D).

Protection of trial subjects:

Serious Adverse Events were documented and reported to the Chief Investigator and to regulatory authorities, in accordance with local and national requirements. The study was approved by Cambridgeshire Research Ethics Committee and all participants gave written informed consent. A Study Steering Committee was responsible for evaluating and reporting the results of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 May 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 348
Worldwide total number of subjects	348
EEA total number of subjects	348

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)	204
From 65 to 84 years	144

85 years and over	0
-------------------	---

## Subject disposition

### Recruitment

Recruitment details:

Between May 15, 2009, and July 8, 2004, we screened 436 patients from 12 secondary and two primary sites in the UK for this 12-month randomized crossover trial

### Pre-assignment

Screening details:

We screened 436 and enrolled 335 patients aged 18-79 with seated CSBP  $\geq 140$  mm Hg (or  $\geq 135$  mm Hg in case of diabetics) and HSBP (18 readings over 4 days)  $\geq 130$  mm Hg, despite treatment for at least 3 months with maximally tolerated doses of three drugs.

### Pre-assignment period milestones

Number of subjects started	436 <sup>[1]</sup>
----------------------------	--------------------

Number of subjects completed	335 <sup>[2]</sup>
------------------------------	--------------------

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	not eligible: 88
----------------------------	------------------

Reason: Number of subjects	did not take study drug: 13
----------------------------	-----------------------------

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 88 patients were excluded as not eligible ,13 did not take study drug

[2] - The number of subjects reported to be in the pre-assignment period is not consistent with the number starting period 1. It is expected that the number completing the pre-assignment period are also present in the arms in period 1.

Justification: 88 patients were excluded as not eligible ,13 did not take study drug

### Period 1

Period 1 title	Overall trial (overall period)
----------------	--------------------------------

Is this the baseline period?	Yes
------------------------------	-----

Allocation method	Randomised - controlled
-------------------	-------------------------

Blinding used	Double blind
---------------	--------------

Roles blinded	Subject, Investigator
---------------	-----------------------

Blinding implementation details:

Patients rotated through 4 cycles of: 1) spironolactone 25-50 mg, 2) doxazosin 4-8 mg, 3) bisoprolol 5-10 mg, and 4) placebo. The complete set of permutations of the sequence order for the treatments were randomly ordered using computer generated pseudo random numbers. Study sites received the allocations for participants via a web-based randomization system. The study drugs were masked by re-encapsulation. Investigators/patients were masked to the identity of drugs, and to their sequence allocation.

### Arms

Are arms mutually exclusive?	No
------------------------------	----

Arm title	Spironolactone
-----------	----------------

Arm description:

Patients received spironolactone 25 mg for weeks 0-6. The dose was doubled in weeks 6-12

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Spironolactone
--	----------------

Investigational medicinal product code	
--	--

Other name	
------------	--

Pharmaceutical forms	Tablet
----------------------	--------

Routes of administration	Oral use
--------------------------	----------

Dosage and administration details:

12 weeks of oral treatment with 25-50 g of spironolactone, in addition to their baseline blood pressure

drugs. The dose was doubled after 6 weeks.

<b>Arm title</b>	doxazosin
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	doxazosin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
12 weeks of once treatment with 4-8 g of doxazosin, in addition to their baseline blood pressure drugs. The dose was doubled after 6 weeks.	
<b>Arm title</b>	bisoprolol
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	bisoprolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
12 weeks of once treatment with 5-10 g of bisoprolol, in addition to their baseline blood pressure drugs. The dose was doubled after 6 weeks.	
<b>Arm title</b>	placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
placebo	

<b>Number of subjects in period 1</b>	Spironolactone	doxazosin	bisoprolol
Started	285	282	285
Completed	267	264	268
Not completed	18	18	17
Adverse event, serious fatal	-	1	-
subject unwilling to continue	3	-	-
Adverse event, non-fatal	4	8	4
patient unwilling to continue	-	5	6

investigator terminated participation	6	1	2
Lost to follow-up	1	-	1
non-compliance	1	-	-
other reason	3	2	4
Protocol deviation	-	1	-

<b>Number of subjects in period 1</b>	placebo
Started	274
Completed	264
Not completed	10
Adverse event, serious fatal	-
subject unwilling to continue	-
Adverse event, non-fatal	3
patient unwilling to continue	1
investigator terminated participation	1
Lost to follow-up	-
non-compliance	-
other reason	4
Protocol deviation	1

## Baseline characteristics

### Reporting groups<sup>[1]</sup>

Reporting group title	Overall trial
-----------------------	---------------

Reporting group description: -

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: 88 patients were excluded as not eligible ,13 did not take study drug

Reporting group values	Overall trial	Total	
Number of subjects	335	335	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	61.4		
standard deviation	± 9.6	-	
Gender categorical			
Units: Subjects			
Female	105	105	
Male	230	230	

## End points

### End points reporting groups

Reporting group title	Spironolactone
Reporting group description: Patients received spironolactone 25 mg for weeks 0-6. The dose was doubled in weeks 6-12	
Reporting group title	doxazosin
Reporting group description: -	
Reporting group title	bisoprolol
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	

### Primary: home systolic blood pressure

End point title	home systolic blood pressure
End point description: recorded in the morning and the evening in triplicate, on 4 consecutive days before study visit. A maximum of the last 18 recordings for each measurement period -ie days 2-4 if all completed. A minimum of 6 blood pressure recordings per measurement period was required for a valid measurement.	
End point type	Primary
End point timeframe: measured throughout the treatment cycle at week 6 and week 12	

End point values	Spironolactone	doxazosin	bisoprolol	placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	285	282	285	274
Units: mmHg				
least squares mean (confidence interval 95%)	134.9 (134.0 to 135.9)	139.0 (138.0 to 140.0)	139.4 (138.4 to 140.4)	143.6 (142.6 to 144.6)

### Statistical analyses

Statistical analysis title	Spironolactone vs placebo
Statistical analysis description: This is the first analysis in a hierarchy whereby a comparison was made if, and only if, all the preceding comparisons were statistically significant	
Comparison groups	Spironolactone v placebo

Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.72
upper limit	-7.69

Notes:

[1] - This is a cross-over study, so the number of subjects is incorrect, but cannot be edited

<b>Statistical analysis title</b>	Spironolactone vs mean bisoprolol and doxazosin
Statistical analysis description:	
This is the second analysis in a hierarchy whereby a comparison was made if, and only if, all the preceding comparisons were statistically significant	
Comparison groups	Spironolactone v doxazosin v bisoprolol
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	superiority <sup>[2]</sup>
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-4.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.13
upper limit	-3.38

Notes:

[2] - this is a cross-over study so the number of subjects is incorrect, but cannot be edited

<b>Statistical analysis title</b>	Spironolactone vs doxazosin
Statistical analysis description:	
This is the third analysis in a hierarchy whereby a comparison was made if, and only if, all the preceding comparisons were statistically significant	
Comparison groups	Spironolactone v doxazosin
Number of subjects included in analysis	567
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-4.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.04
upper limit	-3.02

Notes:

[3] - This is a cross-over study so the number of subjects is incorrect, but cannot be edited

<b>Statistical analysis title</b>	Spironolactone vs bisoprolol
-----------------------------------	------------------------------

Statistical analysis description:

This is the fourth analysis in a hierarchy whereby a comparison was made if, and only if, all the preceding comparisons were statistically significant

Comparison groups	Spironolactone v bisoprolol
Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	superiority <sup>[4]</sup>
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-4.48

Confidence interval

level	95 %
sides	2-sided
lower limit	-5.5
upper limit	-3.46

Notes:

[4] - this is a cross over study so the number of subjects is incorrect but cannot be edited

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

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

### Dictionary used

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

Dictionary version	19.0
--------------------	------

### Reporting groups

Reporting group title	spironolactone
-----------------------	----------------

Reporting group description: -

Reporting group title	doxazosin
-----------------------	-----------

Reporting group description: -

Reporting group title	placebo
-----------------------	---------

Reporting group description: -

Reporting group title	bisoprolol
-----------------------	------------

Reporting group description: -

Serious adverse events	spironolactone	doxazosin	placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 285 (2.11%)	4 / 282 (1.42%)	5 / 274 (1.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma	Additional description: Bladder transitional cell carcinoma		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (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
Squamous cell carcinoma	Additional description: Squamous cell carcinoma		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension	Additional description: Hypertension		

subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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
Surgical and medical procedures			
Cardiac pacemaker insertion	Additional description: Cardiac pacemaker insertion		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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
Hernia repair	Additional description: Hernia repair		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (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
Skin graft	Additional description: Skin graft		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (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
General disorders and administration site conditions			
Chest pain	Additional description: Chest pain		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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
Fatigue	Additional description: Fatigue		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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
Gait disturbance	Additional description: Gait disturbance		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (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
Malaise	Additional description: Malaise		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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

Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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
Dyspnoea exertional	Additional description: Dyspnoea exertional		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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
Pulmonary oedema	Additional description: Pulmonary oedema		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (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
Wheezing	Additional description: Wheezing		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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
Injury, poisoning and procedural complications			
Ankle fracture	Additional description: Ankle fracture		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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
Cardiac disorders			
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (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
Bradycardia	Additional description: Bradycardia		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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
Palpitations	Additional description: Palpitations		

subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (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
Sick sinus syndrome	Additional description: Sick sinus syndrome		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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
Supraventricular tachycardia	Additional description: Supraventricular tachycardia		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (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			
Diabetic neuropathy	Additional description: Diabetic neuropathy		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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
Dizziness	Additional description: Dizziness		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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
Transient ischaemic attack	Additional description: Transient ischaemic attack		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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
Eye disorders			
Retinal haemorrhage	Additional description: Retinal haemorrhage		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
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 disorders			
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (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

Gastrooesophageal reflux disease subjects affected / exposed  occurrences causally related to treatment / all  deaths causally related to treatment / all	Additional description: Gastrooesophageal reflux disease		
	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
	0 / 0	0 / 0	0 / 1
	0 / 0	0 / 0	0 / 0
Nausea subjects affected / exposed  occurrences causally related to treatment / all  deaths causally related to treatment / all	Additional description: Nausea		
	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
	0 / 0	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders Skin ulcer subjects affected / exposed  occurrences causally related to treatment / all  deaths causally related to treatment / all	Additional description: Skin ulcer		
	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
	0 / 1	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0
Renal and urinary disorders Calculus ureteric subjects affected / exposed  occurrences causally related to treatment / all  deaths causally related to treatment / all	Additional description: Calculus ureteric		
	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
	0 / 0	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed  occurrences causally related to treatment / all  deaths causally related to treatment / all	Additional description: Back pain		
	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
	0 / 0	0 / 0	0 / 1
	0 / 0	0 / 0	0 / 0
Infections and infestations Escherichia sepsis subjects affected / exposed  occurrences causally related to treatment / all  deaths causally related to treatment / all	Additional description: Escherichia sepsis		
	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
	0 / 0	0 / 1	0 / 0
	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed  occurrences causally related to treatment / all  deaths causally related to treatment / all	Additional description: Hyperkalaemia		
	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
	1 / 1	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus	Additional description: Type 2 diabetes mellitus		

subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	bisoprolol		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 285 (2.46%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma	Additional description: Bladder transitional cell carcinoma		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma	Additional description: Squamous cell carcinoma		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cardiac pacemaker insertion	Additional description: Cardiac pacemaker insertion		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hernia repair	Additional description: Hernia repair		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin graft	Additional description: Skin graft		

subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain	Additional description: Chest pain		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue	Additional description: Fatigue		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gait disturbance	Additional description: Gait disturbance		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malaise	Additional description: Malaise		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional	Additional description: Dyspnoea exertional		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema	Additional description: Pulmonary oedema		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Wheezing	Additional description: Wheezing		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture	Additional description: Ankle fracture		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bradycardia	Additional description: Bradycardia		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Palpitations	Additional description: Palpitations		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sick sinus syndrome	Additional description: Sick sinus syndrome		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia	Additional description: Supraventricular tachycardia		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Diabetic neuropathy	Additional description: Diabetic neuropathy		

subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness	Additional description: Dizziness		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack	Additional description: Transient ischaemic attack		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal haemorrhage	Additional description: Retinal haemorrhage		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea	Additional description: Nausea		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin ulcer	Additional description: Skin ulcer		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Calculus ureteric	Additional description: Calculus ureteric		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Escherichia sepsis	Additional description: Escherichia sepsis		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus	Additional description: Type 2 diabetes mellitus		
subjects affected / exposed	0 / 285 (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: 0 %

Non-serious adverse events	spironolactone	doxazosin	placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	168 / 285 (58.95%)	173 / 282 (61.35%)	134 / 274 (48.91%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus	Additional description: Melanocytic naevus		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Thyroid neoplasm	Additional description: Thyroid neoplasm		

subjects affected / exposed occurrences (all)	1 / 285 (0.35%) 1	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Vascular disorders			
Aortic aneurysm	Additional description: Aortic aneurysm		
subjects affected / exposed occurrences (all)	1 / 285 (0.35%) 1	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Flushing	Additional description: Flushing		
subjects affected / exposed occurrences (all)	2 / 285 (0.70%) 2	2 / 282 (0.71%) 2	0 / 274 (0.00%) 0
Hypotension	Additional description: Hypotension		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	5 / 282 (1.77%) 5	0 / 274 (0.00%) 0
Lymphoedema	Additional description: Lymphoedema		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Orthostatic hypotension	Additional description: Orthostatic hypotension		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	2 / 282 (0.71%) 2	0 / 274 (0.00%) 0
Peripheral coldness	Additional description: Peripheral coldness		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Thrombophlebitis superficial	Additional description: Thrombophlebitis superficial		
subjects affected / exposed occurrences (all)	1 / 285 (0.35%) 1	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Surgical and medical procedures			
Cataract operation	Additional description: Cataract operation		
subjects affected / exposed occurrences (all)	1 / 285 (0.35%) 1	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Cyst removal	Additional description: Cyst removal		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Endodontic procedure	Additional description: Endodontic procedure		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	1 / 274 (0.36%) 1
Mole excision	Additional description: Mole excision		

subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Orthopedic procedure	Additional description: Orthopedic procedure		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Skin neoplasm excision	Additional description: Skin neoplasm excision		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Tooth extraction	Additional description: Tooth extraction		
subjects affected / exposed	1 / 285 (0.35%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	1	1	0
Tooth repair	Additional description: Tooth repair		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia	Additional description: Asthenia		
subjects affected / exposed	3 / 285 (1.05%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	4	0	0
Chest discomfort	Additional description: Chest discomfort		
subjects affected / exposed	2 / 285 (0.70%)	3 / 282 (1.06%)	0 / 274 (0.00%)
occurrences (all)	2	3	0
Chest pain	Additional description: Chest pain		
subjects affected / exposed	1 / 285 (0.35%)	4 / 282 (1.42%)	1 / 274 (0.36%)
occurrences (all)	1	4	1
Cyst	Additional description: Cyst		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Discomfort	Additional description: Discomfort		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Drug intolerance	Additional description: Drug intolerance		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Exercise tolerance decreased	Additional description: Exercise tolerance decreased		

subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Fatigue	Additional description: Fatigue		
subjects affected / exposed	9 / 285 (3.16%)	19 / 282 (6.74%)	9 / 274 (3.28%)
occurrences (all)	9	19	10
Feeling abnormal	Additional description: Feeling abnormal		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	1	0	1
Gait disturbance	Additional description: Gait disturbance		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	5 / 285 (1.75%)	2 / 282 (0.71%)	2 / 274 (0.73%)
occurrences (all)	5	2	2
Local swelling	Additional description: Local swelling		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Malaise	Additional description: Malaise		
subjects affected / exposed	2 / 285 (0.70%)	5 / 282 (1.77%)	3 / 274 (1.09%)
occurrences (all)	2	5	3
Non-cardiac chest pain	Additional description: Non-cardiac chest pain		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	0 / 285 (0.00%)	13 / 282 (4.61%)	2 / 274 (0.73%)
occurrences (all)	0	16	3
Pain	Additional description: Pain		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Sensation of pressure	Additional description: Sensation of pressure		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Thirst	Additional description: Thirst		
subjects affected / exposed	2 / 285 (0.70%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	2	0	0
Immune system disorders			

Hypersensitivity subjects affected / exposed occurrences (all)	Additional description: Hypersensitivity		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	1 / 274 (0.36%) 1
Seasonal allergy subjects affected / exposed occurrences (all)	Additional description: Seasonal allergy		
	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	1 / 274 (0.36%) 1
Social circumstances Menopause subjects affected / exposed occurrences (all)	Additional description: Menopause		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Stress at work subjects affected / exposed occurrences (all)	Additional description: Stress at work		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Reproductive system and breast disorders Breast enlargement subjects affected / exposed occurrences (all)	Additional description: Breast enlargement		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Breast pain subjects affected / exposed occurrences (all)	Additional description: Breast pain		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	1 / 274 (0.36%) 1
Breast swelling subjects affected / exposed occurrences (all)	Additional description: Breast swelling		
	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Breast tenderness subjects affected / exposed occurrences (all)	Additional description: Breast tenderness		
	1 / 285 (0.35%) 1	1 / 282 (0.35%) 1	1 / 274 (0.36%) 1
Erectile dysfunction subjects affected / exposed occurrences (all)	Additional description: Erectile dysfunction		
	2 / 285 (0.70%) 2	2 / 282 (0.71%) 2	1 / 274 (0.36%) 1
Menorrhagia subjects affected / exposed occurrences (all)	Additional description: Menorrhagia		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	1 / 274 (0.36%) 1
Menstrual disorder subjects affected / exposed occurrences (all)	Additional description: Menstrual disorder		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Menstruation irregular	Additional description: Menstruation irregular		

subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Nipple pain	Additional description: Nipple pain		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Prostatomegaly	Additional description: Prostatomegaly		
subjects affected / exposed	1 / 285 (0.35%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	1	1	0
Sexual dysfunction	Additional description: Sexual dysfunction		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Cough	Additional description: Cough		
subjects affected / exposed	8 / 285 (2.81%)	6 / 282 (2.13%)	6 / 274 (2.19%)
occurrences (all)	8	6	6
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	6 / 285 (2.11%)	12 / 282 (4.26%)	3 / 274 (1.09%)
occurrences (all)	6	12	4
Dyspnoea exertional	Additional description: Dyspnoea exertional		
subjects affected / exposed	1 / 285 (0.35%)	8 / 282 (2.84%)	0 / 274 (0.00%)
occurrences (all)	1	8	0
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	2 / 285 (0.70%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	2	0	0
Increased upper airway secretion	Additional description: Increased upper airway secretion		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Nasal congestion	Additional description: Nasal congestion		
subjects affected / exposed	0 / 285 (0.00%)	2 / 282 (0.71%)	1 / 274 (0.36%)
occurrences (all)	0	3	1
Nocturnal dyspnoea	Additional description: Nocturnal dyspnoea		

subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	2 / 274 (0.73%)
occurrences (all)	1	0	2
Pleurisy	Additional description: Pleurisy		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Productive cough	Additional description: Productive cough		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Reflux laryngitis	Additional description: Reflux laryngitis		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion	Additional description: Respiratory tract congestion		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Respiratory tract inflammation	Additional description: Respiratory tract inflammation		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Sinus congestion	Additional description: Sinus congestion		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Throat tightness	Additional description: Throat tightness		
subjects affected / exposed	0 / 285 (0.00%)	2 / 282 (0.71%)	0 / 274 (0.00%)
occurrences (all)	0	2	0
Wheezing	Additional description: Wheezing		
subjects affected / exposed	2 / 285 (0.70%)	5 / 282 (1.77%)	1 / 274 (0.36%)
occurrences (all)	2	5	1
Psychiatric disorders			
Abnormal dreams	Additional description: Abnormal dreams		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	1 / 274 (0.36%)
occurrences (all)	0	1	1
Anxiety	Additional description: Anxiety		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1

Depressed mood	Additional description: Depressed mood		
subjects affected / exposed	0 / 285 (0.00%)	2 / 282 (0.71%)	0 / 274 (0.00%)
occurrences (all)	0	2	0
Depression	Additional description: Depression		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Depression suicidal	Additional description: Depression suicidal		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Disorientation	Additional description: Disorientation		
subjects affected / exposed	0 / 285 (0.00%)	3 / 282 (1.06%)	0 / 274 (0.00%)
occurrences (all)	0	3	0
Hallucination	Additional description: Hallucination		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Insomnia	Additional description: Insomnia		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	1 / 274 (0.36%)
occurrences (all)	0	1	1
Loss of libido	Additional description: Loss of libido		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Sleep disorder	Additional description: Sleep disorder		
subjects affected / exposed	2 / 285 (0.70%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	2	0	1
Investigations			
Arthroscopy	Additional description: Arthroscopy		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Biopsy prostate	Additional description: Biopsy prostate		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Blood albumin abnormal	Additional description: Blood albumin abnormal		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Blood cholesterol increased	Additional description: Blood cholesterol increased		

subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Blood creatine	Additional description: Blood creatine		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Blood glucose abnormal	Additional description: Blood glucose abnormal		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Blood glucose fluctuation	Additional description: Blood glucose fluctuation		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Blood potassium	Additional description: Blood potassium		
subjects affected / exposed	2 / 285 (0.70%)	0 / 282 (0.00%)	2 / 274 (0.73%)
occurrences (all)	2	0	2
Blood potassium abnormal	Additional description: Blood potassium abnormal		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Blood potassium increased	Additional description: Blood potassium increased		
subjects affected / exposed	4 / 285 (1.40%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	4	0	0
Blood pressure abnormal	Additional description: Blood pressure abnormal		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Blood sodium	Additional description: Blood sodium		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Blood sodium abnormal	Additional description: Blood sodium abnormal		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Blood sodium decreased	Additional description: Blood sodium decreased		
subjects affected / exposed	3 / 285 (1.05%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	4	0	0
Blood test abnormal	Additional description: Blood test abnormal		

subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Blood triglycerides increased	Additional description: Blood triglycerides increased		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Blood urea abnormal	Additional description: Blood urea abnormal		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	1	0	1
Blood urea increased	Additional description: Blood urea increased		
subjects affected / exposed	4 / 285 (1.40%)	1 / 282 (0.35%)	1 / 274 (0.36%)
occurrences (all)	5	1	1
Chlamydia test positive	Additional description: Chlamydia test positive		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Colonoscopy	Additional description: Colonoscopy		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Endoscopy	Additional description: Endoscopy		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Eosinophil count abnormal	Additional description: Eosinophil count abnormal		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Glomerular filtration rate decreased	Additional description: Glomerular filtration rate decreased		
subjects affected / exposed	2 / 285 (0.70%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	2	0	0
Haematocrit decreased	Additional description: Haematocrit decreased		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased	Additional description: Haemoglobin decreased		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Heart rate decreased	Additional description: Heart rate decreased		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Heart rate increased	Additional description: Heart rate increased		

subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Heart rate irregular	Additional description: Heart rate irregular		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Hysteroscopy	Additional description: Hysteroscopy		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Mean cell haemoglobin concentration abnormal	Additional description: Mean cell haemoglobin concentration abnormal		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Mean cell volume abnormal	Additional description: Mean cell volume abnormal		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Occult blood	Additional description: Occult blood		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Pulse abnormal	Additional description: Pulse abnormal		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Red blood cell count abnormal	Additional description: Red blood cell count abnormal		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Red blood cell morphology abnormal	Additional description: Red blood cell morphology abnormal		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Urine output decreased	Additional description: Urine output decreased		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Urine sodium increased	Additional description: Urine sodium increased		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Weight increased	Additional description: Weight increased		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0

Injury, poisoning and procedural complications			
Arthropod bite	Additional description: Arthropod bite		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Contusion	Additional description: Contusion		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	2
Fall	Additional description: Fall		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	2 / 274 (0.73%)
occurrences (all)	1	0	3
Foot fracture	Additional description: Foot fracture		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Head injury	Additional description: Head injury		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Joint dislocation	Additional description: Joint dislocation		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	2 / 274 (0.73%)
occurrences (all)	0	0	2
Joint sprain	Additional description: Joint sprain		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Limb injury	Additional description: Limb injury		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Meniscus lesion	Additional description: Meniscus lesion		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Muscle strain	Additional description: Muscle strain		
subjects affected / exposed	2 / 285 (0.70%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	3	1	0
Procedural pain	Additional description: Procedural pain		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Repetitive strain injury	Additional description: Repetitive strain injury		

subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	2	0	0
Rib fracture	Additional description: Rib fracture		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Thermal burn	Additional description: Thermal burn		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Tooth injury	Additional description: Tooth injury		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Upper limb fracture	Additional description: Upper limb fracture		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Thalassaemia	Additional description: Thalassaemia		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Cardiac disorders			
Angina pectoris	Additional description: Angina pectoris		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	2 / 274 (0.73%)
occurrences (all)	0	0	2
Arrhythmia	Additional description: Arrhythmia		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Bradycardia	Additional description: Bradycardia		
subjects affected / exposed	3 / 285 (1.05%)	2 / 282 (0.71%)	1 / 274 (0.36%)
occurrences (all)	3	2	1
Cardiac failure congestive	Additional description: Cardiac failure congestive		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Palpitations	Additional description: Palpitations		

subjects affected / exposed	3 / 285 (1.05%)	8 / 282 (2.84%)	4 / 274 (1.46%)
occurrences (all)	3	8	5
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	0 / 285 (0.00%)	2 / 282 (0.71%)	0 / 274 (0.00%)
occurrences (all)	0	3	0
Nervous system disorders			
Balance disorder	Additional description: Balance disorder		
subjects affected / exposed	1 / 285 (0.35%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	1	1	0
Burning sensation	Additional description: Burning sensation		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Carpal tunnel syndrome	Additional description: Carpal tunnel syndrome		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Dizziness	Additional description: Dizziness		
subjects affected / exposed	16 / 285 (5.61%)	36 / 282 (12.77%)	15 / 274 (5.47%)
occurrences (all)	16	40	15
Dizziness exertional	Additional description: Dizziness exertional		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Dizziness postural	Additional description: Dizziness postural		
subjects affected / exposed	13 / 285 (4.56%)	5 / 282 (1.77%)	1 / 274 (0.36%)
occurrences (all)	14	5	1
Dysarthria	Additional description: Dysarthria		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Headache	Additional description: Headache		
subjects affected / exposed	11 / 285 (3.86%)	4 / 282 (1.42%)	13 / 274 (4.74%)
occurrences (all)	15	6	14
Hemicephalalgia	Additional description: Hemicephalalgia		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia	Additional description: Hypoaesthesia		
subjects affected / exposed	2 / 285 (0.70%)	2 / 282 (0.71%)	1 / 274 (0.36%)
occurrences (all)	2	3	1

Lethargy	Additional description: Lethargy		
subjects affected / exposed	5 / 285 (1.75%)	4 / 282 (1.42%)	3 / 274 (1.09%)
occurrences (all)	6	4	3
Loss of consciousness	Additional description: Loss of consciousness		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Migraine	Additional description: Migraine		
subjects affected / exposed	1 / 285 (0.35%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	1	1	0
Nerve compression	Additional description: Nerve compression		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Neuropathy peripheral	Additional description: Neuropathy peripheral		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Orthostatic intolerance	Additional description: Orthostatic intolerance		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	4 / 285 (1.40%)	3 / 282 (1.06%)	3 / 274 (1.09%)
occurrences (all)	4	4	3
Parkinsonism	Additional description: Parkinsonism		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Petit mal epilepsy	Additional description: Petit mal epilepsy		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Presyncope	Additional description: Presyncope		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Restless legs syndrome	Additional description: Restless legs syndrome		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Sciatica	Additional description: Sciatica		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1

Sensory disturbance subjects affected / exposed occurrences (all)	Additional description: Sensory disturbance		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	1 / 274 (0.36%) 1
Somnolence subjects affected / exposed occurrences (all)	Additional description: Somnolence		
	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Syncope subjects affected / exposed occurrences (all)	Additional description: Syncope		
	1 / 285 (0.35%) 1	3 / 282 (1.06%) 3	0 / 274 (0.00%) 0
Transient ischaemic attack subjects affected / exposed occurrences (all)	Additional description: Transient ischaemic attack		
	1 / 285 (0.35%) 1	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Tremor subjects affected / exposed occurrences (all)	Additional description: Tremor		
	1 / 285 (0.35%) 1	0 / 282 (0.00%) 0	1 / 274 (0.36%) 1
Vascular dementia subjects affected / exposed occurrences (all)	Additional description: Vascular dementia		
	1 / 285 (0.35%) 1	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	Additional description: Anaemia		
	2 / 285 (0.70%) 2	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Ear and labyrinth disorders			
Ear pain subjects affected / exposed occurrences (all)	Additional description: Ear pain		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	2 / 274 (0.73%) 2
Eustachian tube dysfunction subjects affected / exposed occurrences (all)	Additional description: Eustachian tube dysfunction		
	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Tinnitus subjects affected / exposed occurrences (all)	Additional description: Tinnitus		
	1 / 285 (0.35%) 1	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Vertigo subjects affected / exposed occurrences (all)	Additional description: Vertigo		
	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Vertigo positional	Additional description: Vertigo positional		

subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Eye disorders	Additional description: Cataract		
Cataract			
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Dry eye	Additional description: Dry eye		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Eye disorder	Additional description: Eye disorder		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Eye haemorrhage	Additional description: Eye haemorrhage		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Eye pain	Additional description: Eye pain		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	2 / 282 (0.71%) 2	0 / 274 (0.00%) 0
Lacrimation increased	Additional description: Lacrimation increased		
subjects affected / exposed occurrences (all)	2 / 285 (0.70%) 2	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Photophobia	Additional description: Photophobia		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	1 / 274 (0.36%) 1
Retinal disorder	Additional description: Retinal disorder		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Vision blurred	Additional description: Vision blurred		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0	3 / 282 (1.06%) 3	2 / 274 (0.73%) 2
Visual impairment	Additional description: Visual impairment		
subjects affected / exposed occurrences (all)	1 / 285 (0.35%) 2	0 / 282 (0.00%) 0	1 / 274 (0.36%) 2

Vitreous floaters subjects affected / exposed occurrences (all)	Additional description: Vitreous floaters		
	0 / 285 (0.00%)	0 / 282 (0.00%)	2 / 274 (0.73%)
	0	0	2
Gastrointestinal disorders			
	Additional description: Abdominal discomfort		
	1 / 285 (0.35%)	2 / 282 (0.71%)	1 / 274 (0.36%)
Abdominal discomfort subjects affected / exposed occurrences (all)	1	2	1
Abdominal distension subjects affected / exposed occurrences (all)	Additional description: Abdominal distension		
	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
	1	0	0
Abdominal hernia subjects affected / exposed occurrences (all)	Additional description: Abdominal hernia		
	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
	0	0	0
Abdominal pain subjects affected / exposed occurrences (all)	Additional description: Abdominal pain		
	2 / 285 (0.70%)	1 / 282 (0.35%)	0 / 274 (0.00%)
	2	1	0
Abdominal pain upper subjects affected / exposed occurrences (all)	Additional description: Abdominal pain upper		
	1 / 285 (0.35%)	2 / 282 (0.71%)	0 / 274 (0.00%)
	1	2	0
Abdominal tenderness subjects affected / exposed occurrences (all)	Additional description: Abdominal tenderness		
	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
	1	0	0
Anal fistula subjects affected / exposed occurrences (all)	Additional description: Anal fistula		
	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
	0	0	0
Constipation subjects affected / exposed occurrences (all)	Additional description: Constipation		
	3 / 285 (1.05%)	2 / 282 (0.71%)	0 / 274 (0.00%)
	3	2	0
Diarrhoea subjects affected / exposed occurrences (all)	Additional description: Diarrhoea		
	2 / 285 (0.70%)	6 / 282 (2.13%)	4 / 274 (1.46%)
	2	6	4
Dry mouth subjects affected / exposed occurrences (all)	Additional description: Dry mouth		
	2 / 285 (0.70%)	2 / 282 (0.71%)	2 / 274 (0.73%)
	2	2	2
Dyspepsia	Additional description: Dyspepsia		

subjects affected / exposed	7 / 285 (2.46%)	4 / 282 (1.42%)	2 / 274 (0.73%)
occurrences (all)	7	4	2
Flatulence	Additional description: Flatulence		
subjects affected / exposed	2 / 285 (0.70%)	1 / 282 (0.35%)	1 / 274 (0.36%)
occurrences (all)	2	1	1
Frequent bowel movements	Additional description: Frequent bowel movements		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorder	Additional description: Gastrointestinal disorder		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal motility disorder	Additional description: Gastrointestinal motility disorder		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Gingival hyperplasia	Additional description: Gingival hyperplasia		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Haematochezia	Additional description: Haematochezia		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Lip swelling	Additional description: Lip swelling		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Nausea	Additional description: Nausea		
subjects affected / exposed	6 / 285 (2.11%)	6 / 282 (2.13%)	2 / 274 (0.73%)
occurrences (all)	6	6	2
Oesophageal dilatation	Additional description: Oesophageal dilatation		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Oesophagitis	Additional description: Oesophagitis		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Oral pain	Additional description: Oral pain		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Paraesthesia oral	Additional description: Paraesthesia oral		

subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Rectal haemorrhage	Additional description: Rectal haemorrhage		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Toothache	Additional description: Toothache		
subjects affected / exposed	2 / 285 (0.70%)	0 / 282 (0.00%)	3 / 274 (1.09%)
occurrences (all)	2	0	3
Vomiting	Additional description: Vomiting		
subjects affected / exposed	2 / 285 (0.70%)	2 / 282 (0.71%)	1 / 274 (0.36%)
occurrences (all)	2	2	1
Vomiting projectile	Additional description: Vomiting projectile		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Blister	Additional description: Blister		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Cold sweat	Additional description: Cold sweat		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Dermatitis allergic	Additional description: Dermatitis allergic		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Drug eruption	Additional description: Drug eruption		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Dry skin	Additional description: Dry skin		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	1	0	1
Ecchymosis	Additional description: Ecchymosis		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Eczema	Additional description: Eczema		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0

Erythema	Additional description: Erythema		
	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
subjects affected / exposed	0	1	0
occurrences (all)			
Hyperhidrosis	Additional description: Hyperhidrosis		
	1 / 285 (0.35%)	0 / 282 (0.00%)	1 / 274 (0.36%)
subjects affected / exposed	1	0	1
occurrences (all)			
Intertrigo	Additional description: Intertrigo		
	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
subjects affected / exposed	1	0	0
occurrences (all)			
Pain of skin	Additional description: Pain of skin		
	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
subjects affected / exposed	0	1	0
occurrences (all)			
Papule	Additional description: Papule		
	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
subjects affected / exposed	0	1	0
occurrences (all)			
Pruritus	Additional description: Pruritus		
	4 / 285 (1.40%)	1 / 282 (0.35%)	4 / 274 (1.46%)
subjects affected / exposed	4	1	4
occurrences (all)			
Pruritus generalised	Additional description: Pruritus generalised		
	1 / 285 (0.35%)	0 / 282 (0.00%)	1 / 274 (0.36%)
subjects affected / exposed	1	0	1
occurrences (all)			
Psoriasis	Additional description: Psoriasis		
	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
subjects affected / exposed	0	0	0
occurrences (all)			
Rash	Additional description: Rash		
	3 / 285 (1.05%)	4 / 282 (1.42%)	2 / 274 (0.73%)
subjects affected / exposed	3	5	2
occurrences (all)			
Rash pruritic	Additional description: Rash pruritic		
	0 / 285 (0.00%)	2 / 282 (0.71%)	1 / 274 (0.36%)
subjects affected / exposed	0	2	1
occurrences (all)			
Skin lesion	Additional description: Skin lesion		
	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
subjects affected / exposed	0	0	0
occurrences (all)			
Urticaria	Additional description: Urticaria		
	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
subjects affected / exposed	0	1	0
occurrences (all)			

Renal and urinary disorders			
Dysuria	Additional description: Dysuria		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Haematuria	Additional description: Haematuria		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	2 / 274 (0.73%)
occurrences (all)	1	0	2
Incontinence	Additional description: Incontinence		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Ketonuria	Additional description: Ketonuria		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Micturition urgency	Additional description: Micturition urgency		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Nocturia	Additional description: Nocturia		
subjects affected / exposed	2 / 285 (0.70%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	2	1	0
Pollakiuria	Additional description: Pollakiuria		
subjects affected / exposed	4 / 285 (1.40%)	1 / 282 (0.35%)	2 / 274 (0.73%)
occurrences (all)	4	1	2
Polyuria	Additional description: Polyuria		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Proteinuria	Additional description: Proteinuria		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Renal colic	Additional description: Renal colic		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Renal failure chronic	Additional description: Renal failure chronic		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Renal impairment	Additional description: Renal impairment		

subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Renal pain	Additional description: Renal pain		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	2	0	0
Urinary incontinence	Additional description: Urinary incontinence		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	1 / 274 (0.36%)
occurrences (all)	0	1	1
Urinary retention	Additional description: Urinary retention		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	1	0	1
Urine odour abnormal	Additional description: Urine odour abnormal		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	6 / 285 (2.11%)	4 / 282 (1.42%)	5 / 274 (1.82%)
occurrences (all)	6	4	5
Arthritis	Additional description: Arthritis		
subjects affected / exposed	0 / 285 (0.00%)	2 / 282 (0.71%)	0 / 274 (0.00%)
occurrences (all)	0	2	0
Back pain	Additional description: Back pain		
subjects affected / exposed	2 / 285 (0.70%)	3 / 282 (1.06%)	6 / 274 (2.19%)
occurrences (all)	2	3	6
Joint stiffness	Additional description: Joint stiffness		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	1	0	1
Joint swelling	Additional description: Joint swelling		
subjects affected / exposed	2 / 285 (0.70%)	12 / 282 (4.26%)	4 / 274 (1.46%)
occurrences (all)	2	12	5
Muscle fatigue	Additional description: Muscle fatigue		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Muscle spasms	Additional description: Muscle spasms		

subjects affected / exposed	22 / 285 (7.72%)	3 / 282 (1.06%)	0 / 274 (0.00%)
occurrences (all)	24	3	0
Muscle tightness	Additional description: Muscle tightness		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Muscle twitching	Additional description: Muscle twitching		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Muscular weakness	Additional description: Muscular weakness		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	1 / 274 (0.36%)
occurrences (all)	0	1	1
Musculoskeletal discomfort	Additional description: Musculoskeletal discomfort		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	2 / 285 (0.70%)	1 / 282 (0.35%)	3 / 274 (1.09%)
occurrences (all)	2	1	3
Musculoskeletal stiffness	Additional description: Musculoskeletal stiffness		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	2 / 274 (0.73%)
occurrences (all)	1	0	2
Myalgia	Additional description: Myalgia		
subjects affected / exposed	2 / 285 (0.70%)	5 / 282 (1.77%)	3 / 274 (1.09%)
occurrences (all)	2	6	3
Neck pain	Additional description: Neck pain		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	2 / 274 (0.73%)
occurrences (all)	0	0	2
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	5 / 285 (1.75%)	3 / 282 (1.06%)	6 / 274 (2.19%)
occurrences (all)	7	3	6
Periarthritis	Additional description: Periarthritis		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	1	0	1
Plantar fasciitis	Additional description: Plantar fasciitis		

subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Rheumatoid arthritis	Additional description: Rheumatoid arthritis		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Sensation of heaviness	Additional description: Sensation of heaviness		
subjects affected / exposed	2 / 285 (0.70%)	1 / 282 (0.35%)	1 / 274 (0.36%)
occurrences (all)	2	1	1
Tendon pain	Additional description: Tendon pain		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Abscess oral	Additional description: Abscess oral		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Body tinea	Additional description: Body tinea		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Candidiasis	Additional description: Candidiasis		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	0	0	0
Cellulitis	Additional description: Cellulitis		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Diverticulitis	Additional description: Diverticulitis		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0
Eye infection	Additional description: Eye infection		
subjects affected / exposed	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
occurrences (all)	0	0	1
Fungal infection	Additional description: Fungal infection		
subjects affected / exposed	1 / 285 (0.35%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	1	1	0

Furuncle	Additional description: Furuncle		
	1 / 285 (0.35%) 1	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Gastroenteritis	Additional description: Gastroenteritis		
	1 / 285 (0.35%) 1	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
H1N1 influenza	Additional description: H1N1 influenza		
	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Helicobacter infection	Additional description: Helicobacter infection		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Herpes zoster	Additional description: Herpes zoster		
	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Influenza	Additional description: Influenza		
	1 / 285 (0.35%) 1	4 / 282 (1.42%) 4	5 / 274 (1.82%) 5
Kidney infection	Additional description: Kidney infection		
	1 / 285 (0.35%) 1	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Labyrinthitis	Additional description: Labyrinthitis		
	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
	6 / 285 (2.11%) 6	2 / 282 (0.71%) 2	4 / 274 (1.46%) 4
Nasopharyngitis	Additional description: Nasopharyngitis		
	5 / 285 (1.75%) 5	15 / 282 (5.32%) 15	3 / 274 (1.09%) 3
Onychomycosis	Additional description: Onychomycosis		
	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Oral candidiasis	Additional description: Oral candidiasis		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	1 / 274 (0.36%) 1

Paronychia	Additional description: Paronychia		
	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
subjects affected / exposed	0	1	0
occurrences (all)			
Pharyngitis	Additional description: Pharyngitis		
	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
subjects affected / exposed	1	0	0
occurrences (all)			
Pneumonia	Additional description: Pneumonia		
	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
subjects affected / exposed	1	0	0
occurrences (all)			
Respiratory tract infection	Additional description: Respiratory tract infection		
	0 / 285 (0.00%)	0 / 282 (0.00%)	0 / 274 (0.00%)
subjects affected / exposed	0	0	0
occurrences (all)			
Rhinitis	Additional description: Rhinitis		
	2 / 285 (0.70%)	0 / 282 (0.00%)	6 / 274 (2.19%)
subjects affected / exposed	2	0	6
occurrences (all)			
Sialoadenitis	Additional description: Sialoadenitis		
	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
subjects affected / exposed	0	1	0
occurrences (all)			
Sinusitis	Additional description: Sinusitis		
	1 / 285 (0.35%)	0 / 282 (0.00%)	2 / 274 (0.73%)
subjects affected / exposed	1	0	2
occurrences (all)			
Skin infection	Additional description: Skin infection		
	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
subjects affected / exposed	1	0	0
occurrences (all)			
Tinea infection	Additional description: Tinea infection		
	0 / 285 (0.00%)	0 / 282 (0.00%)	1 / 274 (0.36%)
subjects affected / exposed	0	0	1
occurrences (all)			
Tooth abscess	Additional description: Tooth abscess		
	0 / 285 (0.00%)	1 / 282 (0.35%)	1 / 274 (0.36%)
subjects affected / exposed	0	1	1
occurrences (all)			
Tooth infection	Additional description: Tooth infection		
	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
subjects affected / exposed	2	0	0
occurrences (all)			
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
	2 / 285 (0.70%)	4 / 282 (1.42%)	0 / 274 (0.00%)
subjects affected / exposed	2	4	0
occurrences (all)			

Urinary tract infection subjects affected / exposed occurrences (all)	Additional description: Urinary tract infection		
	2 / 285 (0.70%) 2	4 / 282 (1.42%) 4	4 / 274 (1.46%) 4
Viral diarrhoea subjects affected / exposed occurrences (all)	Additional description: Viral diarrhoea		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Viral infection subjects affected / exposed occurrences (all)	Additional description: Viral infection		
	2 / 285 (0.70%) 2	1 / 282 (0.35%) 1	2 / 274 (0.73%) 2
Viral labyrinthitis subjects affected / exposed occurrences (all)	Additional description: Viral labyrinthitis		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	1 / 274 (0.36%) 1
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	Additional description: Viral upper respiratory tract infection		
	1 / 285 (0.35%) 1	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Metabolism and nutrition disorders Diabetes mellitus inadequate control subjects affected / exposed occurrences (all)	Additional description: Diabetes mellitus inadequate control		
	0 / 285 (0.00%) 0	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Gout subjects affected / exposed occurrences (all)	Additional description: Gout		
	4 / 285 (1.40%) 4	4 / 282 (1.42%) 4	5 / 274 (1.82%) 7
Haemochromatosis subjects affected / exposed occurrences (all)	Additional description: Haemochromatosis		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	1 / 274 (0.36%) 1
Hypercalcaemia subjects affected / exposed occurrences (all)	Additional description: Hypercalcaemia		
	0 / 285 (0.00%) 0	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	Additional description: Hyperglycaemia		
	1 / 285 (0.35%) 1	0 / 282 (0.00%) 0	0 / 274 (0.00%) 0
Hyperkalaemia subjects affected / exposed occurrences (all)	Additional description: Hyperkalaemia		
	4 / 285 (1.40%) 6	1 / 282 (0.35%) 1	0 / 274 (0.00%) 0
Hypokalaemia	Additional description: Hypokalaemia		

subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	2 / 285 (0.70%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	2	0	0
Hypovitaminosis	Additional description: Hypovitaminosis		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Increased appetite	Additional description: Increased appetite		
subjects affected / exposed	0 / 285 (0.00%)	1 / 282 (0.35%)	0 / 274 (0.00%)
occurrences (all)	0	1	0
Salt craving	Additional description: Salt craving		
subjects affected / exposed	1 / 285 (0.35%)	0 / 282 (0.00%)	0 / 274 (0.00%)
occurrences (all)	1	0	0

<b>Non-serious adverse events</b>	bisoprolol		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	180 / 285 (63.16%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus	Additional description: Melanocytic naevus		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Thyroid neoplasm	Additional description: Thyroid neoplasm		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Aortic aneurysm	Additional description: Aortic aneurysm		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Flushing	Additional description: Flushing		
subjects affected / exposed	2 / 285 (0.70%)		
occurrences (all)	2		
Hypotension	Additional description: Hypotension		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Lymphoedema	Additional description: Lymphoedema		

subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Orthostatic hypotension	Additional description: Orthostatic hypotension		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Peripheral coldness	Additional description: Peripheral coldness		
subjects affected / exposed	2 / 285 (0.70%)		
occurrences (all)	2		
Thrombophlebitis superficial	Additional description: Thrombophlebitis superficial		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Cataract operation	Additional description: Cataract operation		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Cyst removal	Additional description: Cyst removal		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Endodontic procedure	Additional description: Endodontic procedure		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Mole excision	Additional description: Mole excision		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Orthopedic procedure	Additional description: Orthopedic procedure		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Skin neoplasm excision	Additional description: Skin neoplasm excision		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Tooth extraction	Additional description: Tooth extraction		
subjects affected / exposed	2 / 285 (0.70%)		
occurrences (all)	2		
Tooth repair	Additional description: Tooth repair		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		

General disorders and administration site conditions			
Asthenia	Additional description: Asthenia		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Chest discomfort	Additional description: Chest discomfort		
subjects affected / exposed	5 / 285 (1.75%)		
occurrences (all)	5		
Chest pain	Additional description: Chest pain		
subjects affected / exposed	2 / 285 (0.70%)		
occurrences (all)	2		
Cyst	Additional description: Cyst		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Discomfort	Additional description: Discomfort		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Drug intolerance	Additional description: Drug intolerance		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Exercise tolerance decreased	Additional description: Exercise tolerance decreased		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Fatigue	Additional description: Fatigue		
subjects affected / exposed	22 / 285 (7.72%)		
occurrences (all)	23		
Feeling abnormal	Additional description: Feeling abnormal		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Gait disturbance	Additional description: Gait disturbance		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	3 / 285 (1.05%)		
occurrences (all)	3		
Local swelling	Additional description: Local swelling		

subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Malaise	Additional description: Malaise		
subjects affected / exposed	2 / 285 (0.70%)		
occurrences (all)	2		
Non-cardiac chest pain	Additional description: Non-cardiac chest pain		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	4 / 285 (1.40%)		
occurrences (all)	4		
Pain	Additional description: Pain		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Sensation of pressure	Additional description: Sensation of pressure		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Thirst	Additional description: Thirst		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Seasonal allergy	Additional description: Seasonal allergy		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Social circumstances			
Menopause	Additional description: Menopause		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Stress at work	Additional description: Stress at work		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Reproductive system and breast disorders			

Breast enlargement subjects affected / exposed occurrences (all)	Additional description: Breast enlargement		
	1 / 285 (0.35%) 1		
Breast pain subjects affected / exposed occurrences (all)	Additional description: Breast pain		
	0 / 285 (0.00%) 0		
Breast swelling subjects affected / exposed occurrences (all)	Additional description: Breast swelling		
	0 / 285 (0.00%) 0		
Breast tenderness subjects affected / exposed occurrences (all)	Additional description: Breast tenderness		
	0 / 285 (0.00%) 0		
Erectile dysfunction subjects affected / exposed occurrences (all)	Additional description: Erectile dysfunction		
	2 / 285 (0.70%) 2		
Menorrhagia subjects affected / exposed occurrences (all)	Additional description: Menorrhagia		
	0 / 285 (0.00%) 0		
Menstrual disorder subjects affected / exposed occurrences (all)	Additional description: Menstrual disorder		
	1 / 285 (0.35%) 1		
Menstruation irregular subjects affected / exposed occurrences (all)	Additional description: Menstruation irregular		
	0 / 285 (0.00%) 0		
Nipple pain subjects affected / exposed occurrences (all)	Additional description: Nipple pain		
	1 / 285 (0.35%) 1		
Prostatomegaly subjects affected / exposed occurrences (all)	Additional description: Prostatomegaly		
	0 / 285 (0.00%) 0		
Sexual dysfunction subjects affected / exposed occurrences (all)	Additional description: Sexual dysfunction		
	0 / 285 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease	
subjects affected / exposed	1 / 285 (0.35%)	
occurrences (all)	1	
Cough	Additional description: Cough	
subjects affected / exposed	12 / 285 (4.21%)	
occurrences (all)	12	
Dyspnoea	Additional description: Dyspnoea	
subjects affected / exposed	7 / 285 (2.46%)	
occurrences (all)	7	
Dyspnoea exertional	Additional description: Dyspnoea exertional	
subjects affected / exposed	4 / 285 (1.40%)	
occurrences (all)	4	
Epistaxis	Additional description: Epistaxis	
subjects affected / exposed	1 / 285 (0.35%)	
occurrences (all)	1	
Increased upper airway secretion	Additional description: Increased upper airway secretion	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Nasal congestion	Additional description: Nasal congestion	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Nocturnal dyspnoea	Additional description: Nocturnal dyspnoea	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Oropharyngeal pain	Additional description: Oropharyngeal pain	
subjects affected / exposed	2 / 285 (0.70%)	
occurrences (all)	2	
Pleurisy	Additional description: Pleurisy	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Productive cough	Additional description: Productive cough	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Reflux laryngitis	Additional description: Reflux laryngitis	

subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Respiratory tract congestion	Additional description: Respiratory tract congestion		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Respiratory tract inflammation	Additional description: Respiratory tract inflammation		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Sinus congestion	Additional description: Sinus congestion		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Throat tightness	Additional description: Throat tightness		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Wheezing	Additional description: Wheezing		
subjects affected / exposed	4 / 285 (1.40%)		
occurrences (all)	4		
Psychiatric disorders			
Abnormal dreams	Additional description: Abnormal dreams		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Anxiety	Additional description: Anxiety		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Depressed mood	Additional description: Depressed mood		
subjects affected / exposed	2 / 285 (0.70%)		
occurrences (all)	2		
Depression	Additional description: Depression		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Depression suicidal	Additional description: Depression suicidal		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Disorientation	Additional description: Disorientation		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		

Hallucination subjects affected / exposed occurrences (all)	Additional description: Hallucination	
	1 / 285 (0.35%)	
	1	
Insomnia subjects affected / exposed occurrences (all)	Additional description: Insomnia	
	0 / 285 (0.00%)	
	0	
Loss of libido subjects affected / exposed occurrences (all)	Additional description: Loss of libido	
	0 / 285 (0.00%)	
	0	
Sleep disorder subjects affected / exposed occurrences (all)	Additional description: Sleep disorder	
	2 / 285 (0.70%)	
	2	
Investigations		
Arthroscopy subjects affected / exposed occurrences (all)	Additional description: Arthroscopy	
	0 / 285 (0.00%)	
	0	
Biopsy prostate subjects affected / exposed occurrences (all)	Additional description: Biopsy prostate	
	0 / 285 (0.00%)	
	0	
Blood albumin abnormal subjects affected / exposed occurrences (all)	Additional description: Blood albumin abnormal	
	0 / 285 (0.00%)	
	0	
Blood cholesterol increased subjects affected / exposed occurrences (all)	Additional description: Blood cholesterol increased	
	0 / 285 (0.00%)	
	0	
Blood creatine subjects affected / exposed occurrences (all)	Additional description: Blood creatine	
	0 / 285 (0.00%)	
	0	
Blood creatinine increased subjects affected / exposed occurrences (all)	Additional description: Blood creatinine increased	
	0 / 285 (0.00%)	
	0	
Blood glucose abnormal subjects affected / exposed occurrences (all)	Additional description: Blood glucose abnormal	
	1 / 285 (0.35%)	
	1	
Blood glucose fluctuation	Additional description: Blood glucose fluctuation	

subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Blood potassium	Additional description: Blood potassium		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Blood potassium abnormal	Additional description: Blood potassium abnormal		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Blood potassium increased	Additional description: Blood potassium increased		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Blood pressure abnormal	Additional description: Blood pressure abnormal		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Blood sodium	Additional description: Blood sodium		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Blood sodium abnormal	Additional description: Blood sodium abnormal		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Blood sodium decreased	Additional description: Blood sodium decreased		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Blood test abnormal	Additional description: Blood test abnormal		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Blood triglycerides increased	Additional description: Blood triglycerides increased		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Blood urea abnormal	Additional description: Blood urea abnormal		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Blood urea increased	Additional description: Blood urea increased		
subjects affected / exposed	4 / 285 (1.40%)		
occurrences (all)	7		
Chlamydia test positive	Additional description: Chlamydia test positive		

subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Colonoscopy	Additional description: Colonoscopy		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Endoscopy	Additional description: Endoscopy		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Eosinophil count abnormal	Additional description: Eosinophil count abnormal		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Glomerular filtration rate decreased	Additional description: Glomerular filtration rate decreased		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	2		
Haematocrit decreased	Additional description: Haematocrit decreased		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Haemoglobin decreased	Additional description: Haemoglobin decreased		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Heart rate decreased	Additional description: Heart rate decreased		
subjects affected / exposed	2 / 285 (0.70%)		
occurrences (all)	2		
Heart rate increased	Additional description: Heart rate increased		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Heart rate irregular	Additional description: Heart rate irregular		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Hysteroscopy	Additional description: Hysteroscopy		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Mean cell haemoglobin concentration abnormal	Additional description: Mean cell haemoglobin concentration abnormal		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		

Mean cell volume abnormal subjects affected / exposed occurrences (all)	Additional description: Mean cell volume abnormal		
	0 / 285 (0.00%) 0		
Occult blood subjects affected / exposed occurrences (all)	Additional description: Occult blood		
	0 / 285 (0.00%) 0		
Pulse abnormal subjects affected / exposed occurrences (all)	Additional description: Pulse abnormal		
	0 / 285 (0.00%) 0		
Red blood cell count abnormal subjects affected / exposed occurrences (all)	Additional description: Red blood cell count abnormal		
	0 / 285 (0.00%) 0		
Red blood cell morphology abnormal subjects affected / exposed occurrences (all)	Additional description: Red blood cell morphology abnormal		
	0 / 285 (0.00%) 0		
Urine output decreased subjects affected / exposed occurrences (all)	Additional description: Urine output decreased		
	1 / 285 (0.35%) 1		
Urine sodium increased subjects affected / exposed occurrences (all)	Additional description: Urine sodium increased		
	0 / 285 (0.00%) 0		
Weight increased subjects affected / exposed occurrences (all)	Additional description: Weight increased		
	0 / 285 (0.00%) 0		
Injury, poisoning and procedural complications			
	Additional description: Arthropod bite		
	0 / 285 (0.00%) 0		
	Additional description: Contusion		
	0 / 285 (0.00%) 0		
	Additional description: Fall		
Fall subjects affected / exposed occurrences (all)	2 / 285 (0.70%) 2		
	Additional description: Foot fracture		
Foot fracture			

subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Head injury	Additional description: Head injury		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	2		
Joint dislocation	Additional description: Joint dislocation		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Joint sprain	Additional description: Joint sprain		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Limb injury	Additional description: Limb injury		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Meniscus lesion	Additional description: Meniscus lesion		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Muscle strain	Additional description: Muscle strain		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Procedural pain	Additional description: Procedural pain		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Repetitive strain injury	Additional description: Repetitive strain injury		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Rib fracture	Additional description: Rib fracture		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Thermal burn	Additional description: Thermal burn		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Tooth injury	Additional description: Tooth injury		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Upper limb fracture	Additional description: Upper limb fracture		

subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0		
Congenital, familial and genetic disorders			
Thalassaemia	Additional description: Thalassaemia		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0		
Cardiac disorders			
Angina pectoris	Additional description: Angina pectoris		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0		
Arrhythmia	Additional description: Arrhythmia		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0		
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed occurrences (all)	1 / 285 (0.35%) 1		
Bradycardia	Additional description: Bradycardia		
subjects affected / exposed occurrences (all)	22 / 285 (7.72%) 22		
Cardiac failure congestive	Additional description: Cardiac failure congestive		
subjects affected / exposed occurrences (all)	1 / 285 (0.35%) 1		
Palpitations	Additional description: Palpitations		
subjects affected / exposed occurrences (all)	3 / 285 (1.05%) 3		
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0		
Nervous system disorders			
Balance disorder	Additional description: Balance disorder		
subjects affected / exposed occurrences (all)	0 / 285 (0.00%) 0		
Burning sensation	Additional description: Burning sensation		
subjects affected / exposed occurrences (all)	1 / 285 (0.35%) 1		
Carpal tunnel syndrome	Additional description: Carpal tunnel syndrome		

subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Dizziness	Additional description: Dizziness		
subjects affected / exposed	17 / 285 (5.96%)		
occurrences (all)	18		
Dizziness exertional	Additional description: Dizziness exertional		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Dizziness postural	Additional description: Dizziness postural		
subjects affected / exposed	2 / 285 (0.70%)		
occurrences (all)	2		
Dysarthria	Additional description: Dysarthria		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Headache	Additional description: Headache		
subjects affected / exposed	10 / 285 (3.51%)		
occurrences (all)	10		
Hemicephalalgia	Additional description: Hemicephalalgia		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Hypoaesthesia	Additional description: Hypoaesthesia		
subjects affected / exposed	5 / 285 (1.75%)		
occurrences (all)	6		
Lethargy	Additional description: Lethargy		
subjects affected / exposed	10 / 285 (3.51%)		
occurrences (all)	10		
Loss of consciousness	Additional description: Loss of consciousness		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Migraine	Additional description: Migraine		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Nerve compression	Additional description: Nerve compression		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Neuropathy peripheral	Additional description: Neuropathy peripheral		

subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Orthostatic intolerance	Additional description: Orthostatic intolerance		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	3 / 285 (1.05%)		
occurrences (all)	3		
Parkinsonism	Additional description: Parkinsonism		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Petit mal epilepsy	Additional description: Petit mal epilepsy		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Presyncope	Additional description: Presyncope		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Restless legs syndrome	Additional description: Restless legs syndrome		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Sciatica	Additional description: Sciatica		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Sensory disturbance	Additional description: Sensory disturbance		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Somnolence	Additional description: Somnolence		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Syncope	Additional description: Syncope		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Transient ischaemic attack	Additional description: Transient ischaemic attack		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Tremor	Additional description: Tremor		

subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Vascular dementia	Additional description: Vascular dementia		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	2 / 285 (0.70%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Ear pain	Additional description: Ear pain		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Eustachian tube dysfunction	Additional description: Eustachian tube dysfunction		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Vertigo	Additional description: Vertigo		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Vertigo positional	Additional description: Vertigo positional		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	4		
Eye disorders			
Cataract	Additional description: Cataract		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Dry eye	Additional description: Dry eye		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Eye disorder	Additional description: Eye disorder		

subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Eye haemorrhage	Additional description: Eye haemorrhage		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Eye pain	Additional description: Eye pain		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Lacrimation increased	Additional description: Lacrimation increased		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Photophobia	Additional description: Photophobia		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Retinal disorder	Additional description: Retinal disorder		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Vision blurred	Additional description: Vision blurred		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Visual impairment	Additional description: Visual impairment		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Vitreous floaters	Additional description: Vitreous floaters		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort	Additional description: Abdominal discomfort		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Abdominal hernia	Additional description: Abdominal hernia		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		

Abdominal pain subjects affected / exposed occurrences (all)	Additional description: Abdominal pain	
	3 / 285 (1.05%) 3	
Abdominal pain upper subjects affected / exposed occurrences (all)	Additional description: Abdominal pain upper	
	1 / 285 (0.35%) 1	
Abdominal tenderness subjects affected / exposed occurrences (all)	Additional description: Abdominal tenderness	
	0 / 285 (0.00%) 0	
Anal fistula subjects affected / exposed occurrences (all)	Additional description: Anal fistula	
	1 / 285 (0.35%) 1	
Constipation subjects affected / exposed occurrences (all)	Additional description: Constipation	
	1 / 285 (0.35%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	Additional description: Diarrhoea	
	11 / 285 (3.86%) 11	
Dry mouth subjects affected / exposed occurrences (all)	Additional description: Dry mouth	
	1 / 285 (0.35%) 1	
Dyspepsia subjects affected / exposed occurrences (all)	Additional description: Dyspepsia	
	3 / 285 (1.05%) 3	
Flatulence subjects affected / exposed occurrences (all)	Additional description: Flatulence	
	2 / 285 (0.70%) 2	
Frequent bowel movements subjects affected / exposed occurrences (all)	Additional description: Frequent bowel movements	
	0 / 285 (0.00%) 0	
Gastrointestinal disorder subjects affected / exposed occurrences (all)	Additional description: Gastrointestinal disorder	
	0 / 285 (0.00%) 0	
Gastrointestinal motility disorder subjects affected / exposed occurrences (all)	Additional description: Gastrointestinal motility disorder	
	0 / 285 (0.00%) 0	

Gingival hyperplasia subjects affected / exposed occurrences (all)	Additional description: Gingival hyperplasia	
	0 / 285 (0.00%) 0	
Haematochezia subjects affected / exposed occurrences (all)	Additional description: Haematochezia	
	0 / 285 (0.00%) 0	
Lip swelling subjects affected / exposed occurrences (all)	Additional description: Lip swelling	
	0 / 285 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	Additional description: Nausea	
	5 / 285 (1.75%) 6	
Oesophageal dilatation subjects affected / exposed occurrences (all)	Additional description: Oesophageal dilatation	
	0 / 285 (0.00%) 0	
Oesophagitis subjects affected / exposed occurrences (all)	Additional description: Oesophagitis	
	0 / 285 (0.00%) 0	
Oral pain subjects affected / exposed occurrences (all)	Additional description: Oral pain	
	0 / 285 (0.00%) 0	
Paraesthesia oral subjects affected / exposed occurrences (all)	Additional description: Paraesthesia oral	
	0 / 285 (0.00%) 0	
Rectal haemorrhage subjects affected / exposed occurrences (all)	Additional description: Rectal haemorrhage	
	0 / 285 (0.00%) 0	
Toothache subjects affected / exposed occurrences (all)	Additional description: Toothache	
	1 / 285 (0.35%) 1	
Vomiting subjects affected / exposed occurrences (all)	Additional description: Vomiting	
	1 / 285 (0.35%) 1	
Vomiting projectile subjects affected / exposed occurrences (all)	Additional description: Vomiting projectile	
	0 / 285 (0.00%) 0	

Skin and subcutaneous tissue disorders			
Blister	Additional description: Blister		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Cold sweat	Additional description: Cold sweat		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Dermatitis allergic	Additional description: Dermatitis allergic		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Drug eruption	Additional description: Drug eruption		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Dry skin	Additional description: Dry skin		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Ecchymosis	Additional description: Ecchymosis		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Eczema	Additional description: Eczema		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Erythema	Additional description: Erythema		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Intertrigo	Additional description: Intertrigo		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Pain of skin	Additional description: Pain of skin		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Papule	Additional description: Papule		

subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Pruritus	Additional description: Pruritus		
subjects affected / exposed	4 / 285 (1.40%)		
occurrences (all)	5		
Pruritus generalised	Additional description: Pruritus generalised		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Psoriasis	Additional description: Psoriasis		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Rash	Additional description: Rash		
subjects affected / exposed	3 / 285 (1.05%)		
occurrences (all)	3		
Rash pruritic	Additional description: Rash pruritic		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Skin lesion	Additional description: Skin lesion		
subjects affected / exposed	3 / 285 (1.05%)		
occurrences (all)	3		
Urticaria	Additional description: Urticaria		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria	Additional description: Dysuria		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Haematuria	Additional description: Haematuria		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Incontinence	Additional description: Incontinence		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Ketonuria	Additional description: Ketonuria		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		

Micturition urgency subjects affected / exposed occurrences (all)	Additional description: Micturition urgency 1 / 285 (0.35%) 1		
Nocturia subjects affected / exposed occurrences (all)	Additional description: Nocturia 2 / 285 (0.70%) 2		
Pollakiuria subjects affected / exposed occurrences (all)	Additional description: Pollakiuria 0 / 285 (0.00%) 0		
Polyuria subjects affected / exposed occurrences (all)	Additional description: Polyuria 0 / 285 (0.00%) 0		
Proteinuria subjects affected / exposed occurrences (all)	Additional description: Proteinuria 1 / 285 (0.35%) 1		
Renal colic subjects affected / exposed occurrences (all)	Additional description: Renal colic 0 / 285 (0.00%) 0		
Renal failure chronic subjects affected / exposed occurrences (all)	Additional description: Renal failure chronic 0 / 285 (0.00%) 0		
Renal impairment subjects affected / exposed occurrences (all)	Additional description: Renal impairment 1 / 285 (0.35%) 1		
Renal pain subjects affected / exposed occurrences (all)	Additional description: Renal pain 0 / 285 (0.00%) 0		
Urinary incontinence subjects affected / exposed occurrences (all)	Additional description: Urinary incontinence 0 / 285 (0.00%) 0		
Urinary retention subjects affected / exposed occurrences (all)	Additional description: Urinary retention 0 / 285 (0.00%) 0		
Urine odour abnormal subjects affected / exposed occurrences (all)	Additional description: Urine odour abnormal 0 / 285 (0.00%) 0		

Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	4 / 285 (1.40%)		
occurrences (all)	4		
Arthritis	Additional description: Arthritis		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Back pain	Additional description: Back pain		
subjects affected / exposed	5 / 285 (1.75%)		
occurrences (all)	5		
Joint stiffness	Additional description: Joint stiffness		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Joint swelling	Additional description: Joint swelling		
subjects affected / exposed	10 / 285 (3.51%)		
occurrences (all)	10		
Muscle fatigue	Additional description: Muscle fatigue		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	3 / 285 (1.05%)		
occurrences (all)	4		
Muscle tightness	Additional description: Muscle tightness		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Muscle twitching	Additional description: Muscle twitching		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Muscular weakness	Additional description: Muscular weakness		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Musculoskeletal discomfort	Additional description: Musculoskeletal discomfort		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Musculoskeletal pain	Additional description: Musculoskeletal pain		

subjects affected / exposed	3 / 285 (1.05%)		
occurrences (all)	3		
Musculoskeletal stiffness	Additional description: Musculoskeletal stiffness		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Myalgia	Additional description: Myalgia		
subjects affected / exposed	2 / 285 (0.70%)		
occurrences (all)	2		
Neck pain	Additional description: Neck pain		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	3 / 285 (1.05%)		
occurrences (all)	3		
Periarthritis	Additional description: Periarthritis		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Plantar fasciitis	Additional description: Plantar fasciitis		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Rheumatoid arthritis	Additional description: Rheumatoid arthritis		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Sensation of heaviness	Additional description: Sensation of heaviness		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Tendon pain	Additional description: Tendon pain		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Abscess oral	Additional description: Abscess oral		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		

Body tinea subjects affected / exposed occurrences (all)	Additional description: Body tinea	
	0 / 285 (0.00%) 0	
Bronchitis subjects affected / exposed occurrences (all)	Additional description: Bronchitis	
	0 / 285 (0.00%) 0	
Candidiasis subjects affected / exposed occurrences (all)	Additional description: Candidiasis	
	1 / 285 (0.35%) 1	
Cellulitis subjects affected / exposed occurrences (all)	Additional description: Cellulitis	
	1 / 285 (0.35%) 1	
Diverticulitis subjects affected / exposed occurrences (all)	Additional description: Diverticulitis	
	1 / 285 (0.35%) 1	
Eye infection subjects affected / exposed occurrences (all)	Additional description: Eye infection	
	0 / 285 (0.00%) 0	
Fungal infection subjects affected / exposed occurrences (all)	Additional description: Fungal infection	
	0 / 285 (0.00%) 0	
Furuncle subjects affected / exposed occurrences (all)	Additional description: Furuncle	
	0 / 285 (0.00%) 0	
Gastroenteritis subjects affected / exposed occurrences (all)	Additional description: Gastroenteritis	
	0 / 285 (0.00%) 0	
H1N1 influenza subjects affected / exposed occurrences (all)	Additional description: H1N1 influenza	
	0 / 285 (0.00%) 0	
Helicobacter infection subjects affected / exposed occurrences (all)	Additional description: Helicobacter infection	
	1 / 285 (0.35%) 1	
Herpes zoster subjects affected / exposed occurrences (all)	Additional description: Herpes zoster	
	0 / 285 (0.00%) 0	

Influenza	Additional description: Influenza	
subjects affected / exposed	2 / 285 (0.70%)	
occurrences (all)	2	
Kidney infection	Additional description: Kidney infection	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Labyrinthitis	Additional description: Labyrinthitis	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Lower respiratory tract infection	Additional description: Lower respiratory tract infection	
subjects affected / exposed	4 / 285 (1.40%)	
occurrences (all)	4	
Nasopharyngitis	Additional description: Nasopharyngitis	
subjects affected / exposed	9 / 285 (3.16%)	
occurrences (all)	10	
Onychomycosis	Additional description: Onychomycosis	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Oral candidiasis	Additional description: Oral candidiasis	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Paronychia	Additional description: Paronychia	
subjects affected / exposed	1 / 285 (0.35%)	
occurrences (all)	2	
Pharyngitis	Additional description: Pharyngitis	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Pneumonia	Additional description: Pneumonia	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Respiratory tract infection	Additional description: Respiratory tract infection	
subjects affected / exposed	1 / 285 (0.35%)	
occurrences (all)	1	
Rhinitis	Additional description: Rhinitis	
subjects affected / exposed	1 / 285 (0.35%)	
occurrences (all)	1	

Sialoadenitis	Additional description: Sialoadenitis	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Sinusitis	Additional description: Sinusitis	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Skin infection	Additional description: Skin infection	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Tinea infection	Additional description: Tinea infection	
subjects affected / exposed	1 / 285 (0.35%)	
occurrences (all)	1	
Tooth abscess	Additional description: Tooth abscess	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Tooth infection	Additional description: Tooth infection	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection	
subjects affected / exposed	2 / 285 (0.70%)	
occurrences (all)	2	
Urinary tract infection	Additional description: Urinary tract infection	
subjects affected / exposed	4 / 285 (1.40%)	
occurrences (all)	4	
Viral diarrhoea	Additional description: Viral diarrhoea	
subjects affected / exposed	1 / 285 (0.35%)	
occurrences (all)	1	
Viral infection	Additional description: Viral infection	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Viral labyrinthitis	Additional description: Viral labyrinthitis	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	
Viral upper respiratory tract infection	Additional description: Viral upper respiratory tract infection	
subjects affected / exposed	0 / 285 (0.00%)	
occurrences (all)	0	

Metabolism and nutrition disorders			
Diabetes mellitus inadequate control	Additional description: Diabetes mellitus inadequate control		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Gout	Additional description: Gout		
subjects affected / exposed	6 / 285 (2.11%)		
occurrences (all)	7		
Haemochromatosis	Additional description: Haemochromatosis		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Hypercalcaemia	Additional description: Hypercalcaemia		
subjects affected / exposed	1 / 285 (0.35%)		
occurrences (all)	1		
Hyperglycaemia	Additional description: Hyperglycaemia		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	2 / 285 (0.70%)		
occurrences (all)	2		
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Hypovitaminosis	Additional description: Hypovitaminosis		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Increased appetite	Additional description: Increased appetite		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		
Salt craving	Additional description: Salt craving		
subjects affected / exposed	0 / 285 (0.00%)		
occurrences (all)	0		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2009	Protocol amended to remove recruitment limiting exclusion criteria, to add pregnancy testing and other safety assessments and patient withdrawal criteria
18 December 2009	Protocol amended to include pharmacogenetic sampling and a short patient treatment break.
26 May 2010	Protocol amended to permit a drug holiday and early randomisation. Changes to inclusion and exclusion criteria and additional visit assessments added.
10 January 2011	Protocol amended to remove recruitment limiting exclusion criteria and to clarify safety reporting timescales.
30 November 2011	Protocol amended to permit open-label (non-blinded) IMP to be used in the trial due to blinded stock issues.
23 August 2012	Protocol blood pressure inclusion criteria expanded to aid recruitment.

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported