



Clinical trial results: Monotherapy vs Dual Therapy for the Initial Treatment of Hypertension (Pathway-1): a Randomised Double-blind Controlled Trial

Summary

EudraCT number	2008-007749-29
Trial protocol	GB
Global end of trial date	31 January 2015

Results information

Result version number	v1 (current)
This version publication date	19 February 2020
First version publication date	19 February 2020
Summary attachment (see zip file)	Pathway 1 Publication (Pathway 1 AHA Publication.pdf)

Trial information

Trial identification

Sponsor protocol code	Pathway 1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00994617
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 (Chief Investigator), William Harvey Research Institute, Queen Mary University of London, morris.brown@qmul.ac.uk
Scientific contact	Morris J Brown (Chief Investigator), 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	30 January 2015
Global end of trial reached?	Yes
Global end of trial date	31 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test whether the current custom of initiating treatment for high blood pressure with a single drug is less effective in the short-term than initial combination therapy, and results in the eventual need for comparatively more drugs for lowering blood pressure.

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	16 February 2010
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: 605
Worldwide total number of subjects	605
EEA total number of subjects	605

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)	471
From 65 to 84 years	134
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled between Feb 2010 to Nov 2013. The trial was conducted in 11 secondary and 2 primary care centres in the United Kingdom

Pre-assignment

Screening details:

Patients aged 18-79 with a diagnosis of essential hypertension, systolic BP>150 mm Hg and diastolic BP>95 mm, and who were never treated or who had received 1 drug class in the previous year. 796 patients were screened, 191 excluded and 605 randomised.

Pre-assignment period milestones

Number of subjects started	796 ^[1]
Number of subjects completed	605

Pre-assignment subject non-completion reasons

Reason: Number of subjects	not eligible: 191
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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: We screened 796 patients and randomized 605 participants, 301 to initial monotherapy and 304 to initial combination therapy

Period 1

Period 1 title	weeks 0-16/initial mono- and combo thera
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Losartan and HCTZ tablets were reencapsulated in identical gelatin capsules. All patients receive two capsules throughout phase 1, in a double-dummy fashion, to maintain masking in the combination and monotherapy groups. In phases 2 and 3, losartan and HCTZ were provided in a single tablet, the identity of which was known to investigators and patients; however masking of the initial assignment was maintained until database loc

Arms

Are arms mutually exclusive?	Yes
Arm title	initial monotherapy

Arm description:

301 patients were randomly assigned to initial monotherapy (losartan and HCTZ crossing over at 8 weeks)

Arm type	Experimental
Investigational medicinal product name	losartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

losartan 50-100 mg crossing over hydrochlorothiazide (HCTZ) 12.5 -25 mg at 8 weeks

Investigational medicinal product name	hydrochlorothiazide
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients were randomly assigned to initial monotherapy (hydrochlorothiazide (HCTZ) 12.5 -25 mg and losartan 50-100 mg or crossing over at 8 weeks)

Arm title	initial combination therapy
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Arm description:

304 eligible participants received 50 mg losartan plus 12.5 mg HCTZ combination therapy. The successive dose permutations at every 4 weeks after initial assignment were losartan/HCTZ 50/25, 100/12.5, and 100/25 mg

Arm type	Active comparator
Investigational medicinal product name	losartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

losartan 50 mg plus hydrochlorothiazide 12.5 mg. In this arm, the successful dose permutations at every 4 weeks after initial assignment were losartan/HCTZ 50/25, 100/12.5, and 100/25 mg.

Investigational medicinal product name	hydrochlorothiazide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

losartan 50 mg plus hydrochlorothiazide 12.5. In this arm, the successful dose permutations at every 4 weeks after initial assignment were losartan/HCTZ 50/25, 100/12.5, and 100/25 mg.

Number of subjects in period 1	initial monotherapy	initial combination therapy
Started	301	304
Completed	287	299
Not completed	14	5
not eligible	14	5

Period 2

Period 2 title	weeks 16-32 (combination therapy)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Losartan and HCTZ combo
Arm description: After 16 weeks (start of period 2) all 586 participants in the intention-to-treat population received the combination of losartan 100 mg plus HCTZ 12.5 mg. At week 24, all participants were force-titrated to losartan 100 mh plus HCTZ 25 mg	
Arm type	Experimental
Investigational medicinal product name	losartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

After 16 weeks (start of period 2) all 586 participants in the intention-to-treat population received the combination of losartan 100 mg with HCTZ orally

Investigational medicinal product name	hydrochlorothiazide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

After 16 weeks (start of period 2) all 586 participants in the intention-to-treat population received the combination of losartan 100 mg plus HCTZ 12.5 mg. At week 24, all participants were force-titrated to losartan 100 mh plus HCTZ 25 mg

Number of subjects in period 2	Losartan and HCTZ combo
Started	586
Completed	586

Period 3

Period 3 title	weeks 33-52 (combination therapy)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Single blind add-on (amlodipine 10mg, doxazosin 4mg)

Arms

Arm title	Losartan and HCTZ combo
Arm description: At week 32 (start of phase 3) all participants received 100 mg losartan plus 25 mg HCTZ. 5/10 mg amlodipine (with or without 4/8 mg doxazosin) was added if systolic BP was >140 mm Hg or diastolic was >90 mm Hg.	
Arm type	Active comparator
Investigational medicinal product name	losartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

At week 32 (start of phase 3) all participants received 100 mg losartan plus 25 mg HCTZ. 5/10 mg amlodipine (with or without 4/8 mg doxazosin) was added if systolic BP was >140 mm Hg or diastolic was >90 mm Hg.

Investigational medicinal product name	hydrochlorothiazide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

At week 32 (start of phase 3) all participants received 100 mg losartan plus 25 mg HCTZ. 5/10 mg amlodipine (with or without 4/8 mg doxazosin) was added if systolic BP was >140 mm Hg or diastolic was >90 mm Hg.

Number of subjects in period 3	Losartan and HCTZ combo
Started	586
Completed	432
Not completed	154
not eligible	154

Baseline characteristics

Reporting groups

Reporting group title	initial monotherapy
Reporting group description: 301 patients were randomly assigned to initial monotherapy (losartan and HCTZ crossing over at 8 weeks)	
Reporting group title	initial combination therapy
Reporting group description: 304 eligible participants received 50 mg losartan plus 12.5 mg HCTZ combination therapy. The successive dose permutations at every 4 weeks after initial assignment were losartan/HCTZ 50/25, 100/12.5, and 100/25 mg	

Reporting group values	initial monotherapy	initial combination therapy	Total
Number of subjects	301	304	605
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	53.9	54.2	
standard deviation	± 12.0	± 12.0	-
Gender categorical Units: Subjects			
Female	103	113	216
Male	198	191	389

Subject analysis sets

Subject analysis set title	monotherapy (HCTZ first)
Subject analysis set type	Sub-group analysis
Subject analysis set description: 151 participants were assigned first to 12.5 mg HCTZ plus 50 mg losartan treatment during weeks 0-16. The participants crossed over at 6 weeks to the alternative drug at the lower dose, which was again force dose-titrated to twice the dose after a further 4 weeks	
Subject analysis set title	monotherapy (losartan first)
Subject analysis set type	Sub-group analysis
Subject analysis set description: 150 participants were assigned first to 50 mg losartan or 12.5-25 mg HCTZ during weeks 0-16 (the participants crossed over at 8 weeks to the alternative drug at the lower dose, which was again forced dose-titrated to twice the dose after a further 4 weeks)	

Reporting group values	monotherapy (HCTZ first)	monotherapy (losartan first)	
Number of subjects	151	150	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	53.4	54.5	
standard deviation	± 11.9	± 12.1	
Gender categorical Units: Subjects			
Female	55	48	
Male	96	102	

End points

End points reporting groups

Reporting group title	initial monotherapy
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Reporting group description:

301 patients were randomly assigned to initial monotherapy (losartan and HCTZ crossing over at 8 weeks)

Reporting group title	initial combination therapy
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Reporting group description:

304 eligible participants received 50 mg losartan plus 12.5 mg HCTZ combination therapy. The successive dose permutations at every 4 weeks after initial assignment were losartan/HCTZ 50/25, 100/12.5, and 100/25 mg

Reporting group title	Losartan and HCTZ combo
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Reporting group description:

After 16 weeks (start of period 2) all 586 participants in the intention-to-treat population received the combination of losartan 100 mg plus HCTZ 12.5 mg. At week 24, all participants were force-titrated to losartan 100 mg plus HCTZ 25 mg

Reporting group title	Losartan and HCTZ combo
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Reporting group description:

At week 32 (start of phase 3) all participants received 100 mg losartan plus 25 mg HCTZ. 5/10 mg amlodipine (with or without 4/8 mg doxazosin) was added if systolic BP was >140 mm Hg or diastolic was >90 mm Hg.

Subject analysis set title	monotherapy (HCTZ first)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

151 participants were assigned first to 12.5 mg HCTZ plus 50 mg losartan treatment during weeks 0-16. The participants crossed over at 6 weeks to the alternative drug at the lower dose, which was again force dose-titrated to twice the dose after a further 4 weeks

Subject analysis set title	monotherapy (losartan first)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

150 participants were assigned first to 50 mg losartan or 12.5-25 mg HCTZ during weeks 0-16 (the participants crossed over at 8 weeks to the alternative drug at the lower dose, which was again forced dose-titrated to twice the dose after a further 4 weeks)

Primary: Mean reduction from baseline HSBP over weeks 0 - 32

End point title	Mean reduction from baseline HSBP over weeks 0 - 32
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End point description:

There were two primary analysis in a hierarchy. The comparison between groups of the endpoints averaged over weeks 0-32, phase 1-2, was tested first. If, and only if, this was statistically significant was the second comparison made of the endpoint observed at week 32 in isolation.

End point type	Primary
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End point timeframe:

Measured at 32 weeks after randomization (average). We test the superiority between losartan plus HCTZ (initial combination group) and the mean of each monotherapy arm

End point values	initial monotherapy	initial combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	304		
Units: mm Hg				
least squares mean (confidence interval 95%)	-14.8 (-15.8 to -13.8)	-19.7 (-20.7 to -18.7)		

Statistical analyses

Statistical analysis title	Mean change from baseline HSBP
Statistical analysis description:	
A sample size of 268 in each group had 90% power to detect a change in HSBP means of 4 mm HG, assuming a common SD of 12 mm Hg using a 2-group t test with $\alpha=0.01$. We used mix-effect models with unstructured covariances for repeated measures within a patient, adjusting for prescribed baselines covariates. Least squares means were estimated. BP control and response rates were analysed using log regression. χ^2 tests were used to compare adverse event rates, and Fisher exact P values are given.	
Comparison groups	initial monotherapy v initial combination therapy
Number of subjects included in analysis	605
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-4.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.04
upper limit	-3.73
Variability estimate	Standard deviation

Primary: Change from baseline HSBP at week 32 in isolation

End point title	Change from baseline HSBP at week 32 in isolation
End point description:	
There were two primary analysis in a hierarchy. The comparison between groups of the endpoints averaged over weeks 0-32, phase 1-2, was tested first. If, and only if, this was statistically significant was the second comparison made of the endpoint observed at week 32 in isolation.	
End point type	Primary
End point timeframe:	
The second primary end point (measured only if the first hypothesis was positive) is the reduction from baseline in HSBP at 32 week, a point in the study when all participants were receiving the same combination treatment (losartan + HCTZ)	

End point values	initial monotherapy	initial combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287	299		
Units: mm Hg				
least squares mean (confidence interval 95%)	-23.4 (-24.8 to -22.0)	-22.2 (-23.6 to -20.8)		

Statistical analyses

Statistical analysis title	reduction in mean HSBP at week 32
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Statistical analysis description:

We used mixed-effect models with unstructured covariances for repeated measures within a patient. We adjusted for prespecified baseline covariates (sex, age etc.). Least square means estimated from these models are presented. Arithmetic mean of last 18 home BP measurements was used to calculate home BP.

Comparison groups	initial monotherapy v initial combination therapy
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	2.82
Variability estimate	Standard deviation

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Combination
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Reporting group description: -

Reporting group title	Monotherapy
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Reporting group description: -

Serious adverse events	Combination	Monotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 304 (3.62%)	10 / 301 (3.32%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer stage II	Additional description: Endometrial cancer stage II		
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm	Additional description: Metastatic neoplasm		
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal cancer	Additional description: Rectal cancer		
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Glomerular filtration rate decreased	Additional description: Glomerular filtration rate decreased		

subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal	Additional description: Liver function test abnormal		
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders	Additional description: Circulatory collapse		
Circulatory collapse	Additional description: Circulatory collapse		
subjects affected / exposed	2 / 304 (0.66%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension	Additional description: Hypotension		
subjects affected / exposed	2 / 304 (0.66%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders	Additional description: Atrial fibrillation		
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease	Additional description: Coronary artery disease		
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia	Additional description: Tachyarrhythmia		
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures	Additional description: Cardiac pacemaker insertion		
Cardiac pacemaker insertion	Additional description: Cardiac pacemaker insertion		
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cholecystectomy subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Cholecystectomy		
	0 / 304 (0.00%)	1 / 301 (0.33%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Renal stone removal subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Renal stone removal		
	0 / 304 (0.00%)	1 / 301 (0.33%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Rotator cuff repair subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Rotator cuff repair		
	0 / 304 (0.00%)	1 / 301 (0.33%)	
	0 / 0	0 / 2	
	0 / 0	0 / 0	
Nervous system disorders Loss of consciousness subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Loss of consciousness		
	1 / 304 (0.33%)	0 / 301 (0.00%)	
	1 / 1	0 / 0	
	0 / 0	0 / 0	
Blood and lymphatic system disorders Thrombocytopenic purpura subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Thrombocytopenic purpura		
	1 / 304 (0.33%)	0 / 301 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Hepatobiliary disorders Cholecystitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Cholecystitis		
	0 / 304 (0.00%)	1 / 301 (0.33%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Nephrolithiasis		
	0 / 304 (0.00%)	1 / 301 (0.33%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Renal colic	Additional description: Renal colic		

subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis	Additional description: Diverticulitis		
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
subjects affected / exposed	1 / 304 (0.33%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration	Additional description: Dehydration		
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Combination	Monotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	278 / 304 (91.45%)	265 / 301 (88.04%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiomyolipoma	Additional description: Angiomyolipoma		
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Benign neoplasm of eyelid	Additional description: Benign neoplasm of eyelid		
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Bowen's disease	Additional description: Bowen's disease		

subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Melanocytic naevus	Additional description: Melanocytic naevus		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Oral neoplasm	Additional description: Oral neoplasm		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Skin papilloma	Additional description: Skin papilloma		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Vascular disorders			
Aortic aneurysm	Additional description: Aortic aneurysm		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Aortic stenosis	Additional description: Aortic stenosis		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Circulatory collapse	Additional description: Circulatory collapse		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	
Deep vein thrombosis	Additional description: Deep vein thrombosis		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Flushing	Additional description: Flushing		
subjects affected / exposed occurrences (all)	5 / 304 (1.64%) 5	1 / 301 (0.33%) 1	
Hot flush	Additional description: Hot flush		
subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 8	3 / 301 (1.00%) 3	
Hypotension	Additional description: Hypotension		
subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 4	7 / 301 (2.33%) 7	
Orthostatic hypotension	Additional description: Orthostatic hypotension		
subjects affected / exposed occurrences (all)	11 / 304 (3.62%) 15	10 / 301 (3.32%) 12	

Peripheral coldness subjects affected / exposed occurrences (all)	Additional description: Peripheral coldness	
	5 / 304 (1.64%) 5	2 / 301 (0.66%) 2
Raynaud's phenomenon subjects affected / exposed occurrences (all)	Additional description: Raynaud's phenomenon	
	3 / 304 (0.99%) 3	1 / 301 (0.33%) 1
Varicose vein subjects affected / exposed occurrences (all)	Additional description: Varicose vein	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Vein disorder subjects affected / exposed occurrences (all)	Additional description: Vein disorder	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Surgical and medical procedures		
Acrochordon excision subjects affected / exposed occurrences (all)	Additional description: Acrochordon excision	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Bartholin's cyst removal subjects affected / exposed occurrences (all)	Additional description: Bartholin's cyst removal	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Bladder neck operation subjects affected / exposed occurrences (all)	Additional description: Bladder neck operation	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Cataract operation subjects affected / exposed occurrences (all)	Additional description: Cataract operation	
	1 / 304 (0.33%) 1	2 / 301 (0.66%) 3
Colostomy subjects affected / exposed occurrences (all)	Additional description: Colostomy	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Dental cleaning subjects affected / exposed occurrences (all)	Additional description: Dental cleaning	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Dental implantation subjects affected / exposed occurrences (all)	Additional description: Dental implantation	
	1 / 304 (0.33%) 2	0 / 301 (0.00%) 0
Dental operation	Additional description: Dental operation	

subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Endodontic procedure	Additional description: Endodontic procedure		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Eye laser surgery	Additional description: Eye laser surgery		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 2	
Fasciectomy	Additional description: Fasciectomy		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Gallbladder operation	Additional description: Gallbladder operation		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Gingival operation	Additional description: Gingival operation		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Hernia repair	Additional description: Hernia repair		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Hip arthroplasty	Additional description: Hip arthroplasty		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Hysterectomy	Additional description: Hysterectomy		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Inguinal hernia repair	Additional description: Inguinal hernia repair		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 2	0 / 301 (0.00%) 0	
Injection	Additional description: Injection		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Intestinal operation	Additional description: Intestinal operation		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Lesion excision	Additional description: Lesion excision		

subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Nasal polypectomy	Additional description: Nasal polypectomy		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Nasal septal operation	Additional description: Nasal septal operation		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Removal of internal fixation	Additional description: Removal of internal fixation		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Shoulder operation	Additional description: Shoulder operation		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Skin lesion excision	Additional description: Skin lesion excision		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Tooth extraction	Additional description: Tooth extraction		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	2 / 301 (0.66%) 3	
Tooth repair	Additional description: Tooth repair		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 2	0 / 301 (0.00%) 0	
Tympanoplasty	Additional description: Tympanoplasty		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Wisdom teeth removal	Additional description: Wisdom teeth removal		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
General disorders and administration site conditions			
Adverse drug reaction	Additional description: Adverse drug reaction		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Adverse reaction	Additional description: Adverse reaction		

subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Asthenia	Additional description: Asthenia		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	4 / 301 (1.33%) 4	
Chest discomfort	Additional description: Chest discomfort		
subjects affected / exposed occurrences (all)	7 / 304 (2.30%) 8	12 / 301 (3.99%) 12	
Chest pain	Additional description: Chest pain		
subjects affected / exposed occurrences (all)	8 / 304 (2.63%) 12	10 / 301 (3.32%) 12	
Chills	Additional description: Chills		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	2 / 301 (0.66%) 2	
Crepitations	Additional description: Crepitations		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Drug resistance	Additional description: Drug resistance		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Facial pain	Additional description: Facial pain		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Fatigue	Additional description: Fatigue		
subjects affected / exposed occurrences (all)	45 / 304 (14.80%) 53	34 / 301 (11.30%) 39	
Feeling abnormal	Additional description: Feeling abnormal		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	1 / 301 (0.33%) 1	
Feeling cold	Additional description: Feeling cold		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	
Feeling hot	Additional description: Feeling hot		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	1 / 301 (0.33%) 1	
Influenza like illness	Additional description: Influenza like illness		

subjects affected / exposed occurrences (all)	13 / 304 (4.28%) 13	6 / 301 (1.99%) 6	
Irritability	Additional description: Irritability		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	3 / 301 (1.00%) 6	
Local swelling	Additional description: Local swelling		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Malaise	Additional description: Malaise		
subjects affected / exposed occurrences (all)	5 / 304 (1.64%) 6	4 / 301 (1.33%) 4	
Non-cardiac chest pain	Additional description: Non-cardiac chest pain		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed occurrences (all)	8 / 304 (2.63%) 8	7 / 301 (2.33%) 7	
Pain	Additional description: Pain		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 4	1 / 301 (0.33%) 1	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	3 / 301 (1.00%) 6	
Sensation of foreign body	Additional description: Sensation of foreign body		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Sensation of pressure	Additional description: Sensation of pressure		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Sluggishness	Additional description: Sluggishness		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Swelling	Additional description: Swelling		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Thirst	Additional description: Thirst		

subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 3	0 / 301 (0.00%) 0	
Vessel puncture site haematoma	Additional description: Vessel puncture site haematoma		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Immune system disorders	Additional description: Drug hypersensitivity		
Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 3	0 / 301 (0.00%) 0	
Seasonal allergy	Additional description: Seasonal allergy		
subjects affected / exposed occurrences (all)	5 / 304 (1.64%) 5	4 / 301 (1.33%) 4	
Social circumstances	Additional description: Bereavement		
Bereavement subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Death of companion	Additional description: Death of companion		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Death of relative	Additional description: Death of relative		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Ex-tobacco user	Additional description: Ex-tobacco user		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Family stress	Additional description: Family stress		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	
Stress at work	Additional description: Stress at work		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	1 / 301 (0.33%) 1	
Reproductive system and breast disorders			

Breast tenderness	Additional description: Breast tenderness	
subjects affected / exposed	0 / 304 (0.00%)	2 / 301 (0.66%)
occurrences (all)	0	3
Dysmenorrhoea	Additional description: Dysmenorrhoea	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	2
Erectile dysfunction	Additional description: Erectile dysfunction	
subjects affected / exposed	12 / 304 (3.95%)	13 / 301 (4.32%)
occurrences (all)	14	14
Gynaecomastia	Additional description: Gynaecomastia	
subjects affected / exposed	0 / 304 (0.00%)	2 / 301 (0.66%)
occurrences (all)	0	3
Menorrhagia	Additional description: Menorrhagia	
subjects affected / exposed	0 / 304 (0.00%)	2 / 301 (0.66%)
occurrences (all)	0	3
Nipple disorder	Additional description: Nipple disorder	
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)
occurrences (all)	1	0
Prostatic intraepithelial neoplasia	Additional description: Prostatic intraepithelial neoplasia	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Vaginal haemorrhage	Additional description: Vaginal haemorrhage	
subjects affected / exposed	0 / 304 (0.00%)	2 / 301 (0.66%)
occurrences (all)	0	2
Respiratory, thoracic and mediastinal disorders		
Asthma	Additional description: Asthma	
subjects affected / exposed	4 / 304 (1.32%)	1 / 301 (0.33%)
occurrences (all)	4	1
Choking sensation	Additional description: Choking sensation	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Cough	Additional description: Cough	
subjects affected / exposed	23 / 304 (7.57%)	24 / 301 (7.97%)
occurrences (all)	25	29
Dry throat	Additional description: Dry throat	

subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 4	2 / 301 (0.66%) 2	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed occurrences (all)	13 / 304 (4.28%) 13	10 / 301 (3.32%) 11	
Dyspnoea exertional	Additional description: Dyspnoea exertional		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 3	2 / 301 (0.66%) 6	
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	4 / 301 (1.33%) 4	
Increased upper airway secretion	Additional description: Increased upper airway secretion		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Nasal congestion	Additional description: Nasal congestion		
subjects affected / exposed occurrences (all)	6 / 304 (1.97%) 6	7 / 301 (2.33%) 9	
Nasal discomfort	Additional description: Nasal discomfort		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Nasal polyps	Additional description: Nasal polyps		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Oropharyngeal blistering	Additional description: Oropharyngeal blistering		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed occurrences (all)	5 / 304 (1.64%) 6	9 / 301 (2.99%) 10	
Productive cough	Additional description: Productive cough		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 4	1 / 301 (0.33%) 1	
Rhinitis allergic	Additional description: Rhinitis allergic		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	1 / 301 (0.33%) 1	
Rhinorrhoea	Additional description: Rhinorrhoea		

subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	4 / 301 (1.33%) 5	
Sinus congestion	Additional description: Sinus congestion		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Sneezing	Additional description: Sneezing		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Snoring	Additional description: Snoring		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Throat irritation	Additional description: Throat irritation		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Wheezing	Additional description: Wheezing		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	3 / 301 (1.00%) 3	
Psychiatric disorders			
Abnormal dreams	Additional description: Abnormal dreams		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Agitation	Additional description: Agitation		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Anxiety	Additional description: Anxiety		
subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 6	6 / 301 (1.99%) 6	
Bradypnea	Additional description: Bradypnea		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 2	
Deja vu	Additional description: Deja vu		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Depressed mood	Additional description: Depressed mood		
subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 4	3 / 301 (1.00%) 3	

Depression	Additional description: Depression	
subjects affected / exposed	2 / 304 (0.66%)	3 / 301 (1.00%)
occurrences (all)	2	3
Disorientation	Additional description: Disorientation	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Dissociation	Additional description: Dissociation	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Emotional distress	Additional description: Emotional distress	
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)
occurrences (all)	1	0
Euphoric mood	Additional description: Euphoric mood	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Insomnia	Additional description: Insomnia	
subjects affected / exposed	6 / 304 (1.97%)	2 / 301 (0.66%)
occurrences (all)	7	2
Libido decreased	Additional description: Libido decreased	
subjects affected / exposed	4 / 304 (1.32%)	0 / 301 (0.00%)
occurrences (all)	5	0
Loss of libido	Additional description: Loss of libido	
subjects affected / exposed	0 / 304 (0.00%)	2 / 301 (0.66%)
occurrences (all)	0	2
Mood altered	Additional description: Mood altered	
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)
occurrences (all)	1	0
Mood swings	Additional description: Mood swings	
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)
occurrences (all)	1	0
Nervousness	Additional description: Nervousness	
subjects affected / exposed	2 / 304 (0.66%)	0 / 301 (0.00%)
occurrences (all)	2	0
Panic attack	Additional description: Panic attack	
subjects affected / exposed	2 / 304 (0.66%)	2 / 301 (0.66%)
occurrences (all)	2	2

Sleep disorder subjects affected / exposed occurrences (all)	Additional description: Sleep disorder	
	5 / 304 (1.64%) 5	4 / 301 (1.33%) 5
Stress subjects affected / exposed occurrences (all)	Additional description: Stress	
	3 / 304 (0.99%) 3	2 / 301 (0.66%) 2
Terminal insomnia subjects affected / exposed occurrences (all)	Additional description: Terminal insomnia	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Investigations		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	Additional description: Alanine aminotransferase increased	
	1 / 304 (0.33%) 1	2 / 301 (0.66%) 2
Arthroscopy subjects affected / exposed occurrences (all)	Additional description: Arthroscopy	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	Additional description: Aspartate aminotransferase increased	
	1 / 304 (0.33%) 1	2 / 301 (0.66%) 3
Aspiration joint subjects affected / exposed occurrences (all)	Additional description: Aspiration joint	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Biopsy prostate subjects affected / exposed occurrences (all)	Additional description: Biopsy prostate	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Biopsy skin subjects affected / exposed occurrences (all)	Additional description: Biopsy skin	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Blood albumin abnormal subjects affected / exposed occurrences (all)	Additional description: Blood albumin abnormal	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Blood albumin increased subjects affected / exposed occurrences (all)	Additional description: Blood albumin increased	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Blood bicarbonate increased	Additional description: Blood bicarbonate increased	

subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Blood calcium increased	Additional description: Blood calcium increased		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 2	
Blood glucose abnormal	Additional description: Blood glucose abnormal		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 2	2 / 301 (0.66%) 3	
Blood glucose increased	Additional description: Blood glucose increased		
subjects affected / exposed occurrences (all)	5 / 304 (1.64%) 7	4 / 301 (1.33%) 6	
Blood parathyroid hormone increased	Additional description: Blood parathyroid hormone increased		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Blood potassium abnormal	Additional description: Blood potassium abnormal		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	3 / 301 (1.00%) 3	
Blood potassium decreased	Additional description: Blood potassium decreased		
subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 5	5 / 301 (1.66%) 6	
Blood pressure decreased	Additional description: Blood pressure decreased		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Blood pressure increased	Additional description: Blood pressure increased		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Blood sodium abnormal	Additional description: Blood sodium abnormal		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 3	0 / 301 (0.00%) 0	
Blood sodium decreased	Additional description: Blood sodium decreased		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	

Blood test abnormal subjects affected / exposed occurrences (all)	Additional description: Blood test abnormal	
	2 / 304 (0.66%) 3	6 / 301 (1.99%) 7
Blood triglycerides increased subjects affected / exposed occurrences (all)	Additional description: Blood triglycerides increased	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Blood urea abnormal subjects affected / exposed occurrences (all)	Additional description: Blood urea abnormal	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Blood urea increased subjects affected / exposed occurrences (all)	Additional description: Blood urea increased	
	7 / 304 (2.30%) 15	4 / 301 (1.33%) 6
Blood uric acid increased subjects affected / exposed occurrences (all)	Additional description: Blood uric acid increased	
	4 / 304 (1.32%) 7	3 / 301 (1.00%) 4
Body temperature increased subjects affected / exposed occurrences (all)	Additional description: Body temperature increased	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Colonoscopy subjects affected / exposed occurrences (all)	Additional description: Colonoscopy	
	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0
Computerised tomogram subjects affected / exposed occurrences (all)	Additional description: Computerised tomogram	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Cystoscopy subjects affected / exposed occurrences (all)	Additional description: Cystoscopy	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Exercise test subjects affected / exposed occurrences (all)	Additional description: Exercise test	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Free prostate-specific antigen increased subjects affected / exposed occurrences (all)	Additional description: Free prostate-specific antigen increased	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Glomerular filtration rate decreased	Additional description: Glomerular filtration rate decreased	

subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	
Glycosylated haemoglobin increased	Additional description: Glycosylated haemoglobin increased		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Haematocrit decreased	Additional description: Haematocrit decreased		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 2	0 / 301 (0.00%) 0	
Haemoglobin decreased	Additional description: Haemoglobin decreased		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Heart rate increased	Additional description: Heart rate increased		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Heart rate irregular	Additional description: Heart rate irregular		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Intraocular pressure increased	Additional description: Intraocular pressure increased		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Liver function test abnormal	Additional description: Liver function test abnormal		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Lymphocyte count abnormal	Additional description: Lymphocyte count abnormal		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Mean cell haemoglobin concentration abnormal	Additional description: Mean cell haemoglobin concentration abnormal		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Mean cell haemoglobin increased	Additional description: Mean cell haemoglobin increased		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 4	3 / 301 (1.00%) 3	
Mean cell volume increased	Additional description: Mean cell volume increased		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	

Myelocyte present subjects affected / exposed occurrences (all)	Additional description: Myelocyte present	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Pulse pressure increased subjects affected / exposed occurrences (all)	Additional description: Pulse pressure increased	
	1 / 304 (0.33%) 2	0 / 301 (0.00%) 0
Red blood cell count decreased subjects affected / exposed occurrences (all)	Additional description: Red blood cell count decreased	
	1 / 304 (0.33%) 2	0 / 301 (0.00%) 0
Red cell distribution width increased subjects affected / exposed occurrences (all)	Additional description: Red cell distribution width increased	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Sigmoidoscopy subjects affected / exposed occurrences (all)	Additional description: Sigmoidoscopy	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Urine colour abnormal subjects affected / exposed occurrences (all)	Additional description: Urine colour abnormal	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Urine potassium increased subjects affected / exposed occurrences (all)	Additional description: Urine potassium increased	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Urine sodium increased subjects affected / exposed occurrences (all)	Additional description: Urine sodium increased	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Weight increased subjects affected / exposed occurrences (all)	Additional description: Weight increased	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
White blood cell count increased subjects affected / exposed occurrences (all)	Additional description: White blood cell count increased	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all)	Additional description: Arthropod bite	
	1 / 304 (0.33%) 1	4 / 301 (1.33%) 5
Arthropod sting	Additional description: Arthropod sting	

subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	1 / 301 (0.33%) 1	
Back injury	Additional description: Back injury		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Cartilage injury	Additional description: Cartilage injury		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Contusion	Additional description: Contusion		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	1 / 301 (0.33%) 1	
Ear injury	Additional description: Ear injury		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Epicondylitis	Additional description: Epicondylitis		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	
Excoriation	Additional description: Excoriation		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Eye injury	Additional description: Eye injury		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	
Fall	Additional description: Fall		
subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 6	5 / 301 (1.66%) 6	
Fibula fracture	Additional description: Fibula fracture		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Head injury	Additional description: Head injury		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Joint dislocation	Additional description: Joint dislocation		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Joint injury	Additional description: Joint injury		

subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	
Joint sprain	Additional description: Joint sprain		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	
Ligament injury	Additional description: Ligament injury		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Limb injury	Additional description: Limb injury		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	4 / 301 (1.33%) 4	
Medication error	Additional description: Medication error		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 3	0 / 301 (0.00%) 0	
Muscle injury	Additional description: Muscle injury		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Muscle rupture	Additional description: Muscle rupture		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Muscle strain	Additional description: Muscle strain		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	4 / 301 (1.33%) 4	
Neck injury	Additional description: Neck injury		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Pelvic fracture	Additional description: Pelvic fracture		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Procedural pain	Additional description: Procedural pain		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Rib fracture	Additional description: Rib fracture		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Skin laceration	Additional description: Skin laceration		

subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Soft tissue injury	Additional description: Soft tissue injury		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Spinal column injury	Additional description: Spinal column injury		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Tendon injury	Additional description: Tendon injury		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Tendon rupture	Additional description: Tendon rupture		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Thermal burn	Additional description: Thermal burn		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Tooth fracture	Additional description: Tooth fracture		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	
Upper limb fracture	Additional description: Upper limb fracture		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Wound complication	Additional description: Wound complication		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Wrist fracture	Additional description: Wrist fracture		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	3 / 301 (1.00%) 3	
Cardiac disorders			
Aortic valve incompetence	Additional description: Aortic valve incompetence		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Arrhythmia	Additional description: Arrhythmia		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	

Atrial fibrillation subjects affected / exposed occurrences (all)	Additional description: Atrial fibrillation	
	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2
Bradycardia subjects affected / exposed occurrences (all)	Additional description: Bradycardia	
	2 / 304 (0.66%) 2	3 / 301 (1.00%) 3
Cardiac flutter subjects affected / exposed occurrences (all)	Additional description: Cardiac flutter	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Extrasystoles subjects affected / exposed occurrences (all)	Additional description: Extrasystoles	
	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2
Myocardial ischaemia subjects affected / exposed occurrences (all)	Additional description: Myocardial ischaemia	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Palpitations subjects affected / exposed occurrences (all)	Additional description: Palpitations	
	13 / 304 (4.28%) 15	13 / 301 (4.32%) 15
Tachycardia subjects affected / exposed occurrences (all)	Additional description: Tachycardia	
	1 / 304 (0.33%) 1	3 / 301 (1.00%) 14
Nervous system disorders		
Altered state of consciousness subjects affected / exposed occurrences (all)	Additional description: Altered state of consciousness	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Amnesia subjects affected / exposed occurrences (all)	Additional description: Amnesia	
	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1
Aphasia subjects affected / exposed occurrences (all)	Additional description: Aphasia	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Aphonia subjects affected / exposed occurrences (all)	Additional description: Aphonia	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Aura	Additional description: Aura	

subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Balance disorder	Additional description: Balance disorder		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	1 / 301 (0.33%) 1	
Burning sensation	Additional description: Burning sensation		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Cerebral haemorrhage	Additional description: Cerebral haemorrhage		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Clumsiness	Additional description: Clumsiness		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Coordination abnormal	Additional description: Coordination abnormal		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Crying	Additional description: Crying		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Disturbance in attention	Additional description: Disturbance in attention		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	2 / 301 (0.66%) 2	
Dizziness	Additional description: Dizziness		
subjects affected / exposed occurrences (all)	73 / 304 (24.01%) 98	62 / 301 (20.60%) 80	
Dizziness exertional	Additional description: Dizziness exertional		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	3 / 301 (1.00%) 3	
Dizziness postural	Additional description: Dizziness postural		
subjects affected / exposed occurrences (all)	16 / 304 (5.26%) 18	12 / 301 (3.99%) 18	
Drug withdrawal headache	Additional description: Drug withdrawal headache		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Dysaesthesia	Additional description: Dysaesthesia		

subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	2 / 301 (0.66%) 2	
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Head discomfort	Additional description: Head discomfort		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Headache	Additional description: Headache		
subjects affected / exposed occurrences (all)	51 / 304 (16.78%) 72	59 / 301 (19.60%) 88	
Hypoaesthesia	Additional description: Hypoaesthesia		
subjects affected / exposed occurrences (all)	6 / 304 (1.97%) 6	5 / 301 (1.66%) 10	
Lethargy	Additional description: Lethargy		
subjects affected / exposed occurrences (all)	20 / 304 (6.58%) 20	22 / 301 (7.31%) 24	
Memory impairment	Additional description: Memory impairment		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Migraine	Additional description: Migraine		
subjects affected / exposed occurrences (all)	6 / 304 (1.97%) 6	7 / 301 (2.33%) 8	
Migraine with aura	Additional description: Migraine with aura		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	2 / 301 (0.66%) 2	
Nerve compression	Additional description: Nerve compression		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	2 / 301 (0.66%) 2	
Neuralgia	Additional description: Neuralgia		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed occurrences (all)	17 / 304 (5.59%) 19	12 / 301 (3.99%) 13	
Poor quality sleep	Additional description: Poor quality sleep		

subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 3	
Presyncope	Additional description: Presyncope		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 3	1 / 301 (0.33%) 1	
Restless legs syndrome	Additional description: Restless legs syndrome		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Sciatica	Additional description: Sciatica		
subjects affected / exposed occurrences (all)	6 / 304 (1.97%) 6	5 / 301 (1.66%) 5	
Sensory disturbance	Additional description: Sensory disturbance		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	3 / 301 (1.00%) 3	
Somnolence	Additional description: Somnolence		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Speech disorder	Additional description: Speech disorder		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Syncope	Additional description: Syncope		
subjects affected / exposed occurrences (all)	5 / 304 (1.64%) 5	4 / 301 (1.33%) 4	
Tension headache	Additional description: Tension headache		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Tremor	Additional description: Tremor		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
VIIth nerve paralysis	Additional description: VIIth nerve paralysis		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Blood and lymphatic system disorders	Additional description: Anaemia		
Anaemia	Additional description: Anaemia		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	

Ear and labyrinth disorders			
Deafness unilateral	Additional description: Deafness unilateral		
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Ear congestion	Additional description: Ear congestion		
subjects affected / exposed	0 / 304 (0.00%)	2 / 301 (0.66%)	
occurrences (all)	0	2	
Ear discomfort	Additional description: Ear discomfort		
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Ear disorder	Additional description: Ear disorder		
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Eustachian tube dysfunction	Additional description: Eustachian tube dysfunction		
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	2 / 304 (0.66%)	4 / 301 (1.33%)	
occurrences (all)	2	5	
Tympanic membrane perforation	Additional description: Tympanic membrane perforation		
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Vertigo	Additional description: Vertigo		
subjects affected / exposed	7 / 304 (2.30%)	1 / 301 (0.33%)	
occurrences (all)	7	6	
Vertigo positional	Additional description: Vertigo positional		
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Blepharitis	Additional description: Blepharitis		
subjects affected / exposed	3 / 304 (0.99%)	0 / 301 (0.00%)	
occurrences (all)	4	0	
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Conjunctival haemorrhage	Additional description: Conjunctival haemorrhage		

subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	3 / 301 (1.00%) 3	
Conjunctivitis allergic	Additional description: Conjunctivitis allergic		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Dry eye	Additional description: Dry eye		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	2 / 301 (0.66%) 2	
Episcleritis	Additional description: Episcleritis		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	3 / 301 (1.00%) 3	
Eye disorder	Additional description: Eye disorder		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Eye irritation	Additional description: Eye irritation		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Eye pain	Additional description: Eye pain		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Eye pruritus	Additional description: Eye pruritus		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Eye swelling	Additional description: Eye swelling		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Eyelid margin crusting	Additional description: Eyelid margin crusting		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Iritis	Additional description: Iritis		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Macular degeneration	Additional description: Macular degeneration		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Ocular hyperaemia	Additional description: Ocular hyperaemia		

subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Retinal tear	Additional description: Retinal tear		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Scleritis	Additional description: Scleritis		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Vision blurred	Additional description: Vision blurred		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	2 / 301 (0.66%) 2	
Visual impairment	Additional description: Visual impairment		
subjects affected / exposed occurrences (all)	5 / 304 (1.64%) 5	3 / 301 (1.00%) 3	
Vitreous floaters	Additional description: Vitreous floaters		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Gastrointestinal disorders			
Abdominal discomfort	Additional description: Abdominal discomfort		
subjects affected / exposed occurrences (all)	10 / 304 (3.29%) 12	9 / 301 (2.99%) 9	
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed occurrences (all)	6 / 304 (1.97%) 6	5 / 301 (1.66%) 5	
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 4	7 / 301 (2.33%) 9	
Abdominal pain lower	Additional description: Abdominal pain lower		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	4 / 301 (1.33%) 4	
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 4	3 / 301 (1.00%) 3	
Anal fissure	Additional description: Anal fissure		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	

Change of bowel habit subjects affected / exposed occurrences (all)	Additional description: Change of bowel habit	
	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	Additional description: Constipation	
	10 / 304 (3.29%) 10	3 / 301 (1.00%) 3
Dental discomfort subjects affected / exposed occurrences (all)	Additional description: Dental discomfort	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Diarrhoea subjects affected / exposed occurrences (all)	Additional description: Diarrhoea	
	20 / 304 (6.58%) 21	13 / 301 (4.32%) 13
Diverticulum subjects affected / exposed occurrences (all)	Additional description: Diverticulum	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Dry mouth subjects affected / exposed occurrences (all)	Additional description: Dry mouth	
	4 / 304 (1.32%) 4	5 / 301 (1.66%) 5
Dyspepsia subjects affected / exposed occurrences (all)	Additional description: Dyspepsia	
	16 / 304 (5.26%) 18	3 / 301 (1.00%) 3
Dysphagia subjects affected / exposed occurrences (all)	Additional description: Dysphagia	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Faeces discoloured subjects affected / exposed occurrences (all)	Additional description: Faeces discoloured	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Flatulence subjects affected / exposed occurrences (all)	Additional description: Flatulence	
	3 / 304 (0.99%) 3	0 / 301 (0.00%) 0
Food poisoning subjects affected / exposed occurrences (all)	Additional description: Food poisoning	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Frequent bowel movements subjects affected / exposed occurrences (all)	Additional description: Frequent bowel movements	
	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0

Gastrointestinal haemorrhage subjects affected / exposed occurrences (all)	Additional description: Gastrointestinal haemorrhage	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Gastrointestinal motility disorder subjects affected / exposed occurrences (all)	Additional description: Gastrointestinal motility disorder	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	Additional description: Gastrooesophageal reflux disease	
	1 / 304 (0.33%) 1	3 / 301 (1.00%) 3
Gingival pain subjects affected / exposed occurrences (all)	Additional description: Gingival pain	
	0 / 304 (0.00%) 0	3 / 301 (1.00%) 3
Gingival recession subjects affected / exposed occurrences (all)	Additional description: Gingival recession	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Haematochezia subjects affected / exposed occurrences (all)	Additional description: Haematochezia	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Haemorrhoids subjects affected / exposed occurrences (all)	Additional description: Haemorrhoids	
	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0
Hiatus hernia subjects affected / exposed occurrences (all)	Additional description: Hiatus hernia	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Irritable bowel syndrome subjects affected / exposed occurrences (all)	Additional description: Irritable bowel syndrome	
	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1
Lip dry subjects affected / exposed occurrences (all)	Additional description: Lip dry	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Lip swelling subjects affected / exposed occurrences (all)	Additional description: Lip swelling	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	Additional description: Nausea	
	20 / 304 (6.58%) 26	14 / 301 (4.65%) 16

Oral pain	Additional description: Oral pain	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Proctalgia	Additional description: Proctalgia	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Rectal haemorrhage	Additional description: Rectal haemorrhage	
subjects affected / exposed	6 / 304 (1.97%)	3 / 301 (1.00%)
occurrences (all)	7	3
Tongue coated	Additional description: Tongue coated	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Tongue geographic	Additional description: Tongue geographic	
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)
occurrences (all)	1	0
Tongue ulceration	Additional description: Tongue ulceration	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Tooth loss	Additional description: Tooth loss	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Toothache	Additional description: Toothache	
subjects affected / exposed	2 / 304 (0.66%)	2 / 301 (0.66%)
occurrences (all)	2	2
Vomiting	Additional description: Vomiting	
subjects affected / exposed	14 / 304 (4.61%)	9 / 301 (2.99%)
occurrences (all)	14	10
Hepatobiliary disorders		
Biliary dilatation	Additional description: Biliary dilatation	
subjects affected / exposed	1 / 304 (0.33%)	0 / 301 (0.00%)
occurrences (all)	1	0
Cholelithiasis	Additional description: Cholelithiasis	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Hepatic steatosis	Additional description: Hepatic steatosis	

subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	2 / 301 (0.66%) 2	
Skin and subcutaneous tissue disorders			
Actinic keratosis	Additional description: Actinic keratosis		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 2	0 / 301 (0.00%) 0	
Alopecia	Additional description: Alopecia		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	3 / 301 (1.00%) 3	
Blood blister	Additional description: Blood blister		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	
Dandruff	Additional description: Dandruff		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Dermal cyst	Additional description: Dermal cyst		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Dermatitis	Additional description: Dermatitis		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Dry skin	Additional description: Dry skin		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	2 / 301 (0.66%) 2	
Eczema	Additional description: Eczema		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Hair texture abnormal	Additional description: Hair texture abnormal		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Heat rash	Additional description: Heat rash		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 5	7 / 301 (2.33%) 7	

Increased tendency to bruise subjects affected / exposed occurrences (all)	Additional description: Increased tendency to bruise	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Intertrigo subjects affected / exposed occurrences (all)	Additional description: Intertrigo	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Night sweats subjects affected / exposed occurrences (all)	Additional description: Night sweats	
	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2
Pain of skin subjects affected / exposed occurrences (all)	Additional description: Pain of skin	
	1 / 304 (0.33%) 2	0 / 301 (0.00%) 0
Papule subjects affected / exposed occurrences (all)	Additional description: Papule	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Pemphigus subjects affected / exposed occurrences (all)	Additional description: Pemphigus	
	1 / 304 (0.33%) 2	0 / 301 (0.00%) 0
Petechiae subjects affected / exposed occurrences (all)	Additional description: Petechiae	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Pruritus subjects affected / exposed occurrences (all)	Additional description: Pruritus	
	6 / 304 (1.97%) 6	11 / 301 (3.65%) 11
Pruritus generalised subjects affected / exposed occurrences (all)	Additional description: Pruritus generalised	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Psoriasis subjects affected / exposed occurrences (all)	Additional description: Psoriasis	
	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	Additional description: Rash	
	12 / 304 (3.95%) 12	16 / 301 (5.32%) 22
Rash erythematous subjects affected / exposed occurrences (all)	Additional description: Rash erythematous	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0

Rash generalised subjects affected / exposed occurrences (all)	Additional description: Rash generalised	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Rash macular subjects affected / exposed occurrences (all)	Additional description: Rash macular	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Rash papular subjects affected / exposed occurrences (all)	Additional description: Rash papular	
	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0
Rash pruritic subjects affected / exposed occurrences (all)	Additional description: Rash pruritic	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Rosacea subjects affected / exposed occurrences (all)	Additional description: Rosacea	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Skin burning sensation subjects affected / exposed occurrences (all)	Additional description: Skin burning sensation	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Skin discolouration subjects affected / exposed occurrences (all)	Additional description: Skin discolouration	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 5
Skin disorder subjects affected / exposed occurrences (all)	Additional description: Skin disorder	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Skin irritation subjects affected / exposed occurrences (all)	Additional description: Skin irritation	
	1 / 304 (0.33%) 1	1 / 301 (0.33%) 2
Skin lesion subjects affected / exposed occurrences (all)	Additional description: Skin lesion	
	1 / 304 (0.33%) 1	2 / 301 (0.66%) 2
Skin plaque subjects affected / exposed occurrences (all)	Additional description: Skin plaque	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Skin sensitisation subjects affected / exposed occurrences (all)	Additional description: Skin sensitisation	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1

Stasis dermatitis subjects affected / exposed occurrences (all)	Additional description: Stasis dermatitis	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Swelling face subjects affected / exposed occurrences (all)	Additional description: Swelling face	
	2 / 304 (0.66%) 2	1 / 301 (0.33%) 1
Urticaria subjects affected / exposed occurrences (all)	Additional description: Urticaria	
	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2
Renal and urinary disorders		
Bladder discomfort subjects affected / exposed occurrences (all)	Additional description: Bladder discomfort	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Dysuria subjects affected / exposed occurrences (all)	Additional description: Dysuria	
	1 / 304 (0.33%) 1	3 / 301 (1.00%) 4
Glycosuria subjects affected / exposed occurrences (all)	Additional description: Glycosuria	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Haematuria subjects affected / exposed occurrences (all)	Additional description: Haematuria	
	1 / 304 (0.33%) 1	2 / 301 (0.66%) 2
Micturition urgency subjects affected / exposed occurrences (all)	Additional description: Micturition urgency	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Nephrolithiasis subjects affected / exposed occurrences (all)	Additional description: Nephrolithiasis	
	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1
Nocturia subjects affected / exposed occurrences (all)	Additional description: Nocturia	
	6 / 304 (1.97%) 6	1 / 301 (0.33%) 1
Oliguria subjects affected / exposed occurrences (all)	Additional description: Oliguria	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Pollakiuria	Additional description: Pollakiuria	

subjects affected / exposed occurrences (all)	10 / 304 (3.29%) 11	12 / 301 (3.99%) 12	
Polyuria	Additional description: Polyuria		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	2 / 301 (0.66%) 2	
Proteinuria	Additional description: Proteinuria		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Urge incontinence	Additional description: Urge incontinence		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Urinary hesitation	Additional description: Urinary hesitation		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Urinary tract disorder	Additional description: Urinary tract disorder		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Urine abnormality	Additional description: Urine abnormality		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Urine flow decreased	Additional description: Urine flow decreased		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Urine odour abnormal	Additional description: Urine odour abnormal		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Endocrine disorders			
Hypothyroidism	Additional description: Hypothyroidism		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Musculoskeletal and connective tissue disorders			
Ankylosing spondylitis	Additional description: Ankylosing spondylitis		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Arthralgia	Additional description: Arthralgia		

subjects affected / exposed occurrences (all)	17 / 304 (5.59%) 17	19 / 301 (6.31%) 27	
Arthritis	Additional description: Arthritis		
subjects affected / exposed occurrences (all)	4 / 304 (1.32%) 4	0 / 301 (0.00%) 0	
Arthropathy	Additional description: Arthropathy		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Back disorder	Additional description: Back disorder		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Back pain	Additional description: Back pain		
subjects affected / exposed occurrences (all)	14 / 304 (4.61%) 15	21 / 301 (6.98%) 23	
Bunion	Additional description: Bunion		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Costochondritis	Additional description: Costochondritis		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Dupuytren's contracture	Additional description: Dupuytren's contracture		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Fibromyalgia	Additional description: Fibromyalgia		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 2	
Flank pain	Additional description: Flank pain		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 2	2 / 301 (0.66%) 3	
Groin pain	Additional description: Groin pain		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	
Joint crepitation	Additional description: Joint crepitation		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Joint stiffness	Additional description: Joint stiffness		

subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Joint swelling	Additional description: Joint swelling		
subjects affected / exposed occurrences (all)	14 / 304 (4.61%) 15	11 / 301 (3.65%) 16	
Limb discomfort	Additional description: Limb discomfort		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Lumbar spinal stenosis	Additional description: Lumbar spinal stenosis		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Muscle fatigue	Additional description: Muscle fatigue		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed occurrences (all)	15 / 304 (4.93%) 18	11 / 301 (3.65%) 15	
Muscle tightness	Additional description: Muscle tightness		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Muscular weakness	Additional description: Muscular weakness		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	4 / 301 (1.33%) 4	
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	14 / 301 (4.65%) 17	
Musculoskeletal stiffness	Additional description: Musculoskeletal stiffness		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	1 / 301 (0.33%) 1	
Myalgia	Additional description: Myalgia		
subjects affected / exposed occurrences (all)	3 / 304 (0.99%) 3	5 / 301 (1.66%) 5	
Neck pain	Additional description: Neck pain		

subjects affected / exposed occurrences (all)	6 / 304 (1.97%) 6	6 / 301 (1.99%) 6	
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Osteoporosis	Additional description: Osteoporosis		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed occurrences (all)	21 / 304 (6.91%) 25	14 / 301 (4.65%) 16	
Pain in jaw	Additional description: Pain in jaw		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Periarthritis	Additional description: Periarthritis		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Pubic pain	Additional description: Pubic pain		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Rotator cuff syndrome	Additional description: Rotator cuff syndrome		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Sensation of heaviness	Additional description: Sensation of heaviness		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	3 / 301 (1.00%) 3	
Spinal osteoarthritis	Additional description: Spinal osteoarthritis		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Synovial cyst	Additional description: Synovial cyst		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Tendonitis	Additional description: Tendonitis		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Trigger finger	Additional description: Trigger finger		

subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Infections and infestations			
Additional description: Acute sinusitis			
Acute sinusitis subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Additional description: Alveolar osteitis			
Alveolar osteitis subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Additional description: Bacterial infection			
Bacterial infection subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Additional description: Bronchitis			
Bronchitis subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Additional description: Candidiasis			
Candidiasis subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Additional description: Cellulitis			
Cellulitis subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Additional description: Cystitis			
Cystitis subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2	
Additional description: Dermatitis infected			
Dermatitis infected subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	
Additional description: Diverticulitis			
Diverticulitis subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Additional description: Ear infection			
Ear infection subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	3 / 301 (1.00%) 4	
Additional description: Eye infection			
Eye infection subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1	

Fungal infection	Additional description: Fungal infection	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Furuncle	Additional description: Furuncle	
subjects affected / exposed	1 / 304 (0.33%)	1 / 301 (0.33%)
occurrences (all)	1	1
Gastroenteritis	Additional description: Gastroenteritis	
subjects affected / exposed	0 / 304 (0.00%)	2 / 301 (0.66%)
occurrences (all)	0	2
Gastroenteritis viral	Additional description: Gastroenteritis viral	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	2
Gastrointestinal viral infection	Additional description: Gastrointestinal viral infection	
subjects affected / exposed	2 / 304 (0.66%)	1 / 301 (0.33%)
occurrences (all)	2	1
Gingival abscess	Additional description: Gingival abscess	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Gingival infection	Additional description: Gingival infection	
subjects affected / exposed	1 / 304 (0.33%)	1 / 301 (0.33%)
occurrences (all)	1	1
Herpes zoster	Additional description: Herpes zoster	
subjects affected / exposed	1 / 304 (0.33%)	2 / 301 (0.66%)
occurrences (all)	1	4
Infected bites	Additional description: Infected bites	
subjects affected / exposed	0 / 304 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	1
Influenza	Additional description: Influenza	
subjects affected / exposed	10 / 304 (3.29%)	9 / 301 (2.99%)
occurrences (all)	10	9
Labyrinthitis	Additional description: Labyrinthitis	
subjects affected / exposed	4 / 304 (1.32%)	1 / 301 (0.33%)
occurrences (all)	4	1
Laryngitis	Additional description: Laryngitis	
subjects affected / exposed	1 / 304 (0.33%)	4 / 301 (1.33%)
occurrences (all)	1	4

Localised infection subjects affected / exposed occurrences (all)	Additional description: Localised infection	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Lower respiratory tract infection subjects affected / exposed occurrences (all)	Additional description: Lower respiratory tract infection	
	9 / 304 (2.96%) 10	11 / 301 (3.65%) 12
Lyme disease subjects affected / exposed occurrences (all)	Additional description: Lyme disease	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Mastoiditis subjects affected / exposed occurrences (all)	Additional description: Mastoiditis	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Myringitis subjects affected / exposed occurrences (all)	Additional description: Myringitis	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Nail infection subjects affected / exposed occurrences (all)	Additional description: Nail infection	
	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	Additional description: Nasopharyngitis	
	48 / 304 (15.79%) 61	39 / 301 (12.96%) 51
Oral candidiasis subjects affected / exposed occurrences (all)	Additional description: Oral candidiasis	
	2 / 304 (0.66%) 2	1 / 301 (0.33%) 1
Oral infection subjects affected / exposed occurrences (all)	Additional description: Oral infection	
	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1
Otitis externa subjects affected / exposed occurrences (all)	Additional description: Otitis externa	
	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2
Otitis media subjects affected / exposed occurrences (all)	Additional description: Otitis media	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Pharyngitis subjects affected / exposed occurrences (all)	Additional description: Pharyngitis	
	4 / 304 (1.32%) 4	4 / 301 (1.33%) 5

Pilonidal cyst subjects affected / exposed occurrences (all)	Additional description: Pilonidal cyst	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Prostate infection subjects affected / exposed occurrences (all)	Additional description: Prostate infection	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Respiratory tract infection subjects affected / exposed occurrences (all)	Additional description: Respiratory tract infection	
	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1
Rhinitis subjects affected / exposed occurrences (all)	Additional description: Rhinitis	
	8 / 304 (2.63%) 8	8 / 301 (2.66%) 10
Sialoadenitis subjects affected / exposed occurrences (all)	Additional description: Sialoadenitis	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Sinusitis subjects affected / exposed occurrences (all)	Additional description: Sinusitis	
	3 / 304 (0.99%) 3	5 / 301 (1.66%) 5
Skin infection subjects affected / exposed occurrences (all)	Additional description: Skin infection	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Subcutaneous abscess subjects affected / exposed occurrences (all)	Additional description: Subcutaneous abscess	
	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0
Tinea pedis subjects affected / exposed occurrences (all)	Additional description: Tinea pedis	
	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0
Tooth abscess subjects affected / exposed occurrences (all)	Additional description: Tooth abscess	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Tooth infection subjects affected / exposed occurrences (all)	Additional description: Tooth infection	
	3 / 304 (0.99%) 4	3 / 301 (1.00%) 3
Upper respiratory tract infection subjects affected / exposed occurrences (all)	Additional description: Upper respiratory tract infection	
	13 / 304 (4.28%) 17	13 / 301 (4.32%) 21

Urinary tract infection subjects affected / exposed occurrences (all)	Additional description: Urinary tract infection	
	8 / 304 (2.63%) 13	7 / 301 (2.33%) 8
Viral infection subjects affected / exposed occurrences (all)	Additional description: Viral infection	
	11 / 304 (3.62%) 12	4 / 301 (1.33%) 4
Viral pharyngitis subjects affected / exposed occurrences (all)	Additional description: Viral pharyngitis	
	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	Additional description: Viral upper respiratory tract infection	
	0 / 304 (0.00%) 0	2 / 301 (0.66%) 2
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	Additional description: Vulvovaginal candidiasis	
	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0
Metabolism and nutrition disorders		
Decreased appetite subjects affected / exposed occurrences (all)	Additional description: Decreased appetite	
	3 / 304 (0.99%) 3	2 / 301 (0.66%) 2
Dehydration subjects affected / exposed occurrences (all)	Additional description: Dehydration	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Diabetes mellitus inadequate control subjects affected / exposed occurrences (all)	Additional description: Diabetes mellitus inadequate control	
	1 / 304 (0.33%) 1	2 / 301 (0.66%) 2
Fluid retention subjects affected / exposed occurrences (all)	Additional description: Fluid retention	
	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0
Glucose tolerance impaired subjects affected / exposed occurrences (all)	Additional description: Glucose tolerance impaired	
	0 / 304 (0.00%) 0	1 / 301 (0.33%) 1
Gout subjects affected / exposed occurrences (all)	Additional description: Gout	
	3 / 304 (0.99%) 3	2 / 301 (0.66%) 3
Hypercalcaemia	Additional description: Hypercalcaemia	

subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Hypercholesterolaemia	Additional description: Hypercholesterolaemia		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Hyperglycaemia	Additional description: Hyperglycaemia		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Hypocalcaemia	Additional description: Hypocalcaemia		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	1 / 301 (0.33%) 1	
Hypokalaemic syndrome	Additional description: Hypokalaemic syndrome		
subjects affected / exposed occurrences (all)	0 / 304 (0.00%) 0	4 / 301 (1.33%) 4	
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	0 / 301 (0.00%) 0	
Hyponatraemic syndrome	Additional description: Hyponatraemic syndrome		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Metabolic syndrome	Additional description: Metabolic syndrome		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	0 / 301 (0.00%) 0	
Type 2 diabetes mellitus	Additional description: Type 2 diabetes mellitus		
subjects affected / exposed occurrences (all)	2 / 304 (0.66%) 2	1 / 301 (0.33%) 1	
Vitamin D deficiency	Additional description: Vitamin D deficiency		
subjects affected / exposed occurrences (all)	1 / 304 (0.33%) 1	2 / 301 (0.66%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2010	Protocol amended to include addition of cardiac MRI scans.
02 August 2010	Protocol amended to update exclusion criteria and add clarifications on concomitant medications, Doxazosin dosing and patient withdrawal criteria.
10 January 2011	Protocol amended to update recruitment limiting inclusion and exclusion criteria
30 November 2011	Protocol amended to permit use of open-label (non-blinded) IMP
26 April 2013	Protocol amended to allow the use of generics and remove recruitment-limiting exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported