



Clinical trial results: Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial Summary

EudraCT number	2007-001039-72
Trial protocol	GB
Global end of trial date	18 January 2017

Results information

Result version number	v1 (current)
This version publication date	11 June 2017
First version publication date	11 June 2017

Trial information

Trial identification

Sponsor protocol code	RP06
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Additional study identifiers

ISRCTN number	ISRCTN91419926
ClinicalTrials.gov id (NCT number)	NCT01581476
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust, jointly with University of Cambridge
Sponsor organisation address	Addenbrooke's Hospital, Hills Rd, Cambridge, United Kingdom, CB2 0QQ
Public contact	Professor David Dunger, University Department of Paediatrics Box 116, Addenbrooke's Hospital Hills Road, Cambridge, CB20QQ, +44 1223762944, dbd25@cam.ac.uk
Scientific contact	Professor David Dunger, University Department of Paediatrics Box 116, Addenbrooke's Hospital Hills Road, Cambridge, CB20QQ, +44 1223762944, dbd25@cam.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	18 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 January 2017
Global end of trial reached?	Yes
Global end of trial date	18 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether intervention with Angiotensin Converting Enzyme Inhibitors (ACEI), Statins, or a combination of both, when compared with placebo, will reduce urinary albumin excretion, decline in renal function and the risk for diabetic nephropathy (DN) and cardiovascular disease (CVD) in adolescents with Type 1 Diabetes (T1D).

Protection of trial subjects:

Informed consent/assent was obtained for all participants. Where participant were under 16, parental consent was obtained in addition to participants assent.

Safety bloods were taken to monitor participants for any side effects from the IMP. Adverse events were recorded at each visit during the trial.

At screening, all subjects were allocated a unique Study ID number based on the country of origin, specific site and sequence of recruitment, which was translated into a barcode used for all subsequent correspondence, transfer of samples and data input. Confidential data was retained at the study sites in a secure study file. At all times the confidentiality of the subjects was maintained, and reports to meetings and publications did not include confidential or data identifying individuals.

Background therapy:

N/A

Evidence for comparator:

The prognosis for young people diagnosed with T1D during childhood remains poor and this may relate to the higher HbA1c levels encountered during puberty. Microalbuminuria (MA) identifies subjects at risk for DN and CVD and it is often observed in adolescent subjects but it is rarely treated before the age of 18 years because at the end of puberty rates of albumin excretion decline and, in some subjects, it will return into the normal range. However, evidence indicates that subjects with "transient" and "persistent MA" have experienced renal and general endothelial damage during puberty and renoprotection to prevent long-term complications is warranted. In adults, use of ACEI and Statins is increasing and in order to determine whether these agents are of value in the adolescent population we need to carry out a pragmatic clinical trial. The major endpoint of such a study would be a change in albumin excretion but secondary endpoints should include markers of CVD, renal function, retinopathy, quality of life combined with detailed assessment of compliance and likely health economic benefits.

Actual start date of recruitment	22 April 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 118
Country: Number of subjects enrolled	Canada: 124
Country: Number of subjects enrolled	Australia: 201
Worldwide total number of subjects	443
EEA total number of subjects	118

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)	184
Adolescents (12-17 years)	259
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject was recruited 22/04/2009. Last subject recruited to the intervention study 17/08/2013. Recruitment was carried out in centres in Australia, Canada and the UK.

Pre-assignment

Screening details:

Participants were screened as part of the NFS study in the UK or in separate screening studies in Australia and Canada. 2 sets of 3 urines were collected and log ACR measures. An algorithm taking a number of factors into account was used to determine risk tertile. Those in high risk upper tertile were invited to join the intervention study

Period 1

Period 1 title	follow-up (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

The study is a 2 by 2 factorial design. Patient were randomised to one of four mutually exclusive groups:

Placebo/Statin, ACE/Statin, Placebo/Placebo, ACE/Placebo

Arms

Are arms mutually exclusive?	No
Arm title	ACE Inhibitor

Arm description:

ACE Inhibitor

Arm type	Experimental
Investigational medicinal product name	Quinapril
Investigational medicinal product code	PL 00057/0514,0515,0516,0517
Other name	Accupro
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

starting dose 5mg increased to 10mg daily after 2 weeks

Arm title	statin
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Arm description:

statin

Arm type	Experimental
Investigational medicinal product name	Atorvastatin
Investigational medicinal product code	PL 39933/0001
Other name	Lipitor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10mg once daily

Arm title	ACE inhibitor matched placebo
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Arm description:

dummy placebo tablets

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

Dosage and administration details:

placebo tablet

Arm title	Statin matched placebo
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Arm description:

dummy placebo tablet

Arm type	Active comparator
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

placebo tablet

Number of subjects in period 1	ACE Inhibitor	statin	ACE inhibitor matched placebo
Started	222	223	221
Completed	204	209	202
Not completed	18	14	19
No endpoint observed	18	14	19

Number of subjects in period 1	Statin matched placebo
Started	220
Completed	197
Not completed	23
No endpoint observed	23

Baseline characteristics

Reporting groups

Reporting group title	ACE Inhibitor
Reporting group description:	
ACE Inhibitor	
Reporting group title	statin
Reporting group description:	
statin	
Reporting group title	ACE inhibitor matched placebo
Reporting group description:	
dummy placebo tablets	
Reporting group title	Statin matched placebo
Reporting group description:	
dummy placebo tablet	

Reporting group values	ACE Inhibitor	statin	ACE inhibitor matched placebo
Number of subjects	222	223	221
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			
age			
Units: years			
arithmetic mean	12.4	12.4	12.4
standard deviation	± 1.4	± 1.4	± 1.4
Gender categorical			
Units: Subjects			
Female	98	101	103
Male	124	122	118

Reporting group values	Statin matched placebo	Total	
Number of subjects	220	443	
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			
age			
Units: years			
arithmetic mean	12.4		
standard deviation	± 1.4	-	
Gender categorical			
Units: Subjects			
Female	102	203	
Male	118	240	

End points

End points reporting groups

Reporting group title	ACE Inhibitor
Reporting group description: ACE Inhibitor	
Reporting group title	statin
Reporting group description: statin	
Reporting group title	ACE inhibitor matched placebo
Reporting group description: dummy placebo tablets	
Reporting group title	Statin matched placebo
Reporting group description: dummy placebo tablet	
Subject analysis set title	Final Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis (or intention-to-treat) population comprises all randomised participants, regardless of eligibility error, post-randomisation withdrawal, and whether the correct, or sufficient, of the two study treatments was received for the two to four years or less, with sufficient or insufficient compliance	

Primary: Annualised Area under Curve of log Albumin to Creatinine Ratio

End point title	Annualised Area under Curve of log Albumin to Creatinine Ratio
End point description: ACR was measured on 3 consecutive days at each 6-monthly visit from urine samples. For the primary outcome, these were aggregated into the mean of the three log10 transformed values. As no further urines were obtained at the time of randomization, the values at this time point were interpolated from those obtained at screening and the first post-randomization visit. The trapezium rule was used to calculate AUC of observations taken at screening through to the final visit, using calendar dates. The time on study was the difference between randomization and final visit dates (after 2-4 years) or withdrawal from study. The AUC was divided by the time on study to provide one, time-standardized value, per patient.	
End point type	Primary
End point timeframe: derived from repeated measurements taken up to 4 years or completion of study, whichever occurs earliest per patient.	

End point values	ACE Inhibitor	statin	ACE inhibitor matched placebo	Statin matched placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	204	209	202	197
Units: unitless				
arithmetic mean (standard deviation)	0.04 (± 0.22)	0.05 (± 0.23)	0.04 (± 0.23)	0.03 (± 0.23)

End point values	Final Analysis Set			
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Subject group type	Subject analysis set			
Number of subjects analysed	406			
Units: unitless				
arithmetic mean (standard deviation)	0.04 (\pm 0.23)			

Statistical analyses

Statistical analysis title	ACEI comparison
Statistical analysis description: ancova comparig the ACEI to placebo groups	
Comparison groups	ACE Inhibitor v ACE inhibitor matched placebo
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.02

Statistical analysis title	Statin comparison
Statistical analysis description: ancova comparig the Statin to placebo groups	
Comparison groups	statin v Statin matched placebo
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.02

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Adverse events were recorded from consent until final study visit was completed.

Adverse event reporting additional description:

AEs were recorded on a rolling log at each visit and reviewed locally and sent to co-ordinating centre.

SAEs were reported to coordinating centre within 24hr of knowledge.

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	ACEI/Placebo
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Reporting group description: -

Reporting group title	ACEI/Statin
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Reporting group description: -

Reporting group title	Placebo/Placebo
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Reporting group description: -

Reporting group title	Placebo/Statin
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Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Non-serious adverse events were not coded.

Serious adverse events	ACEI/Placebo	ACEI/Statin	Placebo/Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 111 (47.75%)	57 / 111 (51.35%)	46 / 109 (42.20%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abscess drainage			

subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystectomy			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenoidectomy			
subjects affected / exposed	0 / 111 (0.00%)	2 / 111 (1.80%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenotonsillectomy			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicectomy			
subjects affected / exposed	2 / 111 (1.80%)	1 / 111 (0.90%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone graft			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus management			
subjects affected / exposed	5 / 111 (4.50%)	4 / 111 (3.60%)	3 / 109 (2.75%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circumcision			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cochlea implant			

subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal sinus repair			
subjects affected / exposed	1 / 111 (0.90%)	2 / 111 (1.80%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Debridement			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Internal fixation of fracture			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laser therapy			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear tube insertion			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device change			
subjects affected / exposed	17 / 111 (15.32%)	13 / 111 (11.71%)	14 / 109 (12.84%)
occurrences causally related to treatment / all	0 / 17	0 / 14	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cyst removal			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee operation			

subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicocele repair			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth extraction			
subjects affected / exposed	4 / 111 (3.60%)	1 / 111 (0.90%)	3 / 109 (2.75%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw operation			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Manipulation			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract operation			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polypectomy			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue tie operation			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillectomy			

subjects affected / exposed	1 / 111 (0.90%)	4 / 111 (3.60%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Therapy change			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sebaceous cyst excision			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Swelling			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device failure			
subjects affected / exposed	3 / 111 (2.70%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Social circumstances			
Clinical trial participant			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol use			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal pain			

subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 111 (0.00%)	2 / 111 (1.80%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eating disorder			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic stress disorder			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnambulism			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Self-injurious ideation			

subjects affected / exposed	0 / 111 (0.00%)	2 / 111 (1.80%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Colonoscopy			
subjects affected / exposed	0 / 111 (0.00%)	2 / 111 (1.80%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 111 (0.90%)	3 / 111 (2.70%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood potassium abnormal			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endoscopy			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tympanometry			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endoscopy upper gastrointestinal tract			
subjects affected / exposed	1 / 111 (0.90%)	3 / 111 (2.70%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinoscopy			

subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthroscopy			
subjects affected / exposed	0 / 111 (0.00%)	2 / 111 (1.80%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biopsy			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	3 / 109 (2.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biopsy kidney			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose increased - Investigations			
subjects affected / exposed	1 / 111 (0.90%)	2 / 111 (1.80%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood sodium increased			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical observation			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	3 / 109 (2.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve conduction studies			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose fluctuation			

subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACTH stimulation test			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric evaluation			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigation			
subjects affected / exposed	3 / 111 (2.70%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental overdose			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nail avulsion			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			

subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropod sting			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	2 / 111 (1.80%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb traumatic amputation			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			

subjects affected / exposed	2 / 111 (1.80%)	1 / 111 (0.90%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column injury			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug dose omission			

subjects affected / exposed	5 / 111 (4.50%)	4 / 111 (3.60%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb crushing injury			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 111 (0.00%)	2 / 111 (1.80%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	1 / 111 (0.90%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dizziness			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic seizure			
subjects affected / exposed	2 / 111 (1.80%)	1 / 111 (0.90%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial mass			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 111 (1.80%)	2 / 111 (1.80%)	4 / 109 (3.67%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	1 / 111 (0.90%)	1 / 111 (0.90%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	5 / 111 (4.50%)	4 / 111 (3.60%)	4 / 109 (3.67%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammatory bowel disease			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Ingrowing nail			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention postoperative			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Skin infection			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess			
subjects affected / exposed	1 / 111 (0.90%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	2 / 111 (1.80%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epstein-Barr virus infection			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 111 (0.00%)	2 / 111 (1.80%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis viral			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			

subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	2 / 111 (1.80%)	1 / 111 (0.90%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 111 (1.80%)	3 / 111 (2.70%)	6 / 109 (5.50%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			

subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 111 (1.80%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	2 / 111 (1.80%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	17 / 111 (15.32%)	9 / 111 (8.11%)	8 / 109 (7.34%)
occurrences causally related to treatment / all	0 / 29	0 / 19	0 / 24
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose increased			
subjects affected / exposed	2 / 111 (1.80%)	2 / 111 (1.80%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 111 (0.90%)	1 / 111 (0.90%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudohyponatraemia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	2 / 111 (1.80%)	1 / 111 (0.90%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			

subjects affected / exposed	3 / 111 (2.70%)	2 / 111 (1.80%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo/Statin		
Total subjects affected by serious adverse events			
subjects affected / exposed	57 / 112 (50.89%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abscess drainage			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystectomy			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenoidectomy			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenotonsillectomy			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Appendicectomy				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bone graft				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus management				
subjects affected / exposed	4 / 112 (3.57%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Circumcision				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cochlea implant				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pilonidal sinus repair				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Debridement				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Internal fixation of fracture				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laser therapy				

subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear tube insertion				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Medical device change				
subjects affected / exposed	12 / 112 (10.71%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 0			
Cyst removal				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Knee operation				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Varicocele repair				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tooth extraction				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jaw operation				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Manipulation				

subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cataract operation			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polypectomy			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tongue tie operation			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillectomy			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Therapy change			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sebaceous cyst excision			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Swelling			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device failure			

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaphylactic reaction			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Clinical trial participant			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alcohol use			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			

subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oropharyngeal pain			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eating disorder			

subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Panic attack			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-traumatic stress disorder			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Somnambulism			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Self-injurious ideation			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Colonoscopy			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood potassium abnormal			

subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endoscopy				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tympanometry				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endoscopy upper gastrointestinal tract				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sinoscopy				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthroscopy				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Biopsy				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Biopsy kidney				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood glucose increased - Investigations				

subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood sodium increased			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Medical observation			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nerve conduction studies			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood glucose fluctuation			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
ACTH stimulation test			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric evaluation			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigation			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Joint dislocation			

subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Accidental overdose				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nail avulsion				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ankle fracture				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulna fracture				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthropod sting				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laceration				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				

subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Limb traumatic amputation				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intentional overdose				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ligament rupture				

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skull fracture			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal column injury			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug dose omission			
subjects affected / exposed	4 / 112 (3.57%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Meniscus injury			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Limb crushing injury			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Seizure				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemic seizure				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial mass				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lethargy				

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	8 / 112 (7.14%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Inflammatory bowel disease			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis acute			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Ingrowing nail			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention postoperative			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			

subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Skin infection			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abscess			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Epstein-Barr virus infection			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear infection			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			

subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Helicobacter infection				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis viral				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonsillar abscess				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis E				

subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection viral			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Periorbital cellulitis			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lactic acidosis			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	18 / 112 (16.07%)		
occurrences causally related to treatment / all	0 / 26		
deaths causally related to treatment / all	0 / 0		
Blood glucose increased			

subjects affected / exposed	4 / 112 (3.57%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudohyponatraemia			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	5 / 112 (4.46%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ACEI/Placebo	ACEI/Statin	Placebo/Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 109 (0.00%)

Non-serious adverse events	Placebo/Statin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 112 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2008	Protocol Version 2 Incorporation of recommendations from ethics committee, steering committee and DMEC (submitted to MREC & MHRA)
02 October 2008	Protocol version 3 Change to study drug Quinapril reference from study drug B to study drug Q throughout protocol. Change in PI for Western Australia from Associate Professor Timothy Jones to Dr. Liz Davis Change in evaluation criteria of Myopathy using CK and ALT levels – Section 8.6.7.2. (page 24). Change to inclusion age range from 11 - 15 years old to 11 - 16 years old throughout protocol. Age range to include 16 years olds screened as 15 year olds and consented late into the trial due to delay in opening the trial. Information Sheet for young people intervention group amended to reflect increase in inclusion age from 15 to 16 years old. Change to drug manufacture of Quinapril placebo to reflect the agreement that Catalent Pharma Solutions are now to produce the Quinapril placebo - Section 8.6.1(page 21) Addition to emergency unblinding requirements. Investigators to provide justification form to CTU - Section 8.6.4 (page 22). Change in terminology for CPK test (Creatine phosphokinase) to CK (Creatine Kinase) - throughout protocol and Section 18.10 (page 68). Change in dose management for Quinapril for cough and hypotension. More guidance on management and possible re-start of study drug - Section 8.6.7.1 (page 23). Change in dose adjustment guidance for Quinapril at two weeks visit (visit 3) – Section 8.7.2 (page 27). Addition of List of contraindicated drug products for Atorvastatin and Quinapril - Section 18.4 (page 62). (Submitted to MREC & MHRA)
12 June 2009	Protocol Version 4 Additional assessments of cardiovascular function and retinal photography: Protocol revised to include these additional measurements throughout. Additional references included in the protocol as a result of including the extra cardiovascular and retinopathy measurements. Changes to secondary study objectives and endpoints in the low-risk non-randomised subjects - minor changes to the secondary objectives and endpoints of the study in the non-intervention group to account for the inclusion of the FMD, PWV and retinopathy assessments. Clarification of information regarding interaction of the IMP with other drugs - necessary to increase the number of possible drug interactions in the light of new findings. Changes to sampling in the non-intervention (low risk) group - inconsistencies in the samples taken and sampling frequencies for the non-intervention study group between the protocol text, study procedures (protocol section 18.6) and information sheets have been resolved. Correction of errors in the study procedures and Visit Schedule for the intervention group - inconsistencies in the samples taken and sampling frequencies for the intervention group between the study procedures (protocol section 18.5) and Visit Schedule resolved. Correction of minor textual errors - including misspellings, changes of title and e-mail address of Principal Investigators. (Submitted to MREC & MHRA)

16 December 2010	Protocol version 5 Update in contact details. Details of eGFR calculation for participants over 18yrs clarified. Various other administrative corrections. (Submitted to MREC & MHRA)
19 August 2011	Protocol version 6 Update in contact details. Eligibility age changed from 11-16 to 10-16yrs. Update in wording with regard insurance at the request of the sponsor. (Submitted to MREC & MHRA)
13 September 2012	Protocol version 7 Update of contact details & addition of new sites in Australia and Canada. Timeline updated. Removal of references to SOPs. Addition of IMP disposal at local sites. (submitted to MREC only)
24 July 2013	Protocol version 8 Update to sponsor contacts, change in statistician, Update to contact details of DMEC member, change in PI at Monash. Addition of study procedures to synopsis that had previously been omitted. As recruitment to the study has continued the minimum period of exposure to intervention has been reduced. All references to a minimum period have been removed. Pubertal staging – added where it acceptable. GFR decline – further information has been added. More information has been added with regard suspension/withdrawal of study medications and also the recommencement of intervention. Study visits – clarification on study visits and what is classed as a missed visit. Data management – updated to reflect changes implemented by sponsor. Update of timelines. (Submitted to MREC only)
29 January 2014	Protocol version 9 Update to the name and contact details of the central cardiovascular laboratory. Changes to the wording in the combined flow chart and through text to allow randomisation to occur prior to visit 2 (initiation of therapy) as this occurs in a number of visits. Test changes to timing of visits from date of initiating therapy rather than date of randomisation. Sample, handling and shipment has been updated to allow the secondary samples retained at site to be shipped and collected by the central coordinating team and stored in a safe repository in the UK. (Submitted to MREC only)
16 January 2015	Protocol version 10 Changes in address details for the CI and Central Co-ordinating Centre for Australia; change of affiliation and contact information for Aardex Ltd; change of name and contact information for study co-ordinator (Australia); request for blood samples collected at annual routine clinic appointments to include also samples required for study visits (Observational study only); request for the collection of an additional blood sample at the Final study visit to allow DNA extraction; request for MA status to be checked locally at the very end of the study to support decisions regarding ongoing medical management; addition of a study publications policy (Submitted to MREC only)
21 October 2015	Protocol version 11 Update of contact information. Addition of information about the collection and analysis of DNA sample at final visit. Additional information added about interaction of study drugs with other drug products. Publication policy added. (Submitted to MREC & MHRA)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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20 July 2009	<p>Recruitment was temporarily suspended 20/07/2009 as an error in the system for assigning eligibility for the trial was identified. Eligibility for AdDIT was based on assessment of the albumin/creatinine ratio from 6 early morning urines, age, gender and duration of disease. In 2 participants tertiles were generated not only on the 2 sets of recently screened urines but also on 2 sets previously collected which remained in the database. In both cases the tertile assignment was different. In one case the participant had been recruited but not randomised. In the second, no approach had been made. The tertile assignments of those 16 participants already randomised were checked and were not compromised.</p> <p>A new procedure including a two-stage system which was reviewed by the sponsor was implemented to ensure that all potential participants were assigned the correct tertile and their eligibility for the trial confirmed.</p> <p>Recruitment was restarted 21/08/2009.</p> <p>Participants already in the study continued participation.</p>	21 August 2009
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Notes:

Limitations and caveats

None reported