



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 |
|-----------------------|------|

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 |
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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 |
|------------------|--------|

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 |
|------------------|-------------------------------|

Arm description:

dummy placebo tablets

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|----------|
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

placebo tablet

| | |
|------------------|------------------------|
| Arm title | Statin matched placebo |
|------------------|------------------------|

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 | | | |
|------------------|--------------------|--|--|--|

| | | | | |
|--------------------------------------|----------------------|--|--|--|
| 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 |
|-----------------|----------------|

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | ACEI/Placebo |
|-----------------------|--------------|

Reporting group description: -

| | |
|-----------------------|-------------|
| Reporting group title | ACEI/Statin |
|-----------------------|-------------|

Reporting group description: -

| | |
|-----------------------|-----------------|
| Reporting group title | Placebo/Placebo |
|-----------------------|-----------------|

Reporting group description: -

| | |
|-----------------------|----------------|
| Reporting group title | Placebo/Statin |
|-----------------------|----------------|

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 |
|------|--------------|--------------|
|------|--------------|--------------|

| | | |
|--------------|--|----------------|
| 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 |
|--------------|--|----------------|

Notes:

Limitations and caveats

None reported