



Clinical trial results:

REVACEPT, AN INHIBITOR OF PLATELET ADHESION IN SYMPTOMATIC CAROTID STENOSIS: A PHASE II, MULTICENTRE; RANDOMISED, DOSE-FINDING, DOUBLE-BLIND AND PLACEBO-CONTROLLED SUPERIORITY STUDY WITH PARALLEL GROUPS

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2011-001006-10 |
| Trial protocol | DE GB |
| Global end of trial date | 23 September 2019 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 15 November 2020 |
| First version publication date | 15 November 2020 |
| Summary attachment (see zip file) | CSR Summary 2020-09-10 (Revacept-CS-02 Clinical Study Synopsis.100920.pdf) |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | Revacept/CS/02 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01645306 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | advanceCOR GmbH |
| Sponsor organisation address | Fraunhoferstraße 9A, Martinsried, Germany, 82152 |
| Public contact | Prof. Dr. med. Götz Münch, advanceCOR GmbH, 0049 892000 20410, muench@advancecor.com |
| Scientific contact | Prof. Dr. med. Götz Münch, advanceCOR GmbH, 0049 892000 20410, muench@advancecor.com |

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 | 23 September 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 23 September 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 September 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Efficacy objectives are:

- Assessment of incidence of microembolic signals (MES) by transcranial Doppler (TCD) examination (before and after treatment)
- Rate of MES per hour (before and after treatment)
- Cerebral lesion analysis by DWI-NMR
- Assessment of neurological status (NIH Stroke Scale)
- Clinical endpoints will be summarised cumulatively i.e. before treatment, after treatment, at 3 months and at 12 months. The following endpoints will be recorded:
 - o Rate of all cause death
 - o Rate of stroke-related death
 - o Any TIA, amaurosis fugax or stroke including haemorrhagic stroke
- Assessment of cardiovascular outcome including myocardial infarction and re-intervention up to 3 and 12 months

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

The study and all substantial amendments were reviewed by an Independent Ethics Committee in the United Kingdom: NRES Committee East of England – Cambridge South, The Old Chapel, Royal Standard Court, Nottingham, NG16FS and the lead Ethics Committee Germany: Ethikkommission der Fakultät für Medizin der Technischen Universität München, Ismaninger Straße 22, 81675 München.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 01 August 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 57 |
| Country: Number of subjects enrolled | Germany: 101 |
| Worldwide total number of subjects | 158 |
| EEA total number of subjects | 158 |

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 59 |
| From 65 to 84 years | 94 |
| 85 years and over | 5 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total 160 subjects were enrolled in the study. Of those randomised, 53 subjects received 120 mg Revacept, 54 patients 40 mg Revacept and 51 patients placebo by a single IV infusion. Two subjects received no study medication because they no longer met the eligibility criteria.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Randomisation (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Data analyst, Carer, Assessor, Subject |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

single dose

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | Phosphate buffered saline (PBS), 1% sucrose, 4% mannitol |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

single dose

| | |
|------------------|----------------|
| Arm title | 40 mg Revacept |
|------------------|----------------|

Arm description:

single dose

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | 40 mg Revacept |
| Investigational medicinal product code | |
| Other name | GPVI-Fc |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

40 mg Revacept, single dose

| | |
|------------------|-----------------|
| Arm title | 120 mg Revacept |
|------------------|-----------------|

Arm description:

single dose

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | 120 mg Revacept |
| Investigational medicinal product code | |
| Other name | GPVI-Fc |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:
120 mg Revacept, single dose

| Number of subjects in period 1 | Placebo | 40 mg Revacept | 120 mg Revacept |
|---------------------------------------|---------|----------------|-----------------|
| Started | 51 | 54 | 53 |
| Completed | 51 | 54 | 53 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Randomisation |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Randomisation | Total | |
|---|---------------|-------|--|
| Number of subjects | 158 | 158 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 59 | 59 | |
| From 65-84 years | 94 | 94 | |
| 85 years and over | 5 | 5 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 68.1 | | |
| standard deviation | ± 10.13 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 38 | 38 | |
| Male | 120 | 120 | |

End points

End points reporting groups

| | |
|---|-----------------|
| Reporting group title | Placebo |
| Reporting group description: single dose | |
| Reporting group title | 40 mg Revacept |
| Reporting group description: single dose | |
| Reporting group title | 120 mg Revacept |
| Reporting group description: single dose | |

Primary: Exploratory

| | |
|--|----------------------------|
| End point title | Exploratory ^[1] |
| End point description: see Synopsis of Clinical Study Report attached | |
| End point type | Primary |
| End point timeframe: exploratory | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Exploratory trial design - see summary of clinical study report attached for details.

| End point values | Placebo | 40 mg Revacept | 120 mg Revacept | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 51 | 54 | 53 | |
| Units: exploratory | | | | |
| number (not applicable) | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

IMP administration to 365 days thereafter.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 22 |
|--------------------|----|

Reporting groups

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

Reporting group description:

single dose

| | |
|-----------------------|----------------|
| Reporting group title | 40 mg Revacept |
|-----------------------|----------------|

Reporting group description:

single dose

| | |
|-----------------------|-----------------|
| Reporting group title | 120 mg Revacept |
|-----------------------|-----------------|

Reporting group description:

single dose

| Serious adverse events | Placebo | 40 mg Revacept | 120 mg Revacept |
|---|------------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 17 / 51 (33.33%) | 17 / 54 (31.48%) | 15 / 53 (28.30%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glottis carcinoma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Laryngeal cancer | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Lung neoplasm malignant | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Sarcoma of skin | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Ischaemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Carotid endarterectomy | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chemotherapy | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Coronary angioplasty | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary arterial stent insertion | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin lesion removal | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Vocal cordectomy | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 | | | |

| | | | |
|---|----------------|----------------|----------------|
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 | | | |
| Panic attack | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Angiogram | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Biopsy larynx | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Cardiac clearance | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Diffusion-weighted brain MRI abnormal | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Weight decreased subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Injury, poisoning and procedural complications | | | |
| Cerebral hyperperfusion syndrome subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Fall subjects affected / exposed | 2 / 51 (3.92%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Rib fracture subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction subjects affected / exposed | 2 / 51 (3.92%) | 2 / 54 (3.70%) | 2 / 53 (3.77%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ataxia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Cerebellar infarction | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 2 / 54 (3.70%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clumsiness | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Headache | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Intracranial aneurysm | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parkinsonism | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Postictal paralysis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Seizure | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status epilepticus | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Stroke in evolution | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Syncope | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 1 / 54 (1.85%) | 4 / 53 (7.55%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (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 | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (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 |
| Ketoacidosis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Placebo | 40 mg Revacept | 120 mg Revacept |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 35 / 51 (68.63%) | 41 / 54 (75.93%) | 32 / 53 (60.38%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Glottis carcinoma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Laryngeal cancer | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lung neoplasm malignant | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sarcoma of skin | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Circulatory collapse | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Haematoma | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 2 / 53 (3.77%) |
| occurrences (all) | 1 | 0 | 2 |
| Hypertension | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 2 / 54 (3.70%) | 2 / 53 (3.77%) |
| occurrences (all) | 4 | 2 | 2 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 54 (3.70%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 2 | 1 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 54 (1.85%) | 2 / 53 (3.77%) |
| occurrences (all) | 1 | 1 | 2 |
| Ischaemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Phlebitis subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 54 (0.00%) 0 | 1 / 53 (1.89%) 1 |
| Surgical and medical procedures | | | |
| Carotid endarterectomy subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 1 / 54 (1.85%) 1 | 1 / 53 (1.89%) 1 |
| Chemotherapy subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Coronary angioplasty subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 54 (0.00%) 0 | 1 / 53 (1.89%) 1 |
| Coronary arterial stent insertion subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Gastrointestinal tube insertion subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Skin lesion removal subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Ureteral catheterisation subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Vocal cordectomy subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Catheter site pain subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Chest discomfort | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Condition aggravated | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Facial pain | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Feeling hot | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Oedema | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 1 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 5 / 54 (9.26%) | 2 / 53 (3.77%) |
| occurrences (all) | 2 | 5 | 2 |
| Pain | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sensation of foreign body | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Vascular stent stenosis | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 54 (3.70%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 2 | 1 |
| Dysphonia | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 1 / 54 (1.85%) | 1 / 53 (1.89%) |
| occurrences (all) | 2 | 1 | 1 |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Emphysema | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Laryngeal oedema | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Wheezing | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Abnormal dreams | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Alcohol abuse | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Depressed mood | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 2 / 53 (3.77%) |
| occurrences (all) | 0 | 1 | 2 |
| Hallucination, visual | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Panic attack | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Panic disorder | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Post stroke depression | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Investigations | | | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Angiocardiogram | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Biopsy larynx | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood creatine increased | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 2 / 54 (3.70%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood urine present | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Breath sounds abnormal | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac clearance | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac murmur | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 1 / 54 (1.85%) | 1 / 53 (1.89%) |
| occurrences (all) | 3 | 1 | 1 |

| | | | |
|--|----------------|----------------|----------------|
| Diffusion-weighted brain MRI abnormal | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 3 / 54 (5.56%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Heart rate decreased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Inflammatory marker increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myocardial necrosis marker increased | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Troponin increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 1 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| White blood cell count increased | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|----------------------------------|----------------|----------------|----------------|
| Burns second degree | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Carotid artery restenosis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cerebral hyperperfusion syndrome | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Contusion | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 1 | 0 | 1 |
| Fall | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 3 | 0 | 1 |
| Foot fracture | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Head injury | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Post procedural contusion | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Post procedural haematoma | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Post procedural oedema | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Post procedural swelling | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Postoperative hypertension subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Postoperative hypotension subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 54 (0.00%) 0 | 2 / 53 (3.77%) 2 |
| Postoperative wound complication subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Procedural haemorrhage subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Procedural headache subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Procedural hypotension subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Procedural nausea subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Procedural pain subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 3 | 1 / 54 (1.85%) 1 | 2 / 53 (3.77%) 2 |
| Rib fracture subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Skin procedural complication subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Synovial rupture subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Wound complication subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 2 / 54 (3.70%) 2 | 0 / 53 (0.00%) 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Wound haematoma subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Wound secretion subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 2 / 54 (3.70%) 2 | 2 / 53 (3.77%) 2 |
| Angina pectoris subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Atrioventricular block complete subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Atrioventricular block first degree subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 54 (0.00%) 0 | 2 / 53 (3.77%) 2 |
| Bundle branch block left subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Cardiac arrest subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 54 (0.00%) 0 | 1 / 53 (1.89%) 1 |
| Cardiac disorder subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Cardiac failure subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 1 / 53 (1.89%) 1 |
| Cardiogenic shock | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Aphasia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Ataxia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Carotid artery disease | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Carotid artery occlusion | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cerebellar infarction | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 2 / 54 (3.70%) | 2 / 53 (3.77%) |
| occurrences (all) | 2 | 2 | 2 |

| | | | |
|-------------------------------|----------------|----------------|----------------|
| Cerebral ischaemia | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 1 | 1 |
| Cerebrovascular insufficiency | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Clonus | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Clumsiness | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 0 / 54 (0.00%) | 2 / 53 (3.77%) |
| occurrences (all) | 2 | 0 | 2 |
| Dysaesthesia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Facial paralysis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 2 / 54 (3.70%) | 1 / 53 (1.89%) |
| occurrences (all) | 1 | 2 | 1 |
| Facial paresis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Headache | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |

| | | | |
|-------------------------------------|----------------|----------------|----------------|
| Hemiplegia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 2 / 54 (3.70%) | 1 / 53 (1.89%) |
| occurrences (all) | 2 | 2 | 1 |
| Hypoglossal nerve paresis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Intracranial aneurysm | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 1 | 1 |
| Monoparesis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 1 | 1 |
| Muscle spasticity | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 3 / 53 (5.66%) |
| occurrences (all) | 0 | 1 | 3 |
| Paralysis recurrent laryngeal nerve | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Parkinsonism | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Peroneal nerve palsy | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Postictal paralysis subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Sciatica subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 54 (0.00%) 0 | 1 / 53 (1.89%) 1 |
| Seizure subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 1 / 54 (1.85%) 1 | 1 / 53 (1.89%) 1 |
| Status epilepticus subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Stroke in evolution subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Subarachnoid haemorrhage subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Syncope subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 2 / 54 (3.70%) 2 | 1 / 53 (1.89%) 1 |
| Transient ischaemic attack subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 1 / 54 (1.85%) 1 | 4 / 53 (7.55%) 4 |
| Visual field defect subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 54 (0.00%) 0 | 1 / 53 (1.89%) 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Leukopenia subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 1 | 0 / 53 (0.00%) 0 |
| Eye disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Blepharospasm subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| blindness subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 54 (0.00%) 0 | 1 / 53 (1.89%) 1 |
| Retinal artery occlusion subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Visual impairment subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 54 (0.00%) 0 | 1 / 53 (1.89%) 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Diverticulum intestinal haemorrhagic subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 54 (0.00%) 0 | 1 / 53 (1.89%) 1 |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Dysphagia subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Mouth haemorrhage subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Nausea | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 51 (1.96%) | 3 / 54 (5.56%) | 1 / 53 (1.89%) |
| occurrences (all) | 1 | 3 | 1 |
| Oesophageal discomfort | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Paraesthesia oral | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 3 / 54 (5.56%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cold sweat | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Erythema | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Generalised erythema | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lividity | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pemphigoid | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Pigmentation disorder subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Pruritus generalised subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 54 (0.00%) 0 | 1 / 53 (1.89%) 1 |
| Rash subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Rash macular subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Rash pruritic subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Scab subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Skin lesion subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Renal and urinary disorders Bladder irritation subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Micturition urgency subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Renal failure subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Urinary retention subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 1 / 54 (1.85%) 1 | 1 / 53 (1.89%) 1 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Ankylosing spondylitis subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 0 / 54 (0.00%) 0 | 1 / 53 (1.89%) 1 |
| Back pain subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 2 / 54 (3.70%) 2 | 1 / 53 (1.89%) 1 |
| Intervertebral disc protrusion subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Joint swelling subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Muscle spasms subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 1 / 53 (1.89%) 1 |
| Muscular weakness subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 1 / 54 (1.85%) 1 | 1 / 53 (1.89%) 1 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Osteonecrosis of jaw subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 3 / 54 (5.56%) 3 | 2 / 53 (3.77%) 2 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 54 (0.00%) 0 | 0 / 53 (0.00%) 0 |
| Cellulitis subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 1 / 54 (1.85%) 1 | 0 / 53 (0.00%) 0 |
| Gastroenteritis viral | | | |

| | | | |
|------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infection | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pathogen resistance | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 1 / 54 (1.85%) | 2 / 53 (3.77%) |
| occurrences (all) | 3 | 1 | 2 |
| Metabolism and nutrition disorders | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Dehydration | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gout | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 0 / 53 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 54 (1.85%) | 0 / 53 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ketoacidosis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 54 (0.00%) | 1 / 53 (1.89%) |
| occurrences (all) | 0 | 0 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 15 April 2013 | Protocol Version 7.1 (15.04.2013): Amendment of eligibility criteria to improve recruitment rates. |
| 12 September 2013 | Protocol Version 7.3 (12.09.2013): Safety Reporting timeframes updated upon request of MHRA. |
| 22 July 2014 | Protocol Version 7.4 (22.07.2014): Amendment of eligibility criteria to improve recruitment rates |
| 27 May 2015 | Prolongation of study due to slower than anticipated recruitment rates. Original proposed study end date: 2015. Revised proposed study end date: 2017. |
| 22 June 2015 | Protocol Version 8 (22.06.2015): Change to exploratory study design upon recommendation of the DSMB due to restrictive eligibility criterion required for primary endpoint. |
| 14 September 2017 | Prolongation of study due to slower than anticipated recruitment rates. Original proposed study end date: 2017. Revised proposed study end date: 2018. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported