# Clinical trial results:
# A Phase 3, Multicenter, Randomized, Double-blind, Active-controlled, Parallel-group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 versus Eltrombopag, in Adults with Chronic ImmuneThrombocytopenia (Idiopathic Thrombocytopenic Purpura)

## Summary

| | |
|---|---|
| EudraCT number | 2011-000831-10 |
| Trial protocol | BE DE AT NL GB ES |
| Global end of trial date | 13 September 2013 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 14 April 2016 |
| First version publication date | 14 April 2016 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | E5501-G000-305 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01433978 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | ASTUTE: E5501-G000-305 |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Eisai |
| Sponsor organisation address | 155 Tice Boullevard, Woodcliff Lake, United States, 07677 |
| Public contact | Medical Information, Eisai Limited, +44 08456761400, LmedInfo@eisai.net |
| Scientific contact | Medical Information, Eisai Limited, +44 08456761400, LmedInfo@eisai.net |

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 | 29 October 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 September 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 September 2013 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

Core study
To compare the efficacy of avatrombopag (in addition to standard) of care to eltrombopag (in addition to standard of care) for the treatment of adult participants with chronic immune thrombocytopenia (idiopathic thrombocytopenic purpura [ITP]) as measured by durable platelet response.

Open-label Extension Phase
To evaluate the safety and tolerability of long-term therapy with avatrombopag in participants with chronic ITP (cITP).

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:
- Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008)
- International Conference on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal
Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed participant consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan’s GCP participant Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 April 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 | Spain: 1 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | Austria: 2 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | Australia: 1 |
| Country: Number of subjects enrolled | United States: 16 |

| | |
|---|---|
| Worldwide total number of subjects | 23 |
| EEA total number of subjects | 6 |

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) | 17 |
| From 65 to 84 years | 6 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Out of 6 participants who entered the Open-label Extension Phase (OLE), zero participants completed the OLE phase and 6 participants discontinued the extension phase. Reason for discontinuation of participants is as follows: study termination by Sponsor (4); lack of efficacy (1); adverse event, non-fatal (1).

### Pre-assignment

Screening details:

One screen-failed participant was randomized into the study in error, but not dosed.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Eltrombopag (Core Study) |

Arm description:

Eltrombopag was administered orally as 25 mg, 50 mg, or 75 mg in a flexible dose design for 26 weeks. Participants received blinded therapy at a starting dose of 50 mg eltrombopag once daily and they were allowed to have their dose titrated up (maximum dose of 75 mg eltrombopag) or down (minimum dose of 25 mg eltrombopag) depending on their response to study drug.

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

Dosage and administration details:

Eltrombopag tablets administered orally as 25-, 50-, or 75-mg doses, in a flexible dose design.

| | |
|---|---|
| **Arm title** | Avatrombopag (Core Study) |

Arm description:

Avatrombopag was administered orally as 5 mg, 10 mg, 20 mg, 30 mg or 40 mg in a flexible dose design for 26 weeks. Participants received blinded therapy at a starting dose of 20 mg avatrombopag, once daily and they were allowed to have their dose titrated up (maximum dose of 40 mg avatrombopag) or down (minimum dose of 5 mg avatrombopag) depending on their response to study drug.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Avatrombopag |
| Investigational medicinal product code | E5501 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Avatrombopag tablets administered orally as 5-, 10-, 20-, 30-, or 40-mg doses, in a flexible dose design.

| **Number of subjects in period 1** | Eltrombopag (Core Study) | Avatrombopag (Core Study) |
|---|---|---|
| Started | 11 | 12 |
| Completed | 0 | 1 |
| Not completed | 11 | 11 |
| Adverse event, non-fatal | - | 1 |
| Study Terminated by Sponsor | 6 | 9 |
| Lack of efficacy | 5 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Eltrombopag (Core Study) |
| Reporting group description: | |
| Eltrombopag was administered orally as 25 mg, 50 mg, or 75 mg in a flexible dose design for 26 weeks. Participants received blinded therapy at a starting dose of 50 mg eltrombopag once daily and they were allowed to have their dose titrated up (maximum dose of 75 mg eltrombopag) or down (minimum dose of 25 mg eltrombopag) depending on their response to study drug. | |
| Reporting group title | Avatrombopag (Core Study) |
| Reporting group description: | |
| Avatrombopag was administered orally as 5 mg, 10 mg, 20 mg, 30 mg or 40 mg in a flexible dose design for 26 weeks. Participants received blinded therapy at a starting dose of 20 mg avatrombopag, once daily and they were allowed to have their dose titrated up (maximum dose of 40 mg avatrombopag) or down (minimum dose of 5 mg avatrombopag) depending on their response to study drug. | |

| Reporting group values | Eltrombopag (Core Study) | Avatrombopag (Core Study) | Total |
|---|---|---|---|
| Number of subjects | 11 | 12 | 23 |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 45.4 | 50.8 | |
| standard deviation | ± 20.09 | ± 23.04 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 7 | 7 | 14 |
| Male | 4 | 5 | 9 |

## End points

### End points reporting groups

| Reporting group title | Eltrombopag (Core Study) |
|---|---|

Reporting group description:

Eltrombopag was administered orally as 25 mg, 50 mg, or 75 mg in a flexible dose design for 26 weeks. Participants received blinded therapy at a starting dose of 50 mg eltrombopag once daily and they were allowed to have their dose titrated up (maximum dose of 75 mg eltrombopag) or down (minimum dose of 25 mg eltrombopag) depending on their response to study drug.

| Reporting group title | Avatrombopag (Core Study) |
|---|---|

Reporting group description:

Avatrombopag was administered orally as 5 mg, 10 mg, 20 mg, 30 mg or 40 mg in a flexible dose design for 26 weeks. Participants received blinded therapy at a starting dose of 20 mg avatrombopag, once daily and they were allowed to have their dose titrated up (maximum dose of 40 mg avatrombopag) or down (minimum dose of 5 mg avatrombopag) depending on their response to study drug.

### Primary: Change from Baseline in Local Platelet Count for the 6 Month Treatment Period

| End point title | Change from Baseline in Local Platelet Count for the 6 Month Treatment Period |
|---|---|

End point description:

Platelet responses to avatrombopag was evaluated using the platelet counts determined at local clinical laboratories. Only participants with non-missing data at both baseline and the relevant post-baseline visit are included in the change from baseline summary statistics. Standard deviation is not applicable for some of the categories, from Visit 14 to Visit 22, as the number of participants analyzed for that visit was 1 individual.

| End point type | Primary |
|---|---|

End point timeframe:

Day 5, Day 8, Week 2, Week 3, Week 4, Week 6, Week 8, Week 10, Week 12, Week 14, Week 16, Week 18, Week 19, Week 20, Week 22, Week 23, Week 24, Week 25, and Week 26

| End point values | Eltrombopag (Core Study) | Avatrombopag (Core Study) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 12 | | |
| Units: 10^9/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 3 (Day 5) N = 10, 10 | 8.6 (± 17.312) | 12.85 (± 16.054) | | |
| Visit 4 (Day 8) N = 11, 11 | 32.5 (± 44.519) | 47 (± 59.69) | | |
| Visit 5 (Week 2) N = 11, 12 | 73.41 (± 79.885) | 171.71 (± 201.736) | | |
| Visit 6 (Week 3) N = 10, 12 | 67.2 (± 95.536) | 114.21 (± 117.172) | | |
| Visit 7 (Week 4) N = 9, 12 | 28.72 (± 38.437) | 108.79 (± 217.036) | | |
| Visit 8 (Week 6) N = 7, 11 | 57.21 (± 57.718) | 150.68 (± 134.902) | | |
| Visit 9 (Week 8) N = 4, 8 | 67.25 (± 46.055) | 121.31 (± 149.04) | | |

| | | | | |
|---|---|---|---|---|
| Visit 10 (Week 10) N = 3, 6 | 92.67 (± 34.649) | 126.25 (± 90.602) | | |
| Visit 11 (Week 12) N = 3, 5 | 87.33 (± 72.616) | 185.1 (± 115.841) | | |
| Visit 12 (Week 14 ) N = 3, 4 | 104.33 (± 77.114) | 159.38 (± 116.746) | | |
| Visit 13 (Week 16) N = 2, 4 | 47.75 (± 2.475) | 123.88 (± 124.474) | | |
| Visit 14 (Week 18) N = 1, 2 | 107.5 (± 0) | 46.5 (± 53.74) | | |
| Visit 15 (Week 19) N = 1, 2 | 13.5 (± 0) | 29.5 (± 22.627) | | |
| Visit 16 (Week 20) N = 0, 1 | 0 (± 0) | 50.5 (± 0) | | |
| Visit 18 (Week 22) N = 0, 1 | 0 (± 0) | 75.5 (± 0) | | |
| Visit 19 (Week 23) N = 0, 1 | 0 (± 0) | 104.5 (± 0) | | |
| Visit 20 (Week 24) N = 0, 1 | 0 (± 0) | 106.5 (± 0) | | |
| Visit 21 (Week 25) N = 0, 1 | 0 (± 0) | 120.5 (± 0) | | |
| Visit 22 (Week 26) N = 0, 1 | 0 (± 0) | 58.5 (± 0) | | |

**Statistical analyses**

| **Statistical analysis title** | Superiority |
|---|---|
| Comparison groups | Eltrombopag (Core Study) v Avatrombopag (Core Study) |
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 42.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -56.2 |
| upper limit | 140.4 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 34 Weeks in the Core Study (including 26 weeks of Treatment, plus Dose Taper and Follow-up for those that did not enter the Extension Phase) and up to 104 weeks in the Extension Phase (including Dose Taper and Follow-up).

Adverse event reporting additional description:

Treatment emergent adverse events were collected. Core Study Safety Analysis Set (SAS): All participants who received at least 1 dose of study drug and had at least 1 postdose safety assessment. OLE SAS: All participants who received at least 1 dose of avatrombopag (either in the Core or Extension Phase) and had a postdose safety assessment.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Avatrombopag (Open-label Extension Phase) |

Reporting group description:

Participants who met the eligibility requirements for the Open-label Extension (OLE) Phase or who discontinued the Core Study early because of lack of treatment effect were eligible to continue into the OLE Phase for up to 104 weeks of open-label avatrombopag therapy. Participants entering the OLE from the Core Study received a starting dose of open-label avatrombopag that was determined by the last dose of study drug at the End of Treatment (EOT) Visit (Visit 22) of the Core Study. Participants who discontinued the Core Study early because of lack of treatment effect and entered the OLE received open-label avatrombopag at a starting dose of 20 mg once daily of open-label avatrombopag.

| | |
|---|---|
| Reporting group title | Eltrombopag (Core Study) |

Reporting group description:

Eltrombopag was administered orally as 25 mg, 50 mg, or 75 mg in a flexible dose design for 26 weeks. Participants received blinded therapy at a starting dose of 50 mg eltrombopag once daily and they were allowed to have their dose titrated up (maximum dose of 75 mg eltrombopag) or down (minimum dose of 25 mg eltrombopag) depending on their response to study drug.

| | |
|---|---|
| Reporting group title | Avatrombopag (Core Study) |

Reporting group description:

Avatrombopag was administered orally as 5 mg, 10 mg, 20 mg, 30 mg or 40 mg in a flexible dose design for 26 weeks. Participants received blinded therapy at a starting dose of 20 mg avatrombopag, once daily and they were allowed to have their dose titrated up (maximum dose of 40 mg avatrombopag) or down (minimum dose of 5 mg avatrombopag) depending on their response to study drug.

| Serious adverse events | Avatrombopag (Open-label Extension Phase) | Eltrombopag (Core Study) | Avatrombopag (Core Study) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 0 / 11 (0.00%) | 2 / 12 (16.67%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Chronic lymphocytic leukaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (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 |
| Blood and lymphatic system disorders | | | |
| Idiopathic thrombocytopenic purpura | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchitis moraxella | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (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 |
| Thrombophlebitis septic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Avatrombopag (Open-label Extension Phase) | Eltrombopag (Core Study) | Avatrombopag (Core Study) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 16 / 17 (94.12%) | 11 / 11 (100.00%) | 11 / 12 (91.67%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Raynaud's phenomenon | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 5 / 11 (45.45%) | 1 / 12 (8.33%) |
| occurrences (all) | 10 | 7 | 2 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |

| | | | |
|---|---|---|---|
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 11 (18.18%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 2 | 1 |
| Nipple pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 11 (18.18%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 2 | 2 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 1 | 2 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 11 (18.18%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pleurisy | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Insomnia | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 1 / 11 (9.09%) | 3 / 12 (25.00%) |
| occurrences (all) | 4 | 1 | 3 |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Investigations | | | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 0 | 1 |
| Platelet count increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Weight increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lymphocyte count increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Electrocardiogram abnormal | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 11 (18.18%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Laceration | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Muscle strain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Scratch | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cartilage injury | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 2 / 11 (18.18%) | 3 / 12 (25.00%) |
| occurrences (all) | 7 | 2 | 6 |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Head discomfort | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Headache | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 3 / 11 (27.27%) | 3 / 12 (25.00%) |
| occurrences (all) | 10 | 4 | 5 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 11 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 2 | 0 | 2 |
| Sinus headache | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Idiopathic thrombocytopenic purpura | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Ear and labyrinth disorders | | | |

| | | | |
|---|---|---|---|
| Ear pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye disorders | | | |
| Abnormal sensation in eye | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 3 | 0 | 3 |
| Eye disorder | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Eye irritation | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Eye pruritus | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye swelling | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 4 | 2 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Constipation | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 3 / 11 (27.27%) | 2 / 12 (16.67%) |
| occurrences (all) | 2 | 3 | 2 |
| Gastrointestinal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 11 (9.09%) | 2 / 12 (16.67%) |
| occurrences (all) | 2 | 1 | 2 |
| Glossodynia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 2 / 11 (18.18%) | 3 / 12 (25.00%) |
| occurrences (all) | 4 | 2 | 4 |
| Oral mucosal blistering | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Swollen tongue | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 1 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Flatulence | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Discomfort | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatobiliary disorders | | | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Papule | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 3 | 0 | 1 |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood blister | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin haemorrhage | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Acne | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 2 / 11 (18.18%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 2 | 1 |
| Limb discomfort | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 0 | 2 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 11 (0.00%) | 3 / 12 (25.00%) |
| occurrences (all) | 3 | 0 | 3 |
| Myalgia | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 11 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 6 | 0 | 4 |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 5 | 0 | 3 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasopharyngitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 17 (23.53%) | 3 / 11 (27.27%) | 2 / 12 (16.67%) |
| occurrences (all) | 4 | 3 | 2 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Bronchitis moraxella | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Thrombophlebitis septic | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Iron deficiency | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early on 22 Jan 2013. After much consideration, the sponsor made the decision to discontinue the study due to significant enrollment challenges.
Results could not be released before 21 July 2015 due to EudraCT Sysyem issues.

Notes: