



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 Immune Thrombocytopenia (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
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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 Boulevard, 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)
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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)
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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)
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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			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	45.4	50.8	
standard deviation	± 20.09	± 23.04	-
Gender categorical			
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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Avatrombopag (Open-label Extension Phase)
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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)
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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)
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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 occurrences (all)	4 / 17 (23.53%) 4	1 / 11 (9.09%) 1	3 / 12 (25.00%) 3
Sleep disorder subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Investigations			
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Platelet count increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Weight increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Lymphocyte count increased subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Electrocardiogram abnormal subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2	2 / 11 (18.18%) 4	0 / 12 (0.00%) 0
Laceration subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Muscle strain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 11 (0.00%) 0	0 / 12 (0.00%) 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 occurrences (all)	1 / 17 (5.88%) 1	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Eye disorders			
Abnormal sensation in eye subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 3	0 / 11 (0.00%) 0	1 / 12 (8.33%) 3
Eye disorder subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Eye irritation subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Eye pruritus subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Eye swelling subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 4	1 / 11 (9.09%) 2	1 / 12 (8.33%) 1
Abdominal pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	1 / 11 (9.09%) 1	1 / 12 (8.33%) 1
Constipation subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Diarrhoea subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	3 / 11 (27.27%) 3	2 / 12 (16.67%) 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			

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

subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 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.
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Notes: