



Clinical trial results:

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 Plus Standard of Care for the Treatment of Thrombocytopenia in Adults with Chronic Immune Thrombocytopenia (Idiopathic Thrombocytopenic Purpura)

Summary

EudraCT number	2011-000830-12
Trial protocol	NL SK BE CZ PL BG GR
Global end of trial date	01 March 2014

Results information

Result version number	v1 (current)
This version publication date	08 May 2016
First version publication date	08 May 2016

Trial information

Trial identification

Sponsor protocol code	E5501-G000-302
-----------------------	----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01438840
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
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	01 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 November 2013
Global end of trial reached?	Yes
Global end of trial date	01 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Core Study

To demonstrate that the efficacy of E5501 (in addition to standard of care) is superior to placebo (in addition to standard of care) for the treatment of adult participants with chronic immune thrombocytopenia (idiopathic thrombocytopenic purpura) (ITP) as measured by cumulative number of weeks of platelet response over 6 months of once daily treatment in adults participants who received at least 1 prior ITP therapy.

Extension Phase

To evaluate the safety and tolerability of long-term therapy with E5501 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, October 2008
- 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 Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed participant consent and IRB regulations and applicable sections of US 21 CFR Part 312
- A waiver from the IRB(s)/IEC(s) was obtained before study initiation for non-US studies conducted under an Investigational New Drug (IND) application.
- 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 (SUSARs) were reported, as required, to the Competent Authorities of all involved EU member states.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 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	Netherlands: 1
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czech Republic: 7

Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Ukraine: 8
Country: Number of subjects enrolled	South Africa: 3
Worldwide total number of subjects	49
EEA total number of subjects	33

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)	45
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Out of 39 participants who entered the extension phase, 29 participants completed and 10 participants discontinued the extension phase. Reason for discontinuation of participants is as follows: adverse event (3); lack of efficacy (2); not specified (1); consent withdrawn by subject (3); and lost to follow-up (1).

Pre-assignment

Screening details:

A total of 100 participants were screened in study. Of these 100 participants, 51 were screen failures and 49 were randomized into the study.

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, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (Core study)

Arm description:

Placebo was administered as 5 mg, 10 mg, 20 mg, 30 mg or 40 mg in a flexible dose design for 26 weeks. Placebo was administered orally at a starting dose of 20 mg, once daily. Afterwards the dose could be titrated up (maximum dose of 40 mg avatrombopag) or down (minimum dose of 5 mg avatrombopag) depending on the participant's response to the study drug; placebo titration was used to maintain the blind.

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

Dosage and administration details:

Placebo 5, 10, 20, 30 and 40 mg were administered orally, once-daily, to match avotrombopag for 26 weeks.

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, one 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	Active comparator
Investigational medicinal product name	Avatrombopag
Investigational medicinal product code	E5501
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

E5501 (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 E5501, once daily and they were allowed to have their dose titrated up (maximum dose of 40 mg E5501) or down (minimum dose of 5 mg E5501) depending on their response to study drug.

Number of subjects in period 1	Placebo (Core study)	Avatrombopag (Core study)
Started	17	32
Completed	1	22
Not completed	16	10
Consent withdrawn by subject	1	-
Adverse event	-	3
Lack of efficacy	15	7

Baseline characteristics

Reporting groups

Reporting group title	Placebo (Core study)
-----------------------	----------------------

Reporting group description:

Placebo was administered as 5 mg, 10 mg, 20 mg, 30 mg or 40 mg in a flexible dose design for 26 weeks. Placebo was administered orally at a starting dose of 20 mg, once daily. Afterwards the dose could be titrated up (maximum dose of 40 mg avatrombopag) or down (minimum dose of 5 mg avatrombopag) depending on the participant's response to the study drug; placebo titration was used to maintain the blind.

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, one 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	Placebo (Core study)	Avatrombopag (Core study)	Total
Number of subjects	17	32	49
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	41.2	46.4	
standard deviation	± 14.7	± 14.2	-
Gender categorical Units: Subjects			
Female	8	23	31
Male	9	9	18

End points

End points reporting groups

Reporting group title	Placebo (Core study)
Reporting group description:	
Placebo was administered as 5 mg, 10 mg, 20 mg, 30 mg or 40 mg in a flexible dose design for 26 weeks. Placebo was administered orally at a starting dose of 20 mg, once daily. Afterwards the dose could be titrated up (maximum dose of 40 mg avatrombopag) or down (minimum dose of 5 mg avatrombopag) depending on the participant's response to the study drug; placebo titration was used to maintain the blind.	
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, one 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: Number of Weeks with Platelet Count Greater Than or Equal to $50 \times 10^9/L$ During 6-Month Treatment Period

End point title	Number of Weeks with Platelet Count Greater Than or Equal to $50 \times 10^9/L$ During 6-Month Treatment Period
End point description:	
The cumulative number of weeks of platelet response is defined as the total numbers of weeks in which the platelet count is greater than or equal to $50 \times 10^9/L$ during 6 months of treatment of core study in the absence of rescue therapy.	
End point type	Primary
End point timeframe:	
Week 1 to Week 26	

End point values	Placebo (Core study)	Avatrombopag (Core study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	32		
Units: Weeks				
median (full range (min-max))	0 (0 to 2)	12.4 (0 to 25)		

Statistical analyses

Statistical analysis title	Wilcoxon (P-value)
Comparison groups	Placebo (Core study) v Avatrombopag (Core study)
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Number of Participants with Platelet Count Greater Than or Equal to $50 \times 10^9/L$ at Day 8

End point title	Number of Participants with Platelet Count Greater Than or Equal to $50 \times 10^9/L$ at Day 8
-----------------	---

End point description:

Participants with platelet response at Day 8 are defined as those who had a platelet count greater than or equal to $50 \times 10^9/L$ at day 8 in the absence of rescue therapy on or before Day 8.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 1 (Day 8)

End point values	Placebo (Core study)	Avatrombopag (Core study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	32		
Units: Participants				
number (not applicable)				
Yes	0	21		
No	17	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with a Reduction in Use of Concomitant Immune/idiopathic Thrombocytopenic Purpura (ITP) Medication

End point title	Number of Participants with a Reduction in Use of Concomitant Immune/idiopathic Thrombocytopenic Purpura (ITP) Medication
-----------------	---

End point description:

Only participants on concomitant ITP medications at baseline were included.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 1 through Week 26

End point values	Placebo (Core study)	Avatrombopag (Core study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: Participants				
number (not applicable)				
Yes	0	5		
No	7	10		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Core Study: up to 39 Weeks (including Screening, Titration, Treatment, Dose Taper, and Follow-up for those who did not enter the Extension Phase). Extension Phase: up to 104 weeks (including Conversion, Maintenance Period, 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. Extension Phase SAS: All participants who received at least 1 dose of avatrombopag (either Core or Extension Phase) and had a postdose safety assessment.

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Avatrombopag (Extension Phase)
-----------------------	--------------------------------

Reporting group description:

Participants who met all eligibility criteria requirements of extension phase and who discontinued the core study because of lack of treatment effect continued into the extension phase. Avatrombopag was administered to participants who entered extension phase, with a starting dose of 20 mg avatrombopag, once daily for 76 weeks and underwent dose titration.

Reporting group title	Placebo (Core Study)
-----------------------	----------------------

Reporting group description:

Placebo was administered as 5 mg, 10 mg, 20 mg, 30 mg or 40 mg in a flexible dose design for 26 weeks. Placebo was administered orally at a starting dose of 20 mg, once daily. Afterwards the dose could be titrated up (maximum dose of 40 mg avatrombopag) or down (minimum dose of 5 mg avatrombopag) depending on the participant's response to the study drug; placebo titration was used to maintain the blind.

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, one 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 (Extension Phase)	Placebo (Core Study)	Avatrombopag (Core Study)
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 47 (31.91%)	1 / 17 (5.88%)	9 / 32 (28.13%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	0 / 32 (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
Aspartate aminotransferase			

increased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	0 / 32 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	0 / 32 (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
Platelet count decreased			
subjects affected / exposed	2 / 47 (4.26%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myelomonocytic leukaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	0 / 32 (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			
Deep vein thrombosis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	2 / 47 (4.26%)	0 / 17 (0.00%)	2 / 32 (6.25%)
occurrences causally related to treatment / all	3 / 3	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	3 / 47 (6.38%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	0 / 47 (0.00%)	1 / 17 (5.88%)	0 / 32 (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			
Polyserositis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Erosive duodenitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	0 / 32 (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
Food poisoning			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis haemorrhagic			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	0 / 32 (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

Gingival bleeding			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	0 / 32 (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
Mouth haemorrhage			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 47 (4.26%)	0 / 17 (0.00%)	2 / 32 (6.25%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			

subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	0 / 32 (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
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 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 (Extension Phase)	Placebo (Core Study)	Avatrombopag (Core Study)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 47 (95.74%)	10 / 17 (58.82%)	31 / 32 (96.88%)
Investigations			
Blood gastrin increased			
subjects affected / exposed	2 / 47 (4.26%)	0 / 17 (0.00%)	2 / 32 (6.25%)
occurrences (all)	2	0	2
Blood urine present			
subjects affected / exposed	0 / 47 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	19 / 47 (40.43%)	4 / 17 (23.53%)	10 / 32 (31.25%)
occurrences (all)	46	20	20
Joint injury			
subjects affected / exposed	0 / 47 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 47 (10.64%)	1 / 17 (5.88%)	2 / 32 (6.25%)
occurrences (all)	5	1	2
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 47 (29.79%)	2 / 17 (11.76%)	12 / 32 (37.50%)
occurrences (all)	24	5	20

Dizziness subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 4	1 / 17 (5.88%) 1	0 / 32 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	1 / 17 (5.88%) 3	0 / 32 (0.00%) 0
Blood and lymphatic system disorders			
Thrombocytopenia subjects affected / exposed occurrences (all)	9 / 47 (19.15%) 11	0 / 17 (0.00%) 0	2 / 32 (6.25%) 2
Anaemia subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 3	0 / 17 (0.00%) 0	2 / 32 (6.25%) 3
Idiopathic thrombocytopenic purpura subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	1 / 17 (5.88%) 1	0 / 32 (0.00%) 0
Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	1 / 17 (5.88%) 1	0 / 32 (0.00%) 0
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	7 / 47 (14.89%) 8	1 / 17 (5.88%) 1	4 / 32 (12.50%) 4
Gastrointestinal disorders			
Gingival bleeding subjects affected / exposed occurrences (all)	8 / 47 (17.02%) 9	0 / 17 (0.00%) 0	4 / 32 (12.50%) 5
Mouth haemorrhage subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 5	0 / 17 (0.00%) 0	3 / 32 (9.38%) 4
Nausea subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 4	0 / 17 (0.00%) 0	3 / 32 (9.38%) 4
Dyspepsia subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	1 / 17 (5.88%) 1	1 / 32 (3.13%) 1

Vomiting subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 2	0 / 17 (0.00%) 0	2 / 32 (6.25%) 2
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	 3 / 47 (6.38%) 3 8 / 47 (17.02%) 40	 0 / 17 (0.00%) 0 3 / 17 (17.65%) 5	 2 / 32 (6.25%) 2 4 / 32 (12.50%) 16
Skin and subcutaneous tissue disorders Petechiae subjects affected / exposed occurrences (all)	7 / 47 (14.89%) 15	1 / 17 (5.88%) 2	4 / 32 (12.50%) 11
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 4	1 / 17 (5.88%) 1	3 / 32 (9.38%) 4
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 5 / 47 (10.64%) 9 4 / 47 (8.51%) 4 3 / 47 (6.38%) 3	 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 1 / 17 (5.88%) 1	 4 / 32 (12.50%) 8 3 / 32 (9.38%) 3 1 / 32 (3.13%) 1
Infections and infestations Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis	 4 / 47 (8.51%) 4 5 / 47 (10.64%) 7	 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0	 2 / 32 (6.25%) 2 3 / 32 (9.38%) 3

subjects affected / exposed	6 / 47 (12.77%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	6	1	0
Upper respiratory tract infection			
subjects affected / exposed	11 / 47 (23.40%)	1 / 17 (5.88%)	6 / 32 (18.75%)
occurrences (all)	20	1	7
Urinary tract infection			
subjects affected / exposed	3 / 47 (6.38%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences (all)	3	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2012	The ability of participants to be permanently discontinued at the discretion of the investigator after 7 days of therapy at the maximum dose if they had dangerously low platelet counts. • P-gP wording was revised to include strong P-gP inhibitor was to be added to avatrombopag therapy or if the dose of a concomitantly administered strong P-gP inhibitor was altered, platelet counts would be monitored weekly for the next 3 weeks in the event a dose adjustment of avatrombopag was required. • Wording was added to the inclusion criteria that patients with neutrophil counts above the reference range may be enrolled upon review and discussion with the Eisai medical monitor. • The fasting gastrin-17 exclusion requirement was increased to 1.5 times ULN for those participants on PPIs or H2 antagonists. Eisai Confidential Page 91 of 2178 Clinical Study Report E5501-G000-302 • Time-to-first bleeding event and time-to-first bleeding event with WHO Bleeding Scale score endpoints were included to align the current study with analyses planned in the E5501-G000-305 study. • Repeat screening laboratory evaluations due to potential laboratory error or a transient and/or reversible condition were to be made available prior to Randomization. • The ability to remove participants based on gastric biomarkers was added. • Lack of treatment effect was defined to allow participants with very low platelet counts to discontinue earlier due to lack of treatment effect and continue into the Extension Phase. • A follow-up endoscopy was requested if there was a significant abnormal endoscopy during the study.
25 March 2013	• A secondary objective was made an exploratory objective. • The secondary objective for the Extension Phase to assess the reduction in the use of steroids and concomitant ITP medication in participants receiving avatrombopag was removed. • The effectiveness assessments for the Extension Phase were revised. • The key secondary endpoint was redefined as exploratory. • The target sample size was changed to 45 participants. • The criterion that 35% of splenectomized participants will be enrolled in the study was removed. • The inclusion criterion for participants enrolling in the Extension Phase to align with study completion was clarified. • The population PK/PD analysis was revised • Study completion was defined

Notes:

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.

Results were ready but could not be released before 21 July 2015 due to EudraCT System issues.

Notes: