Clinical trial results:
A Randomized, Global, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Once-daily Oral Avatrombopag for the Treatment of Adults with Thrombocytopenia Associated with Liver Disease Prior to an Elective Procedure

Summary

EudraCT number	2013-000934-36
Trial protocol	BE DE IT ES CZ
Global end of trial date	21 February 2017

Results information

Result version number	v1 (current)
This version publication date	14 February 2018
First version publication date	14 February 2018

Trial information

Trial identification

Sponsor protocol code	E5501-G000-311

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01976104
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Ltd.
Sponsor organisation address	European Knowledge Center, Mosquitto Way, Hatfield, Hertfordshire, United Kingdom, AL10 9SN UK
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	30 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 January 2017
Global end of trial reached?	Yes
Global end of trial date	21 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a global, multicenter, randomized, double-blind, placebo-controlled, parallel group study using avatrombopag to treat adults with thrombocytopenia associated with liver disease. The study will evaluate avatrombopag in the treatment of thrombocytopenia associated with liver disease prior to an elective procedure to reduce the need for platelet transfusions or any rescue procedure for bleeding due to procedural and post-procedural bleeding complications. Participants will be enrolled into 2 cohorts according to mean baseline platelet count and, within each baseline platelet count cohort will be further stratified by risk of bleeding associated with the elective procedure (low, moderate, or high) and hepatocellular carcinoma (HCC) status (Yes or No).

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 Council 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 Council for Harmonisation of Technical Requirements for Registration 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 subject 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 Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 November 2013
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: 4
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 12

Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	China: 3
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Japan: 50
Country: Number of subjects enrolled	Mexico: 17
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	204
EEA total number of subjects	51

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)	141
From 65 to 84 years	48
85 years and over	15

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 346 participants signed informed consent. Of these 346 participants, 142 were screen failures and 204 were randomized into the study. Of the 142 screen failures, 119 did not meet inclusion/exclusion criteria and 13 withdrew consent, 3 experienced an adverse event, 1 was lost to follow-up and 6 had other not specified reasons.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	60 mg Placebo (lower baseline platelet count)

Arm description:

Participants with a baseline platelet count of less than 40x10^9/liter (L) took three 20 milligrams (mg) matching placebo tablets orally, once daily with a meal on Days 1 through 5.

Arm type	Placebo
Investigational medicinal product name	60 mg Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants took three 20 mg matching placebo tablets orally, once daily with a meal on Days 1 through 5.

Arm title	60 mg Avatrombopag (lower baseline platelet count)

Arm description:

Participants with a baseline platelet count of less than 40x10^9/L took three 20 mg tablets (60 mg total) avatrombopag (2nd generation) orally, once daily with a meal on Days 1 through 5.

Arm type	Experimental
Investigational medicinal product name	60 mg Avatrombopag
Investigational medicinal product code	E5501
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants took three 20 mg tablets (60 mg total) avatrombopag (2nd generation) orally, once daily with a meal on Days 1 through 5.

Arm title	40 mg Placebo (higher baseline platelet count)

Arm description:

Participants with a baseline platelet count of greater than or equal to 40 to 50x10^9/L took two 20 mg matching placebo tablets orally, once daily with a meal on Days 1 through 5.

Arm type	Placebo

Investigational medicinal product name	40 mg Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants took two 20 mg matching placebo tablets orally, once daily with a meal on Days 1 through 5.

Arm title	40 mg Avatrombopag (higher baseline platelet count)

Arm description:

Participants with a baseline platelet count of greater than or equal to 40 to 50x10^9/L took two 20 mg tablets (40 mg total) avatrombopag (2nd generation) orally, once daily with a meal on Days 1 through 5.

Arm type	Experimental
Investigational medicinal product name	40 mg Avatrombopag
Investigational medicinal product code	E5501
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants too two 20 mg tablets (40 mg total) avatrombopag (2nd generation) orally, once daily with a meal on Days 1 through 5.

Number of subjects in period 1	60 mg Placebo (lower baseline platelet count)	60 mg Avatrombopag (lower baseline platelet count)	40 mg Placebo (higher baseline platelet count)
Started	43	70	33
Completed	37	68	31
Not completed	6	2	2
Consent withdrawn by subject	3	-	-
Adverse event, non-fatal	-	-	1
Unspecified	-	1	-
Lost to follow-up	3	-	1
Subject choice	-	1	-

Number of subjects in period 1	40 mg Avatrombopag (higher baseline platelet count)
Started	58
Completed	55
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Unspecified	-
Lost to follow-up	1
Subject choice	1

Baseline characteristics

Reporting groups	
Reporting group title	60 mg Placebo (lower baseline platelet count)
Reporting group description:	
Participants with a baseline platelet count of less than 40x10^9/liter (L) took three 20 milligrams (mg) matching placebo tablets orally, once daily with a meal on Days 1 through 5.	
Reporting group title	60 mg Avatrombopag (lower baseline platelet count)
Reporting group description:	
Participants with a baseline platelet count of less than 40x10^9/L took three 20 mg tablets (60 mg total) avatrombopag (2nd generation) orally, once daily with a meal on Days 1 through 5.	
Reporting group title	40 mg Placebo (higher baseline platelet count)
Reporting group description:	
Participants with a baseline platelet count of greater than or equal to 40 to 50x10^9/L took two 20 mg matching placebo tablets orally, once daily with a meal on Days 1 through 5.	
Reporting group title	40 mg Avatrombopag (higher baseline platelet count)
Reporting group description:	
Participants with a baseline platelet count of greater than or equal to 40 to 50x10^9/L took two 20 mg tablets (40 mg total) avatrombopag (2nd generation) orally, once daily with a meal on Days 1 through 5.	

Reporting group values	60 mg Placebo (lower baseline platelet count)	60 mg Avatrombopag (lower baseline platelet count)	40 mg Placebo (higher baseline platelet count)
Number of subjects	43	70	33
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	57.3	58.6	59.2
standard deviation	± 11.98	± 14.18	± 10.31
Gender categorical Units: Subjects			
Female	16	20	16
Male	27	50	17
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	12	11	7
Not Hispanic or Latino	29	56	25
Unknown or Not Reported	2	3	1

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	10	25	8
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	0
White	27	40	24
More than one race	4	3	0
Unknown or Not Reported	0	0	1

Reporting group values	40 mg Avatrombopag (higher baseline platelet count)	Total	
Number of subjects	58	204	
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	57.9		
standard deviation	± 11.11	-	
Gender categorical Units: Subjects			
Female	25	77	
Male	33	127	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	15	45	
Not Hispanic or Latino	42	152	
Unknown or Not Reported	1	7	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	12	55	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	2	6	
White	40	131	
More than one race	4	11	
Unknown or Not Reported	0	1	

End points

End points reporting groups

Reporting group title	60 mg Placebo (lower baseline platelet count)
Reporting group description:	
Participants with a baseline platelet count of less than 40x10^9/liter (L) took three 20 milligrams (mg) matching placebo tablets orally, once daily with a meal on Days 1 through 5.	
Reporting group title	60 mg Avatrombopag (lower baseline platelet count)
Reporting group description:	
Participants with a baseline platelet count of less than 40x10^9/L took three 20 mg tablets (60 mg total) avatrombopag (2nd generation) orally, once daily with a meal on Days 1 through 5.	
Reporting group title	40 mg Placebo (higher baseline platelet count)
Reporting group description:	
Participants with a baseline platelet count of greater than or equal to 40 to 50x10^9/L took two 20 mg matching placebo tablets orally, once daily with a meal on Days 1 through 5.	
Reporting group title	40 mg Avatrombopag (higher baseline platelet count)
Reporting group description:	
Participants with a baseline platelet count of greater than or equal to 40 to 50x10^9/L took two 20 mg tablets (40 mg total) avatrombopag (2nd generation) orally, once daily with a meal on Days 1 through 5.	

Primary: Percentage of Participants Who Did Not Require a Platelet Transfusion After Randomization and up to 7 Days Following a Scheduled Procedure

End point title	Percentage of Participants Who Did Not Require a Platelet Transfusion After Randomization and up to 7 Days Following a Scheduled Procedure
End point description:	
Responders were defined as participants who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a scheduled procedure. Participants with missing information due to early withdrawal or other reasons were conservatively considered as having received a transfusion in the analysis, (i.e. a Non-responder). The Full Analysis Set (FAS) was analyzed.	
End point type	Primary
End point timeframe:	
Randomization (Visit 2), up to 7 Days following a scheduled procedure	

End point values	60 mg Placebo (lower baseline platelet count)	60 mg Avatrombopag (lower baseline platelet count)	40 mg Placebo (higher baseline platelet count)	40 mg Avatrombopag (higher baseline platelet count)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	70	33	58
Units: Percentage of participants				
number (confidence interval 95%)	34.9 (20.6 to 49.1)	68.6 (57.7 to 79.4)	33.3 (17.2 to 49.4)	87.9 (79.5 to 96.3)

Statistical analyses

Statistical analysis title	60 mg Placebo versus 60 mg Avatrombopag

Statistical analysis description:

The null hypothesis was that the proportion of participants not requiring a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a scheduled procedure was the same between the 60 mg avatrombopag and matched placebo treatment groups.

Comparison groups	60 mg Placebo (lower baseline platelet count) v 60 mg Avatrombopag (lower baseline platelet count)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0006 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of proportion versus placebo
Point estimate	33.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.8
upper limit	51.6

Notes:

[1] - Difference of proportion vs placebo = proportion of Responders for avatrombopag - proportion of Responders for placebo; 95% confidence interval (CI) is calculated based on normal approximation.
[2] - Stratified by the risk of bleeding associated with the scheduled procedure within each Baseline platelet count cohort.

Statistical analysis title	40 mg Placebo versus 40 mg Avatrombopag

Statistical analysis description:

The null hypothesis was that the proportion of participants not requiring a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a scheduled procedure was the same between the 60 mg avatrombopag and matched placebo treatment groups.

Comparison groups	40 mg Placebo (higher baseline platelet count) v 40 mg Avatrombopag (higher baseline platelet count)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of proportion versus placebo
Point estimate	54.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.5
upper limit	72.7

Notes:

[3] - Difference of proportion vs placebo = proportion of Responders for avatrombopag - proportion of Responders for placebo; 95% CI is calculated based on normal approximation.
[4] - Stratified by the risk of bleeding associated with the scheduled procedure within each Baseline platelet count cohort

Secondary: Percentage of participants who achieved a platelet count greater than or equal to 50 x 10^9/L on Scheduled Procedure Day

End point title	Percentage of participants who achieved a platelet count greater than or equal to 50 x 10^9/L on Scheduled Procedure Day

End point description:

Responders were defined as participants who achieved a platelet count greater than or equal to 50 x 10^9/L on the procedure day. Participants missing a platelet count on the procedure day were conservatively considered as not achieving a platelet count of 50x10^9/L in the analysis, (i.e. Non-responders).
FAS was analyzed.

End point type	Secondary

End point timeframe:

Day 10 to Day 13 (Visit 4)

End point values	60 mg Placebo (lower baseline platelet count)	60 mg Avatrombopag (lower baseline platelet count)	40 mg Placebo (higher baseline platelet count)	40 mg Avatrombopag (higher baseline platelet count)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	70	33	58
Units: Percentage of participants				
number (confidence interval 95%)	7.0 (0.0 to 14.6)	67.1 (56.1 to 78.1)	39.4 (22.7 to 56.1)	93.1 (86.6 to 99.6)

Statistical analyses

Statistical analysis title	60 mg Placebo versus 60 mg Avatrombopag

Statistical analysis description:

The null hypothesis was that the proportion of participants not requiring a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a scheduled procedure was the same between the avatrombopag and placebo treatment groups.

Comparison groups	60 mg Placebo (lower baseline platelet count) v 60 mg Avatrombopag (lower baseline platelet count)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of proportion versus placebo
Point estimate	60.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	46.8
upper limit	73.5

Notes:

[5] - Difference of proportion vs placebo = proportion of responders for avatrombopag - proportion of responders for placebo; 95% CI is calculated based on normal approximation.
[6] - Stratified by the risk of bleeding associated with the scheduled procedure within each Baseline platelet count cohort.

Statistical analysis title	40 mg Placebo versus 40 mg Avatrombopag

Statistical analysis description:

The null hypothesis was that the proportion of participants not requiring a platelet transfusion or any

rescue procedure for bleeding after randomization and up to 7 days following a scheduled procedure was the same between the avatrombopag and placebo treatment groups.

Comparison groups	40 mg Placebo (higher baseline platelet count) v 40 mg Avatrombopag (higher baseline platelet count)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of proportion versus placebo
Point estimate	53.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.8
upper limit	71.6

Notes:

[7] - Difference of proportion vs placebo = proportion of responders for avatrombopag - proportion of responders for placebo; 95% CI is calculated based on normal approximation.
[8] - Stratified by the risk of bleeding associated with the scheduled procedure within each Baseline platelet count cohort.

Secondary: Change from baseline in platelet counts on Scheduled Procedure Day

End point title	Change from baseline in platelet counts on Scheduled Procedure Day

End point description:

Last observation carried forward was used for participants with a missing platelet count on the scheduled procedure day. Platelet count was measured preprocedure and before any platelet transfusion.

End point type	Secondary

End point timeframe:

Baseline (Visit 2) to Procedure Day 10 to Day 13 (Visit 4)

End point values	60 mg Placebo (lower baseline platelet count)	60 mg Avatrombopag (lower baseline platelet count)	40 mg Placebo (higher baseline platelet count)	40 mg Avatrombopag (higher baseline platelet count)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	69	33	58
Units: Platelet Count x 10^9				
arithmetic mean (standard deviation)	3.0 (± 10.01)	31.3 (± 24.9)	5.9 (± 14.89)	44.9 (± 32.96)

Statistical analyses

Statistical analysis title	60 mg Placebo 60 mg Avatrombopag
Comparison groups	60 mg Placebo (lower baseline platelet count) v 60 mg Avatrombopag (lower baseline platelet count)

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001 [10]
Method	Wilcoxon Rank Sum Test
Parameter estimate	Difference in change of platelet count
Point estimate	25.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.5
upper limit	32

Notes:

[9] - Difference in change from Baseline of platelet count for avatrombopag versus placebo within each Baseline platelet count cohort was based on Hodges-Lehmann estimation; 95% CI was the asymptotic (Moses) CI

[10] - P-value was based on Wilcoxon Rank Sum Test for each avatrombopag treatment group versus placebo within each Baseline platelet count cohort.

Statistical analysis title	40 mg Placebo versus 40 mg Avatrombopag
Comparison groups	40 mg Placebo (higher baseline platelet count) v 40 mg Avatrombopag (higher baseline platelet count)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	Wilcoxon Rank Sum Test
Parameter estimate	Difference in change of platelet count
Point estimate	36.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.5
upper limit	45.5

Notes:

[11] - Difference in change from baseline of platelet count for avatrombopag vs. placebo within each baseline platelet count cohort is based on Hodges-Lehmann estimation; 95% CI is the asymptotic (Moses) CI.

[12] - P-value was based on Wilcoxon Rank Sum Test for each avatrombopag treatment group versus placebo within each Baseline platelet count cohort.

Other pre-specified: Percentage of Participants with a World Health Organization (WHO) Bleeding Score greater than or equal to 2 after Randomization and up to 7 Days after an Scheduled Procedure

End point title	Percentage of Participants with a World Health Organization (WHO) Bleeding Score greater than or equal to 2 after Randomization and up to 7 Days after an Scheduled Procedure

End point description:

The severity of bleeding events was assessed by the investigator (or appropriately delegated study site personnel) using the WHO bleeding scale. The WHO bleeding scale is a clinical investigator-assessed five-point scale with Grade 0 = No bleeding, Grade 1 = Petechial bleeding, Grade 2 = Mild blood loss (clinically significant), Grade 3 = Gross blood loss requires transfusion (severe), and Grade 4 = Debilitating blood loss, retinal or cerebral associated with fatality. Participants with missing information are considered as having a WHO bleeding score greater than or equal to 2 in the analysis.
FAS was analyzed.

End point type	Other pre-specified

End point timeframe:

Baseline (Visit 2) up to 7 days post scheduled procedure

End point values	60 mg Placebo (lower baseline platelet count)	60 mg Avatrombopag (lower baseline platelet count)	40 mg Placebo (higher baseline platelet count)	40 mg Avatrombopag (higher baseline platelet count)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	70	33	58
Units: Percentage of participants				
number (not applicable)	0.0	1.4	6.1	1.7

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants Experiencing an Adverse Event

End point title	Number of Participants Experiencing an Adverse Event

End point description:

Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events, including platelet transfusion-related complications; routine laboratory evaluation for hematology, serum chemistry, and urine values; periodic measurement of vital signs and electrocardiograms (ECGs); the performance of physical examinations; and Doppler sonography. AE severity was graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, where Grade 1 = mild, Grade 2 = moderate, Grade 3 = Severe, Grade 4 = Life-threatening, and Grade 5 = Death related to the AE. All AEs graded as 4 or 5 were considered to be serious. Treatment-emergent adverse events (TEAEs) were defined as an AE that started on or after the date of first dose of study drug, up to 30 days after the last dose of study drug. Treatment-related AEs were considered by the investigator to be possibly or probably related to study drug.

End point type	Other pre-specified

End point timeframe:

From date of first dose of study drug up to 30 days after the last dose of study drug, up to approximately 3 years and 2 months

End point values	60 mg Placebo (lower baseline platelet count)	60 mg Avatrombopag (lower baseline platelet count)	40 mg Placebo (higher baseline platelet count)	40 mg Avatrombopag (higher baseline platelet count)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	70	33	57
Units: Participants				
number (not applicable)				
TEAEs	22	36	15	28
Treatment-related TEAEs	9	6	2	4
Serious TEAEs	1	1	1	1
TEAEs leading to study drug dose adjustment	0	0	0	0

TEAEs leading to study drug withdrawal	0	0	0	0
TEAEs leading to study drug dose reduction	0	0	0	0
TEAEs leading to study drug dose interruption	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of first dose of study drug up to 30 days after the last dose of study drug, up to approximately 3 years and 2 months

Adverse event reporting additional description:

Treatment-emergent adverse events and treatment-emergent serious adverse events. Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4. Safety analysis set included the group of participants who received at least 1 dose of study drug and had at least 1 post dose safety assessment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	60 mg Placebo (lower baseline platelet count)

Reporting group description:

Participants with a baseline platelet count of less than 40x10^9/L took three 20 mg matching placebo tablets orally, once daily with a meal on Days 1 through 5.

Reporting group title	60 mg Avatrombopag (lower baseline platelet count)

Reporting group description:

Participants with a baseline platelet count of less than 40x10^9/liter (L) took three 20 mg tablets (60 mg total) avatrombopag (2nd generation) orally, once daily with a meal on Days 1 through 5.

Reporting group title	40 mg Placebo (higher baseline platelet count)

Reporting group description:

Participants with a baseline platelet count of greater than or equal to 40 to 50x10^9/L took two 20 mg matching placebo tablets orally, once daily with a meal on Days 1 through 5.

Reporting group title	40 mg Avatrombopag (higher baseline platelet count)

Reporting group description:

Participants with a baseline platelet count of greater than or equal to 40 to 50x10^9/L took two 20 mg tablets (40 mg total) avatrombopag (2nd generation) orally, once daily with a meal on Days 1 through 5.

Serious adverse events	60 mg Placebo (lower baseline platelet count)	60 mg Avatrombopag (lower baseline platelet count)	40 mg Placebo (higher baseline platelet count)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 43 (2.33%)	1 / 70 (1.43%)	1 / 33 (3.03%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 43 (0.00%)	0 / 70 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			

Hepatic encephalopathy			
subjects affected / exposed	1 / 43 (2.33%)	0 / 70 (0.00%)	0 / 33 (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
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 43 (0.00%)	0 / 70 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 70 (1.43%)	0 / 33 (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
Ileus paralytic			
subjects affected / exposed	0 / 43 (0.00%)	0 / 70 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 43 (0.00%)	0 / 70 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	40 mg Avatrombopag (higher baseline platelet count)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 57 (1.75%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus paralytic			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	60 mg Placebo (lower baseline platelet count)	60 mg Avatrombopag (lower baseline platelet count)	40 mg Placebo (higher baseline platelet count)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 43 (51.16%)	30 / 70 (42.86%)	15 / 33 (45.45%)
Injury, poisoning and procedural complications			
Transfusion reaction			

subjects affected / exposed	1 / 43 (2.33%)	0 / 70 (0.00%)	2 / 33 (6.06%)
occurrences (all)	1	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 43 (6.98%)	3 / 70 (4.29%)	1 / 33 (3.03%)
occurrences (all)	3	3	1
Headache			
subjects affected / exposed	4 / 43 (9.30%)	2 / 70 (2.86%)	1 / 33 (3.03%)
occurrences (all)	4	3	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 43 (6.98%)	1 / 70 (1.43%)	0 / 33 (0.00%)
occurrences (all)	3	1	0
Puncture site haemorrhage			
subjects affected / exposed	0 / 43 (0.00%)	0 / 70 (0.00%)	3 / 33 (9.09%)
occurrences (all)	0	0	3
Pyrexia			
subjects affected / exposed	2 / 43 (4.65%)	11 / 70 (15.71%)	4 / 33 (12.12%)
occurrences (all)	2	13	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 43 (6.98%)	2 / 70 (2.86%)	1 / 33 (3.03%)
occurrences (all)	4	2	1
Abdominal pain upper			
subjects affected / exposed	5 / 43 (11.63%)	2 / 70 (2.86%)	3 / 33 (9.09%)
occurrences (all)	7	2	3
Diarrhoea			
subjects affected / exposed	3 / 43 (6.98%)	3 / 70 (4.29%)	0 / 33 (0.00%)
occurrences (all)	3	3	0
Nausea			
subjects affected / exposed	5 / 43 (11.63%)	6 / 70 (8.57%)	2 / 33 (6.06%)
occurrences (all)	5	6	2
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 43 (0.00%)	0 / 70 (0.00%)	2 / 33 (6.06%)
occurrences (all)	0	0	3

Non-serious adverse events	40 mg Avatrombopag (higher baseline platelet count)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 57 (24.56%)		
Injury, poisoning and procedural complications			
Transfusion reaction			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Puncture site haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Nausea			

subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	 0 / 57 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2013	• Addition of tranexamic acid as a rescue procedure for bleeding as requested by the European Union (EU) regulatory agency.
22 June 2015	• Updates to the bleeding risk category classification and revision to the exclusion criteria based on feedback received from the investigators. • Addition of eltrombopag and romiplostim as prohibited medications due to their potential off-label use for participants who have thrombocytopenia with Chromic Liver Disease (CLD). • Addition of an evaluation for platelet aggregation to be measured at selected sites due to a request from Japan's Pharmaceuticals and Medical Devices Agency.
31 May 2016	• Clarification to Inclusion Criterion #3: the word "change" was replaced with the word "increase" as requested by the Food and Drug Administration (FDA).
02 December 2016	• The third secondary endpoint, the proportion of participants with a World Health Organization (WHO) bleeding score ≥2 after randomization and up to 7 days following a scheduled procedure, was changed to an exploratory endpoint. • This amendment also reduced the sample size from 300 to 200 participants.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported