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	2013-000965-34
Trial protocol	BE DE IT GB AT HU ES PT PL
Global end of trial date	27 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-G000-310

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01972529
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Ltd.
Sponsor organisation address	Mosquito 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	27 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 January 2017
Global end of trial reached?	Yes
Global end of trial date	27 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	Poland: 13
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 4

Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	China: 7
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Korea, Republic of: 47
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	Thailand: 10
Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	231
EEA total number of subjects	85

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)	186
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 370 participants signed informed consent. Of these 370 participants, 139 were screening failures and 231 were randomized into the study. Of the 139 screening failures, 120 did not meet the inclusion/exclusion criteria and the other 19 participants failed due to adverse events, lost to follow-up and withdrawal of consent.

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 40 x 10^9/liter (L) took three 20 milligrams (mg) (60 mg total) matching placebo tablets orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.

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:

Avatrombopag-matched placebo was administered as three 20 mg (60 mg total) tablets orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.

Arm title	60 mg Avatrombopag, (lower baseline platelet count)

Arm description:

Participants with a baseline platelet count of less than 40 x 10^9 L took three 20 mg tablets (60 mg total) avatrombopag (2nd generation) orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the elective procedure.

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 was administered as three 20 mg (60 mg total) tablets orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.

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 less than 50 x 10^9/L took two 20 mg matching placebo tablets orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.

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:

Avatrombopag-matched placebo was administered as two 20 mg (40 mg total) tablets orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.

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 less than 50 x 10^9/L took two 20 mg tablets (40 mg total) avatrombopag (2nd generation) orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.

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 was administered as two 20 mg (40 mg total) tablets orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.

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	48	90	34
Completed	46	85	32
Not completed	2	5	2
Participant choice	-	1	-
Adverse event, non-fatal	-	1	-
Not specified	-	-	-
Withdrawal of consent	1	2	-
Lost to follow-up	1	-	-
Not treated	-	1	2

Number of subjects in period 1	40 mg Avatrombopag (higher baseline platelet count)
Started	59
Completed	55
Not completed	4
Participant choice	-

Adverse event, non-fatal	-
Not specified	2
Withdrawal of consent	1
Lost to follow-up	-
Not treated	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 40 x 10^9/liter (L) took three 20 milligrams (mg) (60 mg total) matching placebo tablets orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.	
Reporting group title	60 mg Avatrombopag, (lower baseline platelet count)
Reporting group description:	
Participants with a baseline platelet count of less than 40 x 10^9 L took three 20 mg tablets (60 mg total) avatrombopag (2nd generation) orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the elective procedure.	
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 less than 50 x 10^9/L took two 20 mg matching placebo tablets orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.	
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 less than 50 x 10^9/L took two 20 mg tablets (40 mg total) avatrombopag (2nd generation) orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.	

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	48	90	34
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			
Full analysis set was defined as the group of all randomized participants.			
Units: years arithmetic mean standard deviation	 55.1 ± 11.02	 55.6 ± 9.12	 57.8 ± 11.05
Gender categorical Units: Subjects			
Female Male	16 32	25 65	10 24

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	10	10	3
Not Hispanic or Latino	37	77	31
Unknown or Not Reported	1	3	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	18	32	15
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	3	0
White	28	50	19
More than one race	0	0	0
Unknown or Not Reported	2	5	0

Reporting group values	40 mg Avatrombopag (higher baseline platelet count)	Total	
Number of subjects	59	231	
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			
Full analysis set was defined as the group of all randomized participants.			
Units: years			
arithmetic mean	57.5		
standard deviation	± 10.06	-	
Gender categorical Units: Subjects			
Female	22	73	
Male	37	158	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	30	
Not Hispanic or Latino	51	196	
Unknown or Not Reported	1	5	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	24	89	
Native Hawaiian or Other Pacific Islander	0	0	

Black or African American	2	5	
White	31	128	
More than one race	0	0	
Unknown or Not Reported	2	9	

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 40 x 10^9/liter (L) took three 20 milligrams (mg) (60 mg total) matching placebo tablets orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.	
Reporting group title	60 mg Avatrombopag, (lower baseline platelet count)
Reporting group description:	
Participants with a baseline platelet count of less than 40 x 10^9 L took three 20 mg tablets (60 mg total) avatrombopag (2nd generation) orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the elective procedure.	
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 less than 50 x 10^9/L took two 20 mg matching placebo tablets orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.	
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 less than 50 x 10^9/L took two 20 mg tablets (40 mg total) avatrombopag (2nd generation) orally, once daily with a meal during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.	

Primary: Percentage of Participants Who did not Require a Platelet Transfusion or any Rescue Procedure for Bleeding after Randomization Following a Scheduled Procedure

End point title	Percentage of Participants Who did not Require a Platelet Transfusion or any Rescue Procedure for Bleeding after Randomization 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). Full analysis Set (FAS) was analyzed and was defined as the group of all randomized participants.	
End point type	Primary
End point timeframe:	
Baseline (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	48	90	34	59
Units: Percentage of participants				
number (confidence interval 95%)	22.9 (11.0 to 34.8)	65.6 (55.7 to 75.4)	38.2 (21.9 to 54.6)	88.1 (79.9 to 96.4)

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. Difference of proportion versus (vs) placebo = proportion of Responders for avatrombopag – proportion of Responders for placebo; 95% CI is calculated based on normal approximation.

Comparison groups	60 mg Placebo (lower baseline platelet count) v 60 mg Avatrombopag, (lower baseline platelet count)
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of proportion vs placebo
Point estimate	42.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.2
upper limit	58.1

Notes:

[1] - Stratified by the risk of bleeding associated with the elective 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. Difference of proportion vs placebo = proportion of Responders for avatrombopag - proportion of Responders for placebo; 95% CI is calculated based on normal approximation.

Comparison groups	40 mg Placebo (higher baseline platelet count) v 40 mg Avatrombopag (higher baseline platelet count)
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Other[Difference of proportion vs placeb
Point estimate	49.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.6
upper limit	68.2

Notes:

[2] - Stratified by the risk of bleeding associated with the elective 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 the 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 the 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 with missing a platelet count on the procedure day were conservatively considered as not achieving a platelet count of 50 x 10^9/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	48	90	34	59
Units: Percentage of participants				
number (confidence interval 95%)	4.2 (0.0 to 9.8)	68.9 (59.3 to 78.5)	20.6 (7.0 to 34.2)	88.1 (79.9 to 96.4)

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. Difference of proportion vs placebo = proportion of responders for avatrombopag - proportion of responders for placebo; 95% CI is calculated based on normal approximation.

Comparison groups	60 mg Placebo (lower baseline platelet count) v 60 mg Avatrombopag, (lower baseline platelet count)
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of proportion vs placebo
Point estimate	64.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	53.6
upper limit	75.8

Notes:

[3] - P-value is stratified by the risk of bleeding associated with the elective 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. Difference of proportion vs placebo = proportion of responders for avatrombopag - proportion of responders for placebo; 95% CI is calculated based on normal approximation.

Comparison groups	40 mg Placebo (higher baseline platelet count) v 40 mg Avatrombopag (higher baseline platelet count)
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of percentage vs placebo
Point estimate	67.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	51.6
upper limit	83.4

Notes:

[4] - P-value is stratified by the risk of bleeding associated with the elective procedure within each baseline platelet count cohort.

Secondary: Change from Baseline in Platelet Count on the Scheduled Procedure Day

End point title	Change from Baseline in Platelet Count on the 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. FAS was analyzed.

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	48	88	32	58
Units: Platelet count x 10^9 per liter				

arithmetic mean (standard deviation)	0.8 (± 6.36)	32.0 (± 25.53)	1.0 (± 9.30)	37.1 (± 27.41)

Statistical analyses

Statistical analysis title	60 mg Placebo versus 60 mg Avatrombopag

Statistical analysis description:

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% confidence interval is the asymptotic (Moses) CI.

Comparison groups	60 mg Placebo (lower baseline platelet count) v 60 mg Avatrombopag, (lower baseline platelet count)
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Difference in change of platelet count
Point estimate	27.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.5
upper limit	32.5

Notes:

[5] - P-value is based on Wilcoxon rank sum test for each avatrombopag treatment group vs placebo within each baseline platelet count cohort.

Statistical analysis title	40 mg Placebo versus 40 mg Avatrombopag

Statistical analysis description:

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% confidence interval is the asymptotic (Moses) CI.

Comparison groups	40 mg Placebo (higher baseline platelet count) v 40 mg Avatrombopag (higher baseline platelet count)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Difference in change of platelet count
Point estimate	33
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.5
upper limit	41.5

Notes:

[6] - P-value is based on Wilcoxon rank sum test for each avatrombopag treatment group vs placebo within each baseline platelet count cohort.

Secondary: Percentage of Participants with a World Health Organization (WHO) Bleeding Score greater than or equal to 2 after a Scheduled Procedure

End point title	Percentage of Participants with a World Health Organization (WHO) Bleeding Score greater than or equal to 2 after a 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	Secondary

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	48	90	34	59
Units: Percentage of participants				
number (not applicable)	6.3	5.6	2.9	0

Statistical analyses

No statistical analyses for this end point

Secondary: 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; the performance of physical examinations; and Doppler sonography. AE severity was graded using Common Terminology Criteria for Adverse Events 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.
Safety analysis set was analyzed.

End point type	Secondary

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

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	48	89	32	58
Units: Participants				
TEAEs	31	53	18	31
Treatment-related TEAEs	7	12	2	4
Serious TEAEs	11	10	1	8
TEAEs leading to study drug dose adjustment	0	2	0	0
TEAEs leading to study drug withdrawal	0	2	0	0
TEAEs leading to study drug dose reduction	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 administration of first dose up to 30 days after the last dose, up to approximately 3 years

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 version 4. Safety analysis set included all participants who received at least 1 dose of study drug and had at least 1 post dose safety assessment. This set was analyzed "as treated'.

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 during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.

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 during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.

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 during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.

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 during the Treatment Period on Days 1 through 5, and 5 to 8 days prior to the scheduled procedure.

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	11 / 48 (22.92%)	10 / 89 (11.24%)	1 / 32 (3.13%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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			
Generalised oedema			
subjects affected / exposed	1 / 48 (2.08%)	0 / 89 (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
Pyrexia			
subjects affected / exposed	1 / 48 (2.08%)	1 / 89 (1.12%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Organ dysfunction syndrome			
subjects affected / exposed	0 / 48 (0.00%)	0 / 89 (0.00%)	0 / 32 (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			
Epistaxis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 89 (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
Investigations			
Clostridium test positive			
subjects affected / exposed	1 / 48 (2.08%)	0 / 89 (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	1 / 48 (2.08%)	0 / 89 (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
Injury, poisoning and procedural complications			
Anaphylactic transfusion reaction			
subjects affected / exposed	1 / 48 (2.08%)	0 / 89 (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
Post procedural haemorrhage			

subjects affected / exposed	1 / 48 (2.08%)	1 / 89 (1.12%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural haemorrhage			
subjects affected / exposed	1 / 48 (2.08%)	0 / 89 (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
Procedural pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Transfusion reaction			
subjects affected / exposed	3 / 48 (6.25%)	0 / 89 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Coma hepatic			
subjects affected / exposed	0 / 48 (0.00%)	0 / 89 (0.00%)	0 / 32 (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
Hepatic encephalopathy			
subjects affected / exposed	1 / 48 (2.08%)	1 / 89 (1.12%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenomegaly			

subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Stress polycythaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Haemorrhagic anaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Splenic haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Splenic infarction			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 89 (0.00%)	0 / 32 (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
Abdominal Pain Upper			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Ascites			

subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	0 / 89 (0.00%)	0 / 32 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Haematemesis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Hepatobiliary disorders			
Chronic hepatic failure			
subjects affected / exposed	0 / 48 (0.00%)	0 / 89 (0.00%)	0 / 32 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Azotaemia			

subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 48 (0.00%)	0 / 89 (0.00%)	0 / 32 (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
Myalgia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 89 (0.00%)	0 / 32 (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
Clostridium difficile infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 89 (0.00%)	0 / 32 (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
Pneumonia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Sepsis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 89 (0.00%)	0 / 32 (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
Urinary tract infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 89 (0.00%)	0 / 32 (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

Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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
Hyponatraemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 89 (1.12%)	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

Serious adverse events	40 mg Avatrombopag (higher baseline platelet count)		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 58 (13.79%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple Organ dysfunction syndrome			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			

Epistaxis				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Clostridium test positive				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Anaphylactic transfusion reaction				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Procedural haemorrhage				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transfusion reaction				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Nervous system disorders			
Coma hepatic			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatic encephalopathy			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Splenomegaly			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stress polycythaemia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic anaemia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Splenic haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Splenic infarction				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal Pain Upper				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal varices haemorrhage				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Chronic hepatic failure			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Azotaemia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 58 (1.72%)		
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	13 / 48 (27.08%)	28 / 89 (31.46%)	9 / 32 (28.13%)
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 48 (0.00%)	6 / 89 (6.74%)	0 / 32 (0.00%)
occurrences (all)	0	6	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 48 (6.25%)	5 / 89 (5.62%)	2 / 32 (6.25%)
occurrences (all)	4	5	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 48 (2.08%)	6 / 89 (6.74%)	1 / 32 (3.13%)
occurrences (all)	1	6	1
Oedema peripheral			
subjects affected / exposed	2 / 48 (4.17%)	3 / 89 (3.37%)	1 / 32 (3.13%)
occurrences (all)	2	3	1
Pyrexia			
subjects affected / exposed	5 / 48 (10.42%)	7 / 89 (7.87%)	1 / 32 (3.13%)
occurrences (all)	5	7	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 48 (6.25%)	8 / 89 (8.99%)	3 / 32 (9.38%)
occurrences (all)	3	9	3
Dyspepsia			
subjects affected / exposed	2 / 48 (4.17%)	0 / 89 (0.00%)	2 / 32 (6.25%)
occurrences (all)	2	0	2
Nausea			
subjects affected / exposed	2 / 48 (4.17%)	4 / 89 (4.49%)	2 / 32 (6.25%)
occurrences (all)	3	5	2
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 89 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2

Non-serious adverse events	40 mg Avatrombopag (higher baseline platelet count)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 58 (27.59%)		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	7		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Dyspepsia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	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 Chronic 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