



## 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   |
| <b>Arm title</b>             | 60 mg Placebo (lower baseline platelet count) |

Arm description:

Participants with a baseline platelet count of less than  $40 \times 10^9$ /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.

|                  |  |
|------------------|--|
| <b>Arm title</b> | 60 mg Avatrombopag (lower baseline platelet count) |
|------------------|--|

Arm description:

Participants with a baseline platelet count of less than  $40 \times 10^9$ /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.

|                  |  |
|------------------|--|
| <b>Arm title</b> | 40 mg Placebo (higher baseline platelet count) |
|------------------|--|

Arm description:

Participants with a baseline platelet count of greater than or equal to 40 to  $50 \times 10^9$ /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.

|                  |   |
|------------------|---|
| <b>Arm title</b> | 40 mg Avatrombopag (higher baseline platelet count) |
|------------------|---|

Arm description:

Participants with a baseline platelet count of greater than or equal to 40 to 50x10<sup>9</sup>/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.

| <b>Number of subjects in period 1</b> | 60 mg Placebo<br>(lower baseline platelet count) | 60 mg Avatrombopag<br>(lower baseline platelet count) | 40 mg Placebo<br>(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   | -   |

| <b>Number of subjects in period 1</b> | 40 mg Avatrombopag<br>(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 $40 \times 10^9$ /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 $40 \times 10^9$ /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 $50 \times 10^9$ /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 $50 \times 10^9$ /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<br>(lower baseline<br>platelet count) | 60 mg<br>Avatrombopag<br>(lower baseline<br>platelet count) | 40 mg Placebo<br>(higher baseline<br>platelet count) |
|---|---|---|--|
| Number of subjects  | 43  | 70  | 33   |
| Age categorical<br>Units: Subjects  |   |   |  |
| In utero<br>Preterm newborn infants<br>(gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23<br>months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |   |   |  |
| Age continuous<br>Units: years  |   |   |  |
| arithmetic mean   | 57.3  | 58.6  | 59.2   |
| standard deviation  | ± 11.98   | ± 14.18   | ± 10.31  |
| Gender categorical<br>Units: Subjects   |   |   |  |
| Female  | 16  | 20  | 16   |
| Male  | 27  | 50  | 17   |
| Ethnicity (NIH/OMB)<br>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<br>Avatrombopag<br>(higher baseline<br>platelet count) | Total |  |
|---|--|-------|--|
| Number of subjects                                    | 58   | 204   |  |
| Age categorical                                       |  |       |  |
| Units: Subjects                                       |  |       |  |
| In utero  |  | 0     |  |
| Preterm newborn infants<br>(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:<br>Participants with a baseline platelet count of less than $40 \times 10^9/\text{L}$ 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:<br>Participants with a baseline platelet count of less than $40 \times 10^9/\text{L}$ 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:<br>Participants with a baseline platelet count of greater than or equal to 40 to $50 \times 10^9/\text{L}$ 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:<br>Participants with a baseline platelet count of greater than or equal to 40 to $50 \times 10^9/\text{L}$ 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:<br>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:<br>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

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | 60 mg Placebo versus 60 mg Avatrombopag  |
| Statistical analysis description:<br>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 <sup>[1]</sup>   |
| P-value   | = 0.0006 <sup>[2]</sup>  |
| 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.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | 40 mg Placebo versus 40 mg Avatrombopag  |
| Statistical analysis description:<br>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 <sup>[3]</sup>   |
| P-value   | < 0.0001 <sup>[4]</sup>  |
| 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 $50 \times 10^9/L$ on Scheduled Procedure Day

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

End point description:

Responders were defined as participants who achieved a platelet count greater than or equal to  $50 \times 10^9/L$  on the procedure day. Participants missing a platelet count on the procedure day were conservatively considered as not achieving a platelet count of  $50 \times 10^9/L$  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<br>(lower baseline<br>platelet count) | 60 mg<br>Avatrombopag<br>(lower baseline<br>platelet count) | 40 mg Placebo<br>(higher<br>baseline<br>platelet count) | 40 mg<br>Avatrombopag<br>(higher<br>baseline<br>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<br>14.6)                                | 67.1 (56.1 to<br>78.1)                                      | 39.4 (22.7 to<br>56.1)                                  | 93.1 (86.6 to<br>99.6)  |

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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 <sup>[5]</sup>   |
| P-value                                 | < 0.0001 <sup>[6]</sup>  |
| 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.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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 <sup>[7]</sup>   |
| P-value                                 | < 0.0001 <sup>[8]</sup>  |
| 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 <sup>9</sup> |   |  |  |   |
| 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 <sup>[9]</sup>             |
| P-value                                 | < 0.0001 <sup>[10]</sup>               |
| 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.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[11]</sup>  |
| P-value                                 | < 0.0001 <sup>[12]</sup>   |
| 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

| <b>End point values</b>           | 60 mg Placebo<br>(lower baseline<br>platelet count) | 60 mg<br>Avatrombopag<br>(lower baseline<br>platelet count) | 40 mg Placebo<br>(higher<br>baseline<br>platelet count) | 40 mg<br>Avatrombopag<br>(higher<br>baseline<br>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

| <b>End point values</b>                     | 60 mg Placebo<br>(lower baseline<br>platelet count) | 60 mg<br>Avatrombopag<br>(lower baseline<br>platelet count) | 40 mg Placebo<br>(higher<br>baseline<br>platelet count) | 40 mg<br>Avatrombopag<br>(higher<br>baseline<br>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  $40 \times 10^9/L$  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  $40 \times 10^9/L$  (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  $50 \times 10^9/L$  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  $50 \times 10^9/L$  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<br>(lower baseline platelet count) | 60 mg<br>Avatrombopag<br>(lower baseline platelet count) | 40 mg Placebo<br>(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          |

|   |  |  |  |
|---|--|--|--|
| <b>Serious adverse events</b>                     | 40 mg<br>Avatrombopag<br>(higher baseline<br>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<br>Hepatic encephalopathy<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | 0 / 57 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| General disorders and administration site conditions<br>Multiple organ dysfunction syndrome<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 0 / 57 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Gastrointestinal disorders<br>Haematemesis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | 0 / 57 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Ileus paralytic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 57 (1.75%)<br>0 / 1<br>0 / 0 |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Acute respiratory failure<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                | 1 / 57 (1.75%)<br>0 / 1<br>0 / 0 |  |  |

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

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

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)        | 1 / 43 (2.33%)<br>1 | 0 / 70 (0.00%)<br>0 | 2 / 33 (6.06%)<br>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<br>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                   |

|  |  |  |  |
|--|--|--|--|
| <b>Non-serious adverse events</b>                        | 40 mg<br>Avatrombopag<br>(higher baseline<br>platelet count) |  |  |
| Total subjects affected by non-serious<br>adverse events |  |  |  |
| subjects affected / exposed                              | 14 / 57 (24.56%)   |  |  |
| Injury, poisoning and procedural<br>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<br>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<br>occurrences (all)  | 3 / 57 (5.26%)<br>3 |  |  |
| Renal and urinary disorders<br>Haematuria<br>subjects affected / exposed<br>occurrences (all) | 0 / 57 (0.00%)<br>0 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 12 November 2013 | <ul style="list-style-type: none"><li>• Addition of tranexamic acid as a rescue procedure for bleeding as requested by the European Union (EU) regulatory agency.</li></ul>  |
| 22 June 2015     | <ul style="list-style-type: none"><li>• Updates to the bleeding risk category classification and revision to the exclusion criteria based on feedback received from the investigators.</li><li>• 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).</li><li>• 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.</li></ul> |
| 31 May 2016      | <ul style="list-style-type: none"><li>• Clarification to Inclusion Criterion #3: the word "change" was replaced with the word "increase" as requested by the Food and Drug Administration (FDA).</li></ul>   |
| 02 December 2016 | <ul style="list-style-type: none"><li>• The third secondary endpoint, the proportion of participants with a World Health Organization (WHO) bleeding score <math>\geq 2</math> after randomization and up to 7 days following a scheduled procedure, was changed to an exploratory endpoint.</li><li>• This amendment also reduced the sample size from 300 to 200 participants.</li></ul>   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported