



## Clinical trial results:

**EXTEND (Eltrombopag eXTENDED Dosing Study): An extension study of eltrombopag olamine (SB-497115-GR) in adults, with idiopathic thrombocytopenic purpura (ITP), previously enrolled in an eltrombopag study.**

### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2006-000471-14                               |
| Trial protocol           | SI SE DE ES IE NL GR FR SK GB CZ DK IT FI AT |
| Global end of trial date | 06 July 2015                                 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 22 July 2016 |
| First version publication date | 22 July 2016 |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | TRA105325 |
|-----------------------|-----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00351468 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

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                       | 06 July 2015 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 06 July 2015 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 06 July 2015 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to describe the long-term safety and tolerability of oral eltrombopag treatment of subjects with ITP with or without concomitant ITP medication

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Rescue medication, defined as the addition of new therapies intended to raise the platelet count, including medications, platelet transfusions, splenectomy or the increase of the dose of any concomitant ITP medications was allowed at any time the investigator deemed it necessary.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 23 June 2006 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Australia: 6          |
| Country: Number of subjects enrolled | Austria: 2            |
| Country: Number of subjects enrolled | Canada: 8             |
| Country: Number of subjects enrolled | China: 10             |
| Country: Number of subjects enrolled | Czech Republic: 6     |
| Country: Number of subjects enrolled | Denmark: 3            |
| Country: Number of subjects enrolled | Finland: 1            |
| Country: Number of subjects enrolled | France: 7             |
| Country: Number of subjects enrolled | Germany: 25           |
| Country: Number of subjects enrolled | Greece: 3             |
| Country: Number of subjects enrolled | Hong Kong: 19         |
| Country: Number of subjects enrolled | Italy: 5              |
| Country: Number of subjects enrolled | Korea, Republic of: 4 |
| Country: Number of subjects enrolled | Netherlands: 10       |
| Country: Number of subjects enrolled | New Zealand: 9        |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Pakistan: 4            |
| Country: Number of subjects enrolled | Peru: 11               |
| Country: Number of subjects enrolled | Poland: 17             |
| Country: Number of subjects enrolled | Romania: 2             |
| Country: Number of subjects enrolled | Russian Federation: 29 |
| Country: Number of subjects enrolled | Slovakia: 2            |
| Country: Number of subjects enrolled | Spain: 8               |
| Country: Number of subjects enrolled | Sweden: 3              |
| Country: Number of subjects enrolled | Taiwan: 2              |
| Country: Number of subjects enrolled | Thailand: 2            |
| Country: Number of subjects enrolled | Tunisia: 22            |
| Country: Number of subjects enrolled | Ukraine: 7             |
| Country: Number of subjects enrolled | United Kingdom: 10     |
| Country: Number of subjects enrolled | United States: 62      |
| Country: Number of subjects enrolled | Vietnam: 3             |
| Worldwide total number of subjects   | 302                    |
| EEA total number of subjects         | 104                    |

Notes:

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### 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)                      | 252 |
| From 65 to 84 years                       | 49  |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Subjects were previously enrolled in a study of eltrombopag: TRA100773A, TRA100773B, TRA102537/RAISE, or TRA108057/REPEAT. Eligibility of consenting subjects was assessed during the screening period of up to 28 days prior to Day 1 of treatment.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|           |             |
|-----------|-------------|
| Arm title | Eltrombopag |
|-----------|-------------|

Arm description:

Open-label eltrombopag was supplied in 25 or 50 mg tablets. All subjects started at 50mg once daily and dose was increased or decreased based on platelet count (target range 50-200Gi/L). Alternate days and interruption of dosing was permitted to maintain target range of platelet count. Doses could range from 25 to 75mg. Subjects could remain on treatment up to 2 years.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Eltrombopag   |
| Investigational medicinal product code | SB-497115     |
| Other name                             |               |
| Pharmaceutical forms                   | Coated tablet |
| Routes of administration               | Oral use      |

Dosage and administration details:

Dosing started at 50 mg daily and could be adjusted by the investigator from 25mg to 75 or less than daily depending on platelet counts

| Number of subjects in period 1     | Eltrombopag       |
|------------------------------------|-------------------|
| Started                            | 302               |
| Subjects from TRA100773A           | 51 <sup>[1]</sup> |
| Subjects from TRA100773B           | 61 <sup>[2]</sup> |
| Subjects from TRA102537 Raise      | 146               |
| Subjects from TRA108057 Repeat     | 43 <sup>[3]</sup> |
| Completed                          | 135               |
| Not completed                      | 167               |
| Consent withdrawn by subject       | 39                |
| Adverse event, non-fatal           | 42                |
| Non-compliance                     | 8                 |
| Various -follow up w clinical team | 39                |

|                    |    |
|--------------------|----|
| Lost to follow-up  | 4  |
| Lack of efficacy   | 32 |
| Protocol deviation | 3  |

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: All subjects enrolled in this trial were previously enrolled in one of three eltrombopag trials. Milestones were created to provide number of participants from each of the three trials.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: All subjects enrolled in this trial were previously enrolled in one of three eltrombopag trials. Milestones were created to provide number of participants from each of the three trials.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: All subjects enrolled in this trial were previously enrolled in one of three eltrombopag trials. Milestones were created to provide number of participants from each of the three trials.

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Eltrombopag |
|-----------------------|-------------|

Reporting group description:

Open-label eltrombopag was supplied in 25 or 50 mg tablets. All subjects started at 50mg once daily and dose was increased or decreased based on platelet count (target range 50-200Gi/L). Alternate days and interruption of dosing was permitted to maintain target range of platelet count. Doses could range from 25 to 75mg. Subjects could remain on treatment up to 2 years.

| Reporting group values                             | Eltrombopag | Total |  |
|--|-------------|-------|--|
| Number of subjects                                 | 302         | 302   |  |
| Age categorical                                    |             |       |  |
| Units: Subjects                                    |             |       |  |
| In utero   | 0           | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0           | 0     |  |
| Newborns (0-27 days)                               | 0           | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0           | 0     |  |
| Children (2-11 years)                              | 0           | 0     |  |
| Adolescents (12-17 years)                          | 0           | 0     |  |
| Adults (18-64 years)                               | 252         | 252   |  |
| From 65-84 years                                   | 49          | 49    |  |
| 85 years and over                                  | 1           | 1     |  |
| Age Continuous                                     |             |       |  |
| Units: Years                                       |             |       |  |
| arithmetic mean                                    | 48.9        |       |  |
| standard deviation                                 | ± 15.61     | -     |  |
| Gender, Male/Female                                |             |       |  |
| Units: Participants                                |             |       |  |
| Female   | 201         | 201   |  |
| Male   | 101         | 101   |  |
| Concomitant ITP Medication at Baseline             |             |       |  |
| Units: Subjects                                    |             |       |  |
| Yes  | 101         | 101   |  |
| No   | 201         | 201   |  |
| Splenectomy Status at Baseline                     |             |       |  |
| Units: Subjects                                    |             |       |  |
| Yes  | 115         | 115   |  |
| No   | 187         | 187   |  |
| Baseline Platelet Count                            |             |       |  |
| Units: Subjects                                    |             |       |  |
| <30 Gi/L   | 211         | 211   |  |
| 30 - 50 Gi/L                                       | 52          | 52    |  |
| > 50 Gi/L  | 39          | 39    |  |

## End points

### End points reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Eltrombopag |
| Reporting group description:<br>Open-label eltrombopag was supplied in 25 or 50 mg tablets. All subjects started at 50mg once daily and dose was increased or decreased based on platelet count (target range 50-200Gi/L). Alternate days and interruption of dosing was permitted to maintain target range of platelet count. Doses could range from 25 to 75mg. Subjects could remain on treatment up to 2 years. |             |

### Primary: Safety and tolerability parameters including, clinical laboratory tests, ocular examinations, and frequency of all adverse events

|                 |  |
|-----------------|--|
| End point title | Safety and tolerability parameters including, clinical laboratory tests, ocular examinations, and frequency of all adverse events <sup>[1]</sup> |
|-----------------|--|

End point description:

See Safety Section

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

through study completion estimated to be approximately 5 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This was an open-label study and hence no formal statistical hypothesis tests were done.

|                                     |                 |  |  |  |
|-------------------------------------|-----------------|--|--|--|
| <b>End point values</b>             | Eltrombopag     |  |  |  |
| Subject group type                  | Reporting group |  |  |  |
| Number of subjects analysed         | 302             |  |  |  |
| Units: Incidences of Adverse Events | 302             |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Subjects Achieving Maximum Platelet Counts Greater Than or Equal to 30 Gi/L or 50 Gi/L in the Absence of Rescue Medication

|                 |  |
|-----------------|--|
| End point title | Subjects Achieving Maximum Platelet Counts Greater Than or Equal to 30 Gi/L or 50 Gi/L in the Absence of Rescue Medication |
|-----------------|--|

End point description:

Subjects who achieved maximum platelet count at least once during treatment. All platelet counts after an on-study splenectomy are not classed as responses. Platelet counts within 7 days after a platelet transfusion are not classed as responses. Platelet counts while taking an increased ITP medication or within 6 weeks after the end of an increased ITP medication are not classed as responses.

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

End point timeframe:

Baseline up to 2 years

|  |                 |  |  |  |
|--|-----------------|--|--|--|
| <b>End point values</b>                  | Eltrombopag     |  |  |  |
| Subject group type                       | Reporting group |  |  |  |
| Number of subjects analysed              | 302             |  |  |  |
| Units: Participants                      |                 |  |  |  |
| Baseline Platelet counts $\geq$ 30 Gi/L, | 91              |  |  |  |
| Baseline Platelet counts $\geq$ 50 Gi/L, | 42              |  |  |  |
| Maximum Platelet Count $\geq$ 30 Gi/L    | 276             |  |  |  |
| Maximum Platelet Count $\geq$ 50 Gi/L    | 259             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Summary of Subjects Achieving Platelet Count Levels by Week, in the Absence of Rescue Medication

|                 |  |
|-----------------|--|
| End point title | Summary of Subjects Achieving Platelet Count Levels by Week, in the Absence of Rescue Medication |
|-----------------|--|

End point description:

If a subject has more than 1 platelet count result within a week, the lowest value observed is used to determine response. All platelet counts after an on-study splenectomy are not classed as responses. Platelet counts within 7 days after a platelet transfusion are not classed as responses. Platelet counts while taking an increased ITP medication or within 6 weeks after the end of an increased ITP medication are not classed as responses.

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

End point timeframe:

Baseline up to Year 7/Week 364

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| <b>End point values</b>                           | Eltrombopag     |  |  |  |
| Subject group type                                | Reporting group |  |  |  |
| Number of subjects analysed                       | 302             |  |  |  |
| Units: Participants                               |                 |  |  |  |
| Baseline Platelet counts $\geq$ 30 Gi/L,<br>n=302 | 91              |  |  |  |
| Baseline Platelet counts $\geq$ 50 Gi/L,<br>n=302 | 42              |  |  |  |
| Week 1 Platelet Count $\geq$ 30 Gi/L<br>n=293     | 172             |  |  |  |
| Week 1 Platelet Count $\geq$ 50 Gi/L<br>n=293     | 127             |  |  |  |
| Week 2 Platelet Count $\geq$ 30 Gi/L<br>n=288     | 199             |  |  |  |
| Week 2 Platelet Count $\geq$ 50 Gi/L<br>n=288     | 165             |  |  |  |
| Week 3 Platelet Count $\geq$ 30 Gi/L<br>n=275     | 192             |  |  |  |



|   |     |  |  |  |
|---|-----|--|--|--|
| Week 3 Platelet Count >= 50 Gi/L<br>n=275           | 159 |  |  |  |
| Week 4 Platelet Count >= 30 Gi/L<br>n=275           | 192 |  |  |  |
| Week 4 Platelet Count >= 50 Gi/L<br>n=275           | 149 |  |  |  |
| Week 5 Platelet Count >= 30 Gi/L<br>n=274           | 197 |  |  |  |
| Week 5 Platelet Count >= 50 Gi/L<br>n=274           | 159 |  |  |  |
| Week 6 Platelet Count >= 30 Gi/L<br>n=276           | 203 |  |  |  |
| Week 6 Platelet Count >= 50 Gi/L<br>n=276           | 169 |  |  |  |
| Week 12 Platelet Count >= 30 Gi/L<br>n=197          | 147 |  |  |  |
| Week 12 Platelet Count >= 50 Gi/L<br>n=197          | 120 |  |  |  |
| Month 6/Week 26 Platelet Count >= 30<br>Gi/L n=130  | 93  |  |  |  |
| Month 6/Week 26 Platelet Count >= 50<br>Gi/L n=130  | 82  |  |  |  |
| Year 1/Week 52 Platelet Count >= 30<br>Gi/L n=83    | 62  |  |  |  |
| Year 1/Week 52 Platelet Count >= 50<br>Gi/L n=83    | 50  |  |  |  |
| Year 1.5/Week 78 Platelet Count >= 30<br>Gi/L n=63  | 47  |  |  |  |
| Year 1.5/Week 78 Platelet Count >= 50<br>Gi/L n=63  | 41  |  |  |  |
| Year 2/Week 104 Platelet Count >= 30<br>Gi/L n=59   | 46  |  |  |  |
| Year 2/Week 104 Platelet Count >= 50<br>Gi/L n=59   | 42  |  |  |  |
| Year 2.5/Week 130 Platelet Count >= 30<br>Gi/L n=42 | 32  |  |  |  |
| Year 2.5/Week 130 Platelet Count >= 50<br>Gi/L n=42 | 28  |  |  |  |
| Year 3/Week 156 Platelet Count >= 30<br>Gi/L n=27   | 22  |  |  |  |
| Year 3/Week 156 Platelet Count >= 50<br>Gi/L n=27   | 19  |  |  |  |
| Year 3.5/Week 182 Platelet Count >= 30<br>Gi/L n=23 | 19  |  |  |  |
| Year 3.5/Week 182 Platelet Count >= 50<br>Gi/L n=23 | 17  |  |  |  |
| Year 4/Week 208 Platelet Count >= 30<br>Gi/L n=17   | 12  |  |  |  |
| Year 4/Week 208 Platelet Count >= 50<br>Gi/L n=17   | 11  |  |  |  |
| Year 4.5/Week 234 Platelet Count >= 30<br>Gi/L n=15 | 13  |  |  |  |
| Year 4.5/Week 234 Platelet Count >= 50<br>Gi/L n=15 | 12  |  |  |  |
| Year 5/Week 260 Platelet Count >= 30<br>Gi/L n=9    | 6   |  |  |  |
| Year 5/Week 260 Platelet Count >= 50<br>Gi/L n=9    | 6   |  |  |  |
| Year 5.5/Week 286 Platelet Count >= 30<br>Gi/L n=9  | 7   |  |  |  |
| Year 5.5/Week 286 Platelet Count >= 50<br>Gi/L n=9  | 7   |  |  |  |

|   |   |  |  |  |
|---|---|--|--|--|
| Year 6/Week 312 Platelet Count $\geq$ 30 Gi/L n=9   | 7 |  |  |  |
| Year 6/Week 312 Platelet Count $\geq$ 50 Gi/L n=9   | 7 |  |  |  |
| Year 6.5/Week 338 Platelet Count $\geq$ 30 Gi/L n=5 | 3 |  |  |  |
| Year 6.5/Week 338 Platelet Count $\geq$ 50 Gi/L n=5 | 3 |  |  |  |
| Year 7/Week 364 Platelet Count $\geq$ 30 Gi/L n=3   | 3 |  |  |  |
| Year 7/Week 364 Platelet Count $\geq$ 50 Gi/L n=3   | 3 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects who responded to eltrombopag in a previous study and who respond to retreatment with a rise in platelet count to either $\geq 50,000/\mu\text{L}$ or $\geq 30,000/\mu\text{L}$

|                 |   |
|-----------------|---|
| End point title | Number of subjects who responded to eltrombopag in a previous study and who respond to retreatment with a rise in platelet count to either $\geq 50,000/\mu\text{L}$ or $\geq 30,000/\mu\text{L}$ |
|-----------------|---|

End point description:

- Responder in TRA100773: Platelet count 50 Gi/L and 2 x baseline (BL) at last on-treatment assessment. Responders in EXTEND: Platelet count 50 Gi/L and 2 x baseline (BL), 50 Gi/L, and 30 Gi/L at any time. - Responder in RAISE: Platelet count 50 Gi/L and 2 x baseline at Week 6 assessment. Responders in EXTEND: Platelet count 50 Gi/L and 2 x baseline, 50 Gi/L, and 30 Gi/L at any time. - Responder in REPEAT: Platelet count 50 Gi/L and 2 x baseline (BL) at Week 6 assessment in Cycle 1. Responders in EXTEND: Platelet count 50 Gi/L and 2 x baseline (BL), 50 Gi/L, and 30 Gi/L at any time.

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

End point timeframe:

Baseline up to 2 years

| End point values                                    | Eltrombopag     |  |  |  |
|---|-----------------|--|--|--|
| Subject group type                                  | Reporting group |  |  |  |
| Number of subjects analysed                         | 302             |  |  |  |
| Units: Participants                                 |                 |  |  |  |
| TRA100773 Responders $\geq$ 50 Gi/L in EXTEND, n=51 | 49              |  |  |  |
| TRA100773 $\geq$ 50 Gi/L and 2 x BL in EXTEND, n=51 | 47              |  |  |  |
| TRA100773 Responders $\geq$ 30 Gi/L in EXTEND, n=51 | 49              |  |  |  |
| RAISE Responders $\geq$ 50 Gi/L in EXTEND, n=59     | 54              |  |  |  |
| RAISE $\geq$ 50 Gi/L and 2 x BL in EXTEND, n=59     | 53              |  |  |  |
| RAISE Responders $\geq$ 30 Gi/L in EXTEND, n=51     | 55              |  |  |  |
| REPEAT Responders $\geq$ 50 Gi/L in EXTEND, n=36    | 33              |  |  |  |

|   |    |  |  |  |
|---|----|--|--|--|
| REPEAT $\geq$ 50 Gi/L and 2 x BL in<br>EXTEND, n=36 | 33 |  |  |  |
| REPEAT Responders $\geq$ 30 Gi/L in<br>EXTEND, n=36 | 35 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with reduction and/or sparing of concomitant ITP therapies, while maintaining a platelet count $\geq$ 50,000/mL.

|                 |   |
|-----------------|---|
| End point title | Number of participants with reduction and/or sparing of concomitant ITP therapies, while maintaining a platelet count $\geq$ 50,000/mL. |
|-----------------|---|

End point description:

Sustain reduct = Sustained reduction[1] Denominator is number of subjects taking an ITP medication at baseline. [2] Denominator is number of subjects with a sustained reduction. Note: Sustained reduction defined as reduction from baseline in dose and/or frequency which is maintained for at least 4 weeks. Excludes sustained reductions started more than 1 day after last dose.

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

End point timeframe:

For at least 2 years

| End point values                                  | Eltrombopag     |  |  |  |
|---|-----------------|--|--|--|
| Subject group type                                | Reporting group |  |  |  |
| Number of subjects analysed                       | 302             |  |  |  |
| Units: Participants                               |                 |  |  |  |
| ITP medication at baseline                        | 101             |  |  |  |
| Sustain reduct or stopping at least 1 ITP med [1] | 71              |  |  |  |
| Permanently stopping at least 1 ITP med [1]       | 53              |  |  |  |
| Sustained reduction[1]                            | 70              |  |  |  |
| Maximum sustained reduction $\geq$ 24 weeks[2]    | 66              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects who required Rescue Therapy during treatment with eltrombopag.

|                 |   |
|-----------------|---|
| End point title | Number of subjects who required Rescue Therapy during treatment with eltrombopag. |
|-----------------|---|

End point description:

Rescue treatment is defined as a composite of: new ITP medication, increased dose of a concomitant ITP medication, platelet transfusion, and splenectomy. Subjects may have received more than 1 type of rescue therapy

|                        |           |
|------------------------|-----------|
| End point type         | Secondary |
| End point timeframe:   |           |
| Baseline up to 2 years |           |

|  |                 |  |  |  |
|--|-----------------|--|--|--|
| <b>End point values</b>                          | Eltrombopag     |  |  |  |
| Subject group type                               | Reporting group |  |  |  |
| Number of subjects analysed                      | 302             |  |  |  |
| Units: Participants                              |                 |  |  |  |
| New ITP medication, n=103                        | 82              |  |  |  |
| Increase in dose of ITP med from baseline, n=103 | 27              |  |  |  |
| Platelet transfusion, n=103                      | 21              |  |  |  |
| Splenectomy, n=103                               | 3               |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum ITP Bleeding Score at any time during the study during all stages.

|                 |  |
|-----------------|--|
| End point title | Maximum ITP Bleeding Score at any time during the study during all stages. |
|-----------------|--|

End point description:

The ITP bleeding score is a tool which has been designed specifically to assess the bruising and bleeding in patients with ITP across body sites, ranging from mild to severe. The WHO Grades were dichotomized into the following categories: Grade 0: No bleeding Grade 1 to 4: Any bleeding Grade 0 to 1: No clinically significant bleeding Grade 2 to 4: Clinically significant bleeding

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

End point timeframe:

Baseline up to 2 years

|                                |                 |  |  |  |
|--------------------------------|-----------------|--|--|--|
| <b>End point values</b>        | Eltrombopag     |  |  |  |
| Subject group type             | Reporting group |  |  |  |
| Number of subjects analysed    | 302             |  |  |  |
| Units: Participants            |                 |  |  |  |
| Epistaxis n=300 Grade 0        | 204             |  |  |  |
| Epistaxis n=300 Grade 1        | 65              |  |  |  |
| Epistaxis n=300 Grade 2        | 31              |  |  |  |
| Gastrointestinal n=300 Grade 0 | 264             |  |  |  |
| Gastrointestinal n=300 Grade 1 | 26              |  |  |  |
| Gastrointestinal n=300 Grade 2 | 10              |  |  |  |
| Genitourinary n=300 Grade 0    | 262             |  |  |  |
| Genitourinary n=300 Grade 1    | 29              |  |  |  |
| Genitourinary n=300 Grade 2    | 9               |  |  |  |
| Gynecologic n=108 Grade 0      | 68              |  |  |  |

|  |     |  |  |  |
|--|-----|--|--|--|
| Gynecologic n=108 Grade 1              | 15  |  |  |  |
| Gynecologic n=108 Grade 2              | 25  |  |  |  |
| Intracerebral hemorrhage n=300 Grade 0 | 297 |  |  |  |
| Intracerebral hemorrhage n=300 Grade 1 | 3   |  |  |  |
| Intracerebral hemorrhage n=300 Grade 2 | 0   |  |  |  |
| Ocular n=300 Grade 0                   | 258 |  |  |  |
| Ocular n=300 Grade 1                   | 37  |  |  |  |
| Ocular n=300 Grade 2                   | 5   |  |  |  |
| Oral n=300 Grade 0                     | 191 |  |  |  |
| Oral n=300 Grade 1                     | 81  |  |  |  |
| Oral n=300 Grade 2                     | 28  |  |  |  |
| Pulmonary n=300 Grade 0                | 287 |  |  |  |
| Pulmonary n=300 Grade 1                | 13  |  |  |  |
| Pulmonary n=300 Grade 2                | 0   |  |  |  |
| Skin, ecchymosis n=300 Grade 0         | 74  |  |  |  |
| Skin, ecchymosis n=300 Grade 1         | 159 |  |  |  |
| Skin, ecchymosis n=300 Grade 2         | 67  |  |  |  |
| Skin, petechiae n=300 Grade 0          | 142 |  |  |  |
| Skin, petechiae n=300 Grade 1          | 126 |  |  |  |
| Skin, petechiae n=300 Grade 2          | 32  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Best Post-Baseline Change in SF-36v2 Questionnaire Score Compared with Baseline - All Patients

|                 |  |
|-----------------|--|
| End point title | Best Post-Baseline Change in SF-36v2 Questionnaire Score Compared with Baseline - All Patients |
|-----------------|--|

End point description:

The SF-36v2 assessment tool was used to obtain information about subjects' general health status and health-related quality of life. The tool was to be completed by each subject prior to any other intervention, including physician interaction, at the baseline visit, prior to completion of a Stage, and upon withdrawal or completion of the study. Until a formal assessment of minimal clinically important differences (MCID) is performed, changes from baseline of more than 0.5 standard deviations are suggested as clinically meaningful. Scores were transformed to a 0-100 point scale, with higher scores representing more positive answers. Scores were normalized to have a mean of 50 and SD of 10 to allow for comparison with outcomes from other chronic diseases. Recall period is the past week prior to administration.

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

End point timeframe:

Baseline, transitioning between stages, withdrawal/completion of study up to two years

| End point values                           | Eltrombopag         |  |  |  |
|--|---------------------|--|--|--|
| Subject group type                         | Reporting group     |  |  |  |
| Number of subjects analysed                | 302                 |  |  |  |
| Units: Points on a scale                   |                     |  |  |  |
| arithmetic mean (confidence interval 95%)  |                     |  |  |  |
| SF-36v2 Physical function (n=273)          | 12 (9.6 to 14.5)    |  |  |  |
| SF-36v2 Physical role (n=273)              | 14.2 (11.5 to 16.9) |  |  |  |
| SF-36v2 Bodily pain (n=273)                | 14.5 (11.6 to 17.4) |  |  |  |
| SF-36v2 General health (n=273)             | 11.1 (9 to 13.1)    |  |  |  |
| SF-36v2 Vitality (n=290)                   | 13.9 (11.6 to 16.3) |  |  |  |
| SF-36v2 Social function (n=290)            | 12.6 (10.2 to 15.1) |  |  |  |
| SF-36v2 Emotional role (n=290)             | 11.4 (8.7 to 14)    |  |  |  |
| SF-36v2 Mental health (n=290)              | 11.3 (9.4 to 13.3)  |  |  |  |
| SF-36v2 Physical component summary (n=273) | 5.3 (4.5 to 6.2)    |  |  |  |
| SF-36v2 Mental component summary (n=290)   | 5.8 (4.6 to 6.9)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Best Post-Baseline Change in the short form of the Motivation and Energy Scale (MEI-SF) compared with Baseline - All Patients

|                 |   |
|-----------------|---|
| End point title | Best Post-Baseline Change in the short form of the Motivation and Energy Scale (MEI-SF) compared with Baseline - All Patients |
|-----------------|---|

End point description:

The MEI-SF (18 questions) was used to measure the reductions in mental energy, physical energy, and social motivation, either as symptoms of chronic ITP or as a side effect of pharmacotherapy. Minimal clinically important differences are estimated as 0.5 standard deviations or 7.5 points. All items use either a 7-level (0 to 6) or 5-level (0 to 4) response scale; items with a 5-level response scale were rescaled to 7-levels, and items were reverse-scored as necessary such that higher scores represent higher HRQoL. Total score ranges from 0 to 108 points. Recall period is past week prior to administration. n=292

|                      |  |
|----------------------|--|
| End point type       | Secondary  |
| End point timeframe: | Baseline, transitioning between stages, withdrawal/completion of study up to two years |

|   |                    |  |  |  |
|---|--------------------|--|--|--|
| <b>End point values</b>                   | Eltrombopag        |  |  |  |
| Subject group type                        | Reporting group    |  |  |  |
| Number of subjects analysed               | 302                |  |  |  |
| Units: Points on a scale                  |                    |  |  |  |
| arithmetic mean (confidence interval 95%) | 11.2 (9.1 to 13.5) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Best Post-Baseline Change in the FACIT-Fatigue 13 Item Subscale Score Baseline, prior to completion of a Stage, and upon withdrawal or at completion of the study - All Patients

|                 |  |
|-----------------|--|
| End point title | Best Post-Baseline Change in the FACIT-Fatigue 13 Item Subscale Score Baseline, prior to completion of a Stage, and upon withdrawal or at completion of the study - All Patients |
|-----------------|--|

End point description:

The FACIT-Fatigue consists of 13 questions in which patients rate the frequency (0-4) of symptoms of fatigue, in terms of tiredness, weakness, and fatigue. Items were reverse-scored as necessary such that higher scores represent higher HRQoL. Total score ranges from 0 to 52. Using anchor-based estimates, the minimally important difference in this subscale is 3.0 points. Recall period is past week prior to administration.

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

End point timeframe:

Baseline, prior to completion of a Stage, and upon withdrawal or at completion of the study up to 2 years

|   |                  |  |  |  |
|---|------------------|--|--|--|
| <b>End point values</b>                   | Eltrombopag      |  |  |  |
| Subject group type                        | Reporting group  |  |  |  |
| Number of subjects analysed               | 302              |  |  |  |
| Units: Points on a scale                  |                  |  |  |  |
| arithmetic mean (confidence interval 95%) | 6.9 (5.7 to 8.1) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Best Post-Baseline Change in the FACT-TH6 (Baseline, prior to completion of a Stage, and upon withdrawal or at completion of the study) - All Patients

|                 |  |
|-----------------|--|
| End point title | Best Post-Baseline Change in the FACT-TH6 (Baseline, prior to completion of a Stage, and upon withdrawal or at completion of the study) - All Patients |
|-----------------|--|

End point description:

The FACT-TH6 consists of 6 questions in which patients rate (0-4) their general degree of worry related

to bleeding and bruising, and resulting activity impairment and frustration. Although the six items do not constitute a formal domain or subscale of the FACTTh assessment tool, these items had been identified by focus groups of patients with chronic ITP as important indicators of their HRQoL. Items were reverse-scored as necessary such that higher scores represent higher HRQoL. Total scores ranged from 0 to 24. Recall period is not specified. n=288

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

End point timeframe:

Baseline, transitioning between stages, withdrawal/completion of study up to two years

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| <b>End point values</b>                   | Eltrombopag     |  |  |  |
| Subject group type                        | Reporting group |  |  |  |
| Number of subjects analysed               | 302             |  |  |  |
| Units: Points on a scale                  |                 |  |  |  |
| arithmetic mean (confidence interval 95%) | 4 (3.4 to 4.6)  |  |  |  |

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment + 1 Day: start date was between the first dose of investigational product and up to the day after the last dose . Post-therapy: start date was more than 1 day after the last dose and up to 30 days after last dose of investigational product

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.0   |

### Reporting groups

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Eltrombopag, Treatment + 1 day |
|-----------------------|--------------------------------|

Reporting group description:

Eltrombopag, Treatment + 1 day

|                       |   |
|-----------------------|---|
| Reporting group title | Eltrombopag, gt 1 to 30 Days Post-Therapy |
|-----------------------|---|

Reporting group description:

Eltrombopag, gt 1 to 30 Days Post-Therapy

| Serious adverse events  | Eltrombopag,<br>Treatment + 1 day | Eltrombopag, gt 1 to<br>30 Days Post-<br>Therapy |  |
|---|-----------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                   |  |  |
| subjects affected / exposed   | 96 / 302 (31.79%)                 | 10 / 302 (3.31%)                                 |  |
| number of deaths (all causes)                                       | 3                                 | 0  |  |
| number of deaths resulting from adverse events                      | 0                                 | 0  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                   |  |  |
| Adenocarcinoma  |                                   |  |  |
| subjects affected / exposed   | 1 / 302 (0.33%)                   | 0 / 302 (0.00%)                                  |  |
| occurrences causally related to treatment / all                     | 0 / 1                             | 0 / 0  |  |
| deaths causally related to treatment / all                          | 0 / 1                             | 0 / 0  |  |
| B-cell unclassifiable lymphoma low grade                            |                                   |  |  |
| subjects affected / exposed   | 1 / 302 (0.33%)                   | 0 / 302 (0.00%)                                  |  |
| occurrences causally related to treatment / all                     | 0 / 1                             | 0 / 0  |  |
| deaths causally related to treatment / all                          | 0 / 0                             | 0 / 0  |  |
| Basal cell carcinoma  |                                   |  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Breast cancer                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hodgkin's disease                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphoma  |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ovarian cancer                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Papillary thyroid cancer                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transitional cell carcinoma                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Arteriovenous fistula                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                            |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 4 / 302 (1.32%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all      | 3 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Haematoma  |                 |                 |  |
| subjects affected / exposed                          | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Hypertension   |                 |                 |  |
| subjects affected / exposed                          | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Hypotension  |                 |                 |  |
| subjects affected / exposed                          | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Thrombophlebitis superficial                         |                 |                 |  |
| subjects affected / exposed                          | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Thrombosis   |                 |                 |  |
| subjects affected / exposed                          | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pregnancy, puerperium and perinatal conditions       |                 |                 |  |
| Ectopic pregnancy                                    |                 |                 |  |
| subjects affected / exposed                          | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Death   |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Gait disturbance                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Generalised oedema                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Local swelling                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Medical device pain                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Multi-organ failure                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Non-cardiac chest pain                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyrexia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Drug hypersensitivity                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Ovarian cyst ruptured                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 302 (0.00%) | 1 / 302 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Uterine polyp                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vaginal haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vaginal prolapse                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Asthma  |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 4 / 302 (1.32%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoptysis                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 302 (0.66%) | 1 / 302 (0.33%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary infarction                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 302 (0.00%) | 1 / 302 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mental status changes                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 302 (0.00%) | 1 / 302 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Alanine aminotransferase increased<br>subjects affected / exposed | 5 / 302 (1.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to<br>treatment / all                | 3 / 5           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           |  |
| Aspartate aminotransferase<br>increased                           |                 |                 |  |
| subjects affected / exposed                                       | 4 / 302 (1.32%) | 0 / 302 (0.00%) |  |
| occurrences causally related to<br>treatment / all                | 2 / 4           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           |  |
| Blood bilirubin increased   |                 |                 |  |
| subjects affected / exposed                                       | 4 / 302 (1.32%) | 0 / 302 (0.00%) |  |
| occurrences causally related to<br>treatment / all                | 2 / 4           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           |  |
| Hepatic enzyme increased  |                 |                 |  |
| subjects affected / exposed                                       | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to<br>treatment / all                | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           |  |
| Platelet count decreased  |                 |                 |  |
| subjects affected / exposed                                       | 3 / 302 (0.99%) | 0 / 302 (0.00%) |  |
| occurrences causally related to<br>treatment / all                | 0 / 3           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           |  |
| Transaminases increased   |                 |                 |  |
| subjects affected / exposed                                       | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to<br>treatment / all                | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural<br>complications                 |                 |                 |  |
| Brain contusion   |                 |                 |  |
| subjects affected / exposed                                       | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to<br>treatment / all                | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           |  |
| Cataract traumatic  |                 |                 |  |
| subjects affected / exposed                                       | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to<br>treatment / all                | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Eye injury                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femoral neck fracture                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Forearm fracture                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hip fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radius fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Road traffic accident                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Spinal cord injury                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arrhythmia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery occlusion                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 302 (0.00%) | 1 / 302 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mitral valve incompetence                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Supraventricular tachycardia                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 302 (0.00%) | 1 / 302 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tachyarrhythmia                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebral haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral infarction                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral ischaemia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 1 / 302 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Embolic cerebral infarction                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Memory impairment                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Optic neuritis                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraesthesia                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 302 (0.00%) | 1 / 302 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Presyncope                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subarachnoid haemorrhage                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Toxic neuropathy                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 5 / 302 (1.66%) | 1 / 302 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Bone marrow oedema                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemolytic anaemia                              |                 |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 302 (0.33%)  | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Immune thrombocytopenic purpura                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%)  | 1 / 302 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Neutropenia                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%)  | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Splenic cyst                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%)  | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Thrombocytopenia                                |                  |                 |  |
| subjects affected / exposed                     | 2 / 302 (0.66%)  | 1 / 302 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Eye disorders                                   |                  |                 |  |
| Cataract  |                  |                 |  |
| subjects affected / exposed                     | 16 / 302 (5.30%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 8 / 17           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cataract subcapsular                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%)  | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Choroidal neovascularisation                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%)  | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrointestinal disorders                      |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 302 (0.00%) | 1 / 302 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroduodenitis haemorrhagic                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gingival bleeding                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematemesis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhoidal haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhoids                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Incarcerated umbilical hernia                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine polyp                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Melaena   |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mouth haemorrhage                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal haemorrhage                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical hernia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hepatobiliary disorders</b>                  |                 |                 |  |
| Cholangitis acute                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gallbladder pain                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperbilirubinaemia                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Skin and subcutaneous tissue disorders</b>   |                 |                 |  |
| Erythema nodosum                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Swelling face                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Renal and urinary disorders</b>              |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Calculus urinary                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lupus nephritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal mass                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscle haemorrhage                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rotator cuff syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic sinusitis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis viral                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                                   | 2 / 302 (0.66%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Infective exacerbation of chronic obstructive airways disease |                 |                 |  |
| subjects affected / exposed                                   | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Influenza   |                 |                 |  |
| subjects affected / exposed                                   | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Kidney infection  |                 |                 |  |
| subjects affected / exposed                                   | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection                             |                 |                 |  |
| subjects affected / exposed                                   | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Paronychia  |                 |                 |  |
| subjects affected / exposed                                   | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Pneumonia   |                 |                 |  |
| subjects affected / exposed                                   | 8 / 302 (2.65%) | 1 / 302 (0.33%) |  |
| occurrences causally related to treatment / all               | 2 / 8           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 1           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                                   | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Septic shock  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Subcutaneous abscess                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tooth abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 3 / 302 (0.99%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Wound infection                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic ketoacidosis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperosmolar state                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) | 0 / 302 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Eltrombopag,<br>Treatment + 1 day | Eltrombopag, gt 1 to<br>30 Days Post-<br>Therapy |  |
|---|-----------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                                   |  |  |
| subjects affected / exposed                           | 253 / 302 (83.77%)                | 28 / 302 (9.27%)                                 |  |
| Investigations  |                                   |  |  |
| Alanine aminotransferase increased                    |                                   |  |  |
| subjects affected / exposed                           | 23 / 302 (7.62%)                  | 0 / 302 (0.00%)                                  |  |
| occurrences (all)                                     | 36                                | 0  |  |
| Aspartate aminotransferase increased                  |                                   |  |  |
| subjects affected / exposed                           | 21 / 302 (6.95%)                  | 0 / 302 (0.00%)                                  |  |
| occurrences (all)                                     | 37                                | 0  |  |
| Vascular disorders                                    |                                   |  |  |
| Hypertension  |                                   |  |  |
| subjects affected / exposed                           | 22 / 302 (7.28%)                  | 1 / 302 (0.33%)                                  |  |
| occurrences (all)                                     | 26                                | 1  |  |
| Nervous system disorders                              |                                   |  |  |
| Dizziness   |                                   |  |  |
| subjects affected / exposed                           | 26 / 302 (8.61%)                  | 0 / 302 (0.00%)                                  |  |
| occurrences (all)                                     | 34                                | 0  |  |
| Headache  |                                   |  |  |
| subjects affected / exposed                           | 86 / 302 (28.48%)                 | 3 / 302 (0.99%)                                  |  |
| occurrences (all)                                     | 178                               | 5  |  |
| Blood and lymphatic system disorders                  |                                   |  |  |
| Anaemia   |                                   |  |  |
| subjects affected / exposed                           | 26 / 302 (8.61%)                  | 1 / 302 (0.33%)                                  |  |
| occurrences (all)                                     | 62                                | 1  |  |

|  |                   |                 |  |
|--|-------------------|-----------------|--|
| General disorders and administration site conditions |                   |                 |  |
| Fatigue  |                   |                 |  |
| subjects affected / exposed                          | 50 / 302 (16.56%) | 4 / 302 (1.32%) |  |
| occurrences (all)                                    | 73                | 4               |  |
| Influenza like illness                               |                   |                 |  |
| subjects affected / exposed                          | 25 / 302 (8.28%)  | 1 / 302 (0.33%) |  |
| occurrences (all)                                    | 37                | 1               |  |
| Pyrexia  |                   |                 |  |
| subjects affected / exposed                          | 27 / 302 (8.94%)  | 2 / 302 (0.66%) |  |
| occurrences (all)                                    | 36                | 2               |  |
| Gastrointestinal disorders                           |                   |                 |  |
| Abdominal pain                                       |                   |                 |  |
| subjects affected / exposed                          | 18 / 302 (5.96%)  | 0 / 302 (0.00%) |  |
| occurrences (all)                                    | 34                | 0               |  |
| Abdominal pain upper                                 |                   |                 |  |
| subjects affected / exposed                          | 18 / 302 (5.96%)  | 1 / 302 (0.33%) |  |
| occurrences (all)                                    | 23                | 1               |  |
| Constipation   |                   |                 |  |
| subjects affected / exposed                          | 26 / 302 (8.61%)  | 2 / 302 (0.66%) |  |
| occurrences (all)                                    | 33                | 2               |  |
| Diarrhoea  |                   |                 |  |
| subjects affected / exposed                          | 46 / 302 (15.23%) | 3 / 302 (0.99%) |  |
| occurrences (all)                                    | 78                | 3               |  |
| Nausea   |                   |                 |  |
| subjects affected / exposed                          | 34 / 302 (11.26%) | 1 / 302 (0.33%) |  |
| occurrences (all)                                    | 65                | 1               |  |
| Vomiting   |                   |                 |  |
| subjects affected / exposed                          | 19 / 302 (6.29%)  | 2 / 302 (0.66%) |  |
| occurrences (all)                                    | 23                | 2               |  |
| Respiratory, thoracic and mediastinal disorders      |                   |                 |  |
| Cough  |                   |                 |  |
| subjects affected / exposed                          | 32 / 302 (10.60%) | 0 / 302 (0.00%) |  |
| occurrences (all)                                    | 51                | 0               |  |
| Epistaxis  |                   |                 |  |
| subjects affected / exposed                          | 23 / 302 (7.62%)  | 2 / 302 (0.66%) |  |
| occurrences (all)                                    | 51                | 3               |  |

|   |                         |                      |  |
|---|-------------------------|----------------------|--|
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)  | 27 / 302 (8.94%)<br>45  | 1 / 302 (0.33%)<br>1 |  |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all)            | 17 / 302 (5.63%)<br>22  | 1 / 302 (0.33%)<br>1 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 25 / 302 (8.28%)<br>48  | 0 / 302 (0.00%)<br>0 |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 27 / 302 (8.94%)<br>33  | 2 / 302 (0.66%)<br>2 |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 45 / 302 (14.90%)<br>83 | 0 / 302 (0.00%)<br>0 |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 39 / 302 (12.91%)<br>63 | 0 / 302 (0.00%)<br>0 |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)   | 28 / 302 (9.27%)<br>43  | 0 / 302 (0.00%)<br>0 |  |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                     | 25 / 302 (8.28%)<br>34  | 0 / 302 (0.00%)<br>0 |  |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)  | 16 / 302 (5.30%)<br>24  | 0 / 302 (0.00%)<br>0 |  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)   | 29 / 302 (9.60%)<br>36  | 0 / 302 (0.00%)<br>0 |  |
| Nasopharyngitis   |                         |                      |  |

|                                   |                   |                 |  |
|-----------------------------------|-------------------|-----------------|--|
| subjects affected / exposed       | 74 / 302 (24.50%) | 2 / 302 (0.66%) |  |
| occurrences (all)                 | 156               | 2               |  |
| Pharyngitis                       |                   |                 |  |
| subjects affected / exposed       | 21 / 302 (6.95%)  | 0 / 302 (0.00%) |  |
| occurrences (all)                 | 28                | 0               |  |
| Sinusitis                         |                   |                 |  |
| subjects affected / exposed       | 20 / 302 (6.62%)  | 1 / 302 (0.33%) |  |
| occurrences (all)                 | 36                | 1               |  |
| Upper respiratory tract infection |                   |                 |  |
| subjects affected / exposed       | 69 / 302 (22.85%) | 5 / 302 (1.66%) |  |
| occurrences (all)                 | 135               | 5               |  |
| Urinary tract infection           |                   |                 |  |
| subjects affected / exposed       | 32 / 302 (10.60%) | 2 / 302 (0.66%) |  |
| occurrences (all)                 | 63                | 2               |  |
| Viral infection                   |                   |                 |  |
| subjects affected / exposed       | 23 / 302 (7.62%)  | 0 / 302 (0.00%) |  |
| occurrences (all)                 | 35                | 0               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 22 May 2007       | Modification of eligibility criteria for clarity and to meet regulatory feedback. Addition of a secondary endpoint to evaluate retreatment with eltrombopag based on regulatory input. Addition of Liver Chemistry stopping criteria. Addition of platelet count assessment after treatment interruption. Modification of lifestyle wording concerning precautions to direct sunlight and/or UV exposure. Revision of prohibited medications based on new data.   |
| 10 September 2007 | Addition of enhanced monitoring for the potential presence of renal toxicity. Inclusion of Tunisian study population regulatory requirements. Addition of bone marrow biopsy for subjects who were dosed with eltrombopag for longer than one year in this study.   |
| 16 January 2009   | Requirement for regular bone marrow biopsies (including after 12 and 24 months of treatment), addition of central bone marrow morphology review, and addition of bone marrow biopsy stopping criteria. Requirement of a single ocular exam for subjects who were bilaterally pseudophakic or aphakic. Inclusion of Pharmacogenetic (PGx) sample collection. Modification of the requirements to change between stages of study. Update to the estimate of the number of subjects to be enrolled. Modification of the requirement for transitioning subjects to commercially available medication. Dietary and cation-containing product restrictions were updated to be consistent with current guidelines.   |
| 11 June 2009      | A country-specific amendment for the UK to include a definitive date for the end of the study, as required by the UK regulatory authority.  |
| 13 April 2010     | Inclusion of thrombophilia risk factor testing, and permitted continuation of subjects following a thrombotic event based upon Investigator assessment of individual risk-benefit assessment. Reduction in the frequency of required investigator/ GlaxoSmithKline (GSK) medical monitor contact, physical exams, ECGs, ocular exams, anti-platelet antibody testing, proteomic sample collection, pharmacokinetic (PK) sampling, renal assessments, and visit frequency. Follow-up requirements for subjects continuing on commercial eltrombopag were reduced. Removal of specific tests within clinical chemistry panel. Removal of ITP Bleeding Score assessment. Removal of phototoxicity precaution statement based on results of photoirritancy study. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported



