



Clinical trial results:

A non-randomized, open label, multi-center, Phase II study to assess the safety and efficacy of eltrombopag in combination with rabbit anti-thymocyte globulin (r-ATG) and cyclosporine A (CsA) in East-Asian patients with treatment naive severe aplastic anemia (REACTS)

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2024-000602-14 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 06 December 2024 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 20 June 2025 |
| First version publication date | 20 June 2025 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CETB115G2201 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04328727 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com |

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? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 06 December 2024 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 December 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of eltrombopag in combination with r-ATG and CsA in terms of complete response (CR) rate at 6 months in East-Asian patients with treatment naive severe aplastic anemia (SAA).

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

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.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 04 November 2020 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 3 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | China: 26 |
| Country: Number of subjects enrolled | Japan: 5 |
| Country: Number of subjects enrolled | Taiwan: 2 |
| Country: Number of subjects enrolled | Korea, Republic of: 3 |
| Worldwide total number of subjects | 36 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

| | |
|--|----|
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 4 |
| Adolescents (12-17 years) | 4 |
| Adults (18-64 years) | 26 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 12 sites in 4 different countries

Pre-assignment

Screening details:

there was an up to 30 days screening period (day -30 to -1) before first treatment (day 1).

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:

Participants received eltrombopag in combination with r-ATG and CsA. • Eltrombopag was administered orally once daily with initial doses of 75mg/day for ≥ 12 years old and 37.5 mg/day for participants between ≥ 6 and < 12 years. Doses could be adjusted based on platelet count • r-ATG was administered intravenously at a dose of 2.5 to 3.5 mg/kg/day on Days 1-5 • CsA was administered orally every 12 h at a starting dose of 3-6 mg/kg/day

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | eltrombopag |
| Investigational medicinal product code | ETB115 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Eltrombopag was administered orally once daily with initial doses of 75mg/day for ≥ 12 years old and 37.5 mg/day for participants between ≥ 6 and < 12 years. Doses could be adjusted based on platelet count

| | |
|--|------------------------|
| Investigational medicinal product name | cyclosporine A |
| Investigational medicinal product code | |
| Other name | CsA |
| Pharmaceutical forms | Capsule, Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

CsA was administered orally every 12 h at a starting dose of 3-6 mg/kg/day

| | |
|--|--|
| Investigational medicinal product name | rabbit anti-thymocyte globulin |
| Investigational medicinal product code | |
| Other name | r-ATG |
| Pharmaceutical forms | Powder for solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

r-ATG was administered intravenously at a dose of 2.5 to 3.5 mg/kg/day on Days 1-5

| Number of subjects in period 1 | eltrombopag |
|---------------------------------------|-------------|
| Started | 36 |
| Started extension part | 28 |
| Started long term follow up | 34 |
| Completed | 28 |
| Not completed | 8 |
| Participant decision | 4 |
| Death | 3 |
| Guardian Decision | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | eltrombopag |
|-----------------------|-------------|

Reporting group description:

Participants received eltrombopag in combination with r-ATG and CsA. • Eltrombopag was administered orally once daily with initial doses of 75mg/day for ≥ 12 years old and 37.5 mg/day for participants between ≥ 6 and < 12 years. Doses could be adjusted based on platelet count • r-ATG was administered intravenously at a dose of 2.5 to 3.5 mg/kg/day on Days 1-5 • CsA was administered orally every 12 h at a starting dose of 3-6 mg/kg/day

| Reporting group values | eltrombopag | Total | |
|---|-------------|-------|--|
| Number of subjects | 36 | 36 | |
| Age Categorical | | | |
| Units: participants | | | |
| <=18 years | 8 | 8 | |
| Between 18 and 65 years | 26 | 26 | |
| >=65 years | 2 | 2 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 34.7 | | |
| standard deviation | ± 18.97 | - | |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 21 | 21 | |
| Male | 15 | 15 | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 36 | 36 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 0 | 0 | |
| White | 0 | 0 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 0 | 0 | |

End points

End points reporting groups

| | |
|--|-------------|
| Reporting group title | eltrombopag |
| Reporting group description: | |
| Participants received eltrombopag in combination with r-ATG and CsA. • Eltrombopag was administered orally once daily with initial doses of 75mg/day for ≥ 12 years old and 37.5 mg/day for participants between ≥ 6 and < 12 years. Doses could be adjusted based on platelet count • r-ATG was administered intravenously at a dose of 2.5 to 3.5 mg/kg/day on Days 1-5 • CsA was administered orally every 12 h at a starting dose of 3-6 mg/kg/day | |

Primary: Complete response (CR) rate at week 26

| | |
|--|---|
| End point title | Complete response (CR) rate at week 26 ^[1] |
| End point description: | |
| Complete response rate was defined as percentage of patients achieving complete response (CR). | |
| Complete response was defined as subjects meeting all the three criteria on two consecutive serial blood count measurements at least one week apart but not more than four weeks apart: | |
| <ul style="list-style-type: none">• Absolute neutrophil count $> 1.0 \times 10^9/L$• Platelet count $> 100 \times 10^9/L$• Hemoglobin > 100 g/L | |
| The participants who discontinued from the trial before Week 26 and those that received blood products prior to response assessment (7 days prior for platelet transfusions, 14 days for RBC transfusion and 21 days for growth factors) were treated as non-responders. | |
| No hypothesis test was planned for this primary outcome. | |
| End point type | Primary |
| End point timeframe: | |
| Week 26 (6 months after starting study treatment) | |
| 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: No statistical hypothesis test was planned for this primary outcome | |

| End point values | eltrombopag | | | |
|-----------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| All participants | 16.7 (6.4 to 32.8) | | | |
| < 18 years | 25 (3.2 to 65.1) | | | |
| 18-64 years | 15.4 (4.4 to 34.9) | | | |
| ≥ 65 years | 0 (0.0 to 84.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Complete response (CR) rate

| | |
|-----------------|-----------------------------|
| End point title | Complete response (CR) rate |
|-----------------|-----------------------------|

End point description:

Complete response rate was defined as percentage of patients achieving complete response (CR).

Complete response was defined as subjects meeting all the three criteria on two consecutive serial blood count measurements at least one week apart but not more than four weeks apart:

- Absolute neutrophil count $> 1.0 \times 10^9/L$
- Platelet count $> 100 \times 10^9/L$
- Hemoglobin $> 100 \text{ g/L}$

The participants who discontinued from the trial before Week 26 and those that received blood products prior to response assessment (7 days prior for platelet transfusions, 14 days for RBC transfusion and 21 days for growth factors) were treated as non-responders.

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

End point timeframe:

Week 13 (3 months), Week 52 (12 months) and yearly after up to 3 years

| End point values | eltrombopag | | | |
|-----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 13 | 5.6 (0.7 to 18.7) | | | |
| Week 52 | 30.6 (16.3 to 48.1) | | | |
| Year 2 | 30.6 (16.3 to 48.1) | | | |
| Year 3 | 30.6 (16.3 to 48.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response (ORR) rate

| | |
|-----------------|-----------------------------|
| End point title | Overall response (ORR) rate |
|-----------------|-----------------------------|

End point description:

Overall response rate was defined as percentage of patients achieving complete response (CR) or partial response (PR).

Partial response (PR) was defined as blood counts no longer meeting the standard criteria for severe pancytopenia in SAA, equivalent to at least 2 of the 3 criteria below, but not sufficient for a CR:

- Absolute neutrophil count $\geq 0.5 \times 10^9/L$
- Platelet count $\geq 20 \times 10^9/L$
- Reticulocyte count $\geq 20 \times 10^9/L$

Complete response (CR) was defined as subjects meeting all the three criteria on two consecutive serial

blood count measurements at least one week apart but not more than four weeks apart:

- Absolute neutrophil count > $1.0 \times 10^9/L$
- Platelet count > $100 \times 10^9/L$
- Hemoglobin > 100 g/L

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 13 (3 months), 26 weeks (6 months), 52 weeks and yearly after up to 3 years | |

| | | | | |
|-----------------------------------|---------------------|--|--|--|
| End point values | eltrombopag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 13 | 66.7 (49.0 to 81.4) | | | |
| Week 26 | 77.8 (60.8 to 89.9) | | | |
| Week 52 | 66.7 (49.0 to 81.4) | | | |
| Year 2 | 50.0 (32.9 to 67.1) | | | |
| Year 3 | 41.7 (25.5 to 59.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of complete response

| | |
|-----------------|-------------------------------|
| End point title | Duration of complete response |
|-----------------|-------------------------------|

End point description:

Duration of response was derived as the time from first documented and confirmed complete response (CR) until the time of relapse or death, whichever occurred first. Duration of response was estimated using Kaplan-Meier method.

Clinical relapse was considered as the occurrence of any of the following events in a participant who had achieved a hematological response (CR) but had subsequently lost response (not explained by any other independent concomitant medical conditions) in one blood count measurements:

- Meeting again the criteria for SAA
- Requirement for transfusion again for subjects who had been transfusion independent
- Decrease in any of the peripheral blood counts to absolute neutrophil count < $0.5 \times 10^9/L$ or platelets < $20 \times 10^9/L$.

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 3 years | |

| | | | | |
|----------------------------------|-------------------|--|--|--|
| End point values | eltrombopag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 ^[2] | | | |
| Units: months | | | | |
| number (confidence interval 95%) | 999 (999 to 999) | | | |

Notes:

[2] - Not estimable due to insufficient number of participants with relapse or death

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of overall response

| | |
|-----------------|------------------------------|
| End point title | Duration of overall response |
|-----------------|------------------------------|

End point description:

Duration of response was derived as the time from first documented and confirmed response (either CR or PR) until the time of relapse or death, whichever occurred first. Duration of response was estimated using Kaplan-Meier method.

Clinical relapse was considered as the occurrence of any of the following events in a participant who had achieved a hematological response (CR or PR) but had subsequently lost response (not explained by any other independent concomitant medical conditions) in one blood count measurements:

- Meeting again the criteria for SAA
- Requirement for transfusion again for subjects who had been transfusion independent
- Decrease in any of the peripheral blood counts to absolute neutrophil count $< 0.5 \times 10^9/L$ or platelets $< 20 \times 10^9/L$.

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

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

End point timeframe:

Up to approximately 3 years

| | | | | |
|----------------------------------|-------------------|--|--|--|
| End point values | eltrombopag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 ^[3] | | | |
| Units: months | | | | |
| number (confidence interval 95%) | 999 (3.1 to 999) | | | |

Notes:

[3] - Not estimable due to median duration of overall response not being achieved from the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall survival (OS) |
|-----------------|-----------------------|

End point description:

OS was defined as the time from the date of the first dose of study treatment to the date of death due to any cause. If a subject was not known to have died, survival was censored at the date of last contact.

The distribution function of OS was estimated using the Kaplan- Meier method.

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 3 years | |

| | | | | |
|----------------------------------|-------------------|--|--|--|
| End point values | eltrombopag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36 ^[4] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 999 (999 to 999) | | | |

Notes:

[4] - Not estimable due to median duration of OS being not evaluable from the Kaplan-Meier analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) rate

| | |
|-----------------|----------------------------|
| End point title | Overall survival (OS) rate |
|-----------------|----------------------------|

End point description:

OS was defined as the time from the date of the first dose of study treatment to the date of death due to any cause. The OS rate is the estimated probability that a patient will remain event-free up to the specified time point and was obtained from the Kaplan-Meier survival estimates. If a subject was not known to have died, survival was censored at the date of last contact.

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

End point timeframe:

Week 26, Week 52 and yearly after up to 3 years

| | | | | |
|----------------------------------|---------------------|--|--|--|
| End point values | eltrombopag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36 | | | |
| Units: percent probability | | | | |
| number (confidence interval 95%) | | | | |
| Week 26 | 97.2 (81.9 to 99.6) | | | |
| Week 52 | 97.2 (81.9 to 99.6) | | | |
| Year 2 | 94.1 (78.3 to 95.5) | | | |
| Year 3 | 90.9 (74.4 to 97.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Red blood cells (RBC) and platelet transfusion-free interval before Week 13 and 26

| | |
|---|--|
| End point title | Red blood cells (RBC) and platelet transfusion-free interval before Week 13 and 26 |
| End point description: Transfusion-free interval was defined as the time from most recent RBC/platelet transfusion preceding response assessment to the date of response assessment. | |
| End point type | Secondary |
| End point timeframe: Week 13, 26 | |

| | | | | |
|--|-----------------|--|--|--|
| End point values | eltrombopag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| RBC transfusion-free interval - Week 13 n=34 | 36.3 (± 25.62) | | | |
| RBC transfusion-free interval - Week 26 n=32 | 98.9 (± 57.97) | | | |
| Platelet transfusion-free interval - Week 13 n=34 | 34.0 (± 25.64) | | | |
| Platelet transfusion-free interval - Week 26 n=32 | 97.3 (± 58.93) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who become RBC transfusion independent

| | |
|--|---|
| End point title | Percentage of participants who become RBC transfusion independent |
| End point description: Transfusion independent participants were defined as those participants who were transfusion dependent at baseline but became transfusion free for a period of ≥ 8 weeks post-baseline for RBCs. | |
| End point type | Secondary |
| End point timeframe: From date of first dose to approximately 3 years | |

| | | | | |
|-----------------------------------|-----------------|--|--|--|
| End point values | eltrombopag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 86.2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time from the date of first dose of investigational treatment to the date of first occurrence of any clonal evolution events

| | |
|-----------------|--|
| End point title | Time from the date of first dose of investigational treatment to the date of first occurrence of any clonal evolution events |
|-----------------|--|

End point description:

Clonal evolution events were assessed by karyotyping (G-banding) and FISH (Fluorescence in situ hybridization) targeting abnormalities including, but not restricted to chromosome 3q del,5q del, monosomy 7, trisomy 8 and those associated with SAA (Severe aplastic anemia), MDS (Myelodysplastic syndrome), AML (Acute myeloid leukemia). Time to clonal evolution was to be estimated using the Kaplan-Meier method.

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

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

End point timeframe:

From date of first dose to approximately 3 years

| | | | | |
|----------------------------------|------------------|--|--|--|
| End point values | eltrombopag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 ^[5] | | | |
| Units: weeks | | | | |
| number (confidence interval 95%) | 999 (999 to 999) | | | |

Notes:

[5] - Not estimable due to insufficient number of participants with events

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who become platelet transfusion independent

| | |
|-----------------|--|
| End point title | Percentage of participants who become platelet transfusion independent |
|-----------------|--|

End point description:

Transfusion independent participants were defined as those participants who were transfusion dependent at baseline but became transfusion free for a period of ≥ 4 weeks post-baseline for platelets.

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

End point timeframe:

From date of first dose to approximately 3 years

| | | | | |
|-----------------------------------|-----------------|--|--|--|
| End point values | eltrombopag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 88.2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma pharmacokinetics (PK) parameters of eltrombopag: AUClast

| | |
|-----------------|---|
| End point title | Plasma pharmacokinetics (PK) parameters of eltrombopag: AUClast |
|-----------------|---|

End point description:

AUClast is the area under the curve from time zero to the last measurable concentration sampling time.

Blood samples were collected from patients to assess the plasma concentrations of eltrombopag using a validated liquid chromatography – tandem mass spectrometry assay (LC-MS/MS) approach.

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

End point timeframe:

Pre-dose, and 2, 4, 6, 8 and 24 hours post-dose on Day 14 after initial dose

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | eltrombopag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: ng*h/mL | | | | |
| arithmetic mean (standard deviation) | 602000 (± 239000) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma pharmacokinetics (PK) parameters of eltrombopag: AUCtau

| | |
|-----------------|--|
| End point title | Plasma pharmacokinetics (PK) parameters of eltrombopag: AUCtau |
|-----------------|--|

End point description:

AUCtau is area under the curve calculated to the end of a dosing interval (tau) at steady-state

Blood samples were collected from patients to assess the plasma concentrations of eltrombopag using a

validated liquid chromatography – tandem mass spectrometry assay (LC-MS/MS) approach.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Pre-dose, and 2, 4, 6, 8 and 24 hours post-dose on Day 14 after initial dose | |

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | eltrombopag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: ng*h/mL | | | | |
| arithmetic mean (standard deviation) | 585000 (± 231000) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma pharmacokinetics (PK) parameters of eltrombopag: Ctrough

| | |
|-----------------|---|
| End point title | Plasma pharmacokinetics (PK) parameters of eltrombopag: Ctrough |
|-----------------|---|

End point description:

Ctrough is the pre-dose concentration at the end of dose interval.

Blood samples were collected to assess the plasma concentrations of eltrombopag using a validated liquid chromatography – tandem mass spectrometry assay (LC-MS/MS) approach.

Eltrombopag was administered orally once daily with initial doses of 75mg/day for ≥ 12 years old and 37.5 mg/day for participants between ≥ 6 and < 12 years.

Doses could be adjusted based on platelet count every 2 weeks by decreasing it by 25 mg/day (12.5 mg/day, for participants below 12 years old) if the platelet count was above $200 \times 10^9/L$. or interrupted if platelet count rose above $400 \times 10^9/L$. In partial response participants dose could be restarted or increased to that before the decrease if platelet counts $< 30 \times 10^9/L$, Hb < 90 g/L, ANC $< 0.5 \times 10^9/L$ or participant needed transfusion. In complete response participants dose could be restarted or increased to that before decrease if blood counts dropped to not meet CR criteria.

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

End point timeframe:

Pre-dose on day 15 after initiation of eltrombopag and and pre-dose on the 15th day after each new dose up to week 26

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | eltrombopag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 26 ^[6] | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 20200 (± 9410) | | | |

Notes:

[6] - Number of measurements 36

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma pharmacokinetics (PK) parameters of eltrombopag: C_{max}

| | |
|-----------------|--|
| End point title | Plasma pharmacokinetics (PK) parameters of eltrombopag: C _{max} |
|-----------------|--|

End point description:

C_{max} is the The maximum (peak) observed plasma drug concentration after dose administration.

Blood samples were collected from patients to assess the plasma concentrations of eltrombopag using a validated liquid chromatography – tandem mass spectrometry assay (LC-MS/MS) approach.

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

End point timeframe:

Pre-dose, and 2, 4, 6, 8 and 24 hours post-dose on Day 14 after initial dose

| End point values | eltrombopag | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: ng/mL | | | | |
| median (standard deviation) | 32500 (± 12300) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma pharmacokinetics (PK) parameters of eltrombopag: T_{max}

| | |
|-----------------|--|
| End point title | Plasma pharmacokinetics (PK) parameters of eltrombopag: T _{max} |
|-----------------|--|

End point description:

T_{max} is the time to reach maximum (peak) plasma drug concentration after dose administration.

Blood samples were collected from patients to assess the plasma concentrations of eltrombopag using a validated liquid chromatography – tandem mass spectrometry assay (LC-MS/MS) approach.

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

End point timeframe:

Pre-dose, and 2, 4, 6, 8 and 24 hours post-dose on Day 14 after initial dose

| End point values | eltrombopag | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 5.59 (± 5.64) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma pharmacokinetics (PK) parameters of eltrombopag: CLss/F

| | |
|-----------------|--|
| End point title | Plasma pharmacokinetics (PK) parameters of eltrombopag: CLss/F |
|-----------------|--|

End point description:
CLss/F is Apparent systemic (or total body) clearance at steady state from plasma.

Blood samples were collected from patients to assess the plasma concentrations of eltrombopag using a validated liquid chromatography – tandem mass spectrometry assay (LC-MS/MS) approach.

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

End point timeframe:
Pre-dose, and 2, 4, 6, 8 and 24 hours post-dose on Day 14 after initial dose

| | | | | |
|--------------------------------------|------------------|--|--|--|
| End point values | eltrombopag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: Liter/hour | | | | |
| arithmetic mean (standard deviation) | 0.148 (± 0.0618) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: from first dose of study treatment up to 2 years after last dose including post-treatment long term follow up period.

Serious and Other Adverse Events: from first dose of study treatment until 30 days after last dose.

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 | 27.1 |

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | eltrombopag |
|-----------------------|-------------|

Reporting group description:

Participants received eltrombopag in combination with r-ATG and CsA.

| Serious adverse events | eltrombopag | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 36 (38.89%) | | |
| number of deaths (all causes) | 3 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood bilirubin increased | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Breast hyperplasia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Heavy menstrual bleeding | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Hydronephrosis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | | |
| occurrences causally related to treatment / all | 1 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|-------------------|--|--|
| Non-serious adverse events | eltrombopag | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 36 / 36 (100.00%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 7 / 36 (19.44%) | | |
| occurrences (all) | 10 | | |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | | |
| occurrences (all) | 4 | | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 3 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Pyrexia | | | |
| subjects affected / exposed | 12 / 36 (33.33%) | | |
| occurrences (all) | 20 | | |
| Immune system disorders | | | |
| Serum sickness | | | |
| subjects affected / exposed | 9 / 36 (25.00%) | | |
| occurrences (all) | 9 | | |
| Allergy to immunoglobulin therapy | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | | |
| occurrences (all) | 8 | | |
| Immunodeficiency | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Productive cough | | | |

| | | | |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 3 | | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 13 / 36 (36.11%) | | |
| occurrences (all) | 19 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 8 | | |
| Bilirubin conjugated increased | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 6 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 3 | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 7 / 36 (19.44%) | | |
| occurrences (all) | 11 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 7 / 36 (19.44%) | | |
| occurrences (all) | 10 | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 13 / 36 (36.11%) | | |
| occurrences (all) | 21 | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 6 | | |
| Blood urea increased | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | | |
| occurrences (all) | 8 | | |
| Gamma-glutamyltransferase increased | | | |

| | | | |
|--|--|--|--|
| subjects affected / exposed occurrences (all) | 10 / 36 (27.78%) 14 | | |
| Injury, poisoning and procedural complications Allergic transfusion reaction subjects affected / exposed occurrences (all) | 4 / 36 (11.11%) 4 | | |
| Cardiac disorders Cardiac failure subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 4 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 4 / 36 (11.11%) 4 | | |
| Blood and lymphatic system disorders Febrile neutropenia subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 3 | | |
| Eye disorders Cataract subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 3 | | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia | 2 / 36 (5.56%) 5 8 / 36 (22.22%) 8 9 / 36 (25.00%) 10 | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 3 | | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | | |
| occurrences (all) | 5 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Mouth ulceration | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | | |
| occurrences (all) | 6 | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Stomatitis | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | | |
| occurrences (all) | 5 | | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | | |
| occurrences (all) | 6 | | |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | | |
| occurrences (all) | 6 | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 11 / 36 (30.56%) | | |
| occurrences (all) | 32 | | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Dry skin | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Rash | | | |
| subjects affected / exposed | 7 / 36 (19.44%) | | |
| occurrences (all) | 7 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 5 | | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Renal impairment | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | | |
| occurrences (all) | 7 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| Cytomegalovirus infection reactivation | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Infection | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | | |
| occurrences (all) | 7 | | |
| Neutropenic infection | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 3 | | |
| Oral infection | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 3 | | |
| Pneumonia | | | |

| | | | |
|------------------------------------|------------------|--|--|
| subjects affected / exposed | 6 / 36 (16.67%) | | |
| occurrences (all) | 6 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 8 / 36 (22.22%) | | |
| occurrences (all) | 8 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 6 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 3 | | |
| Fluid retention | | | |
| subjects affected / exposed | 9 / 36 (25.00%) | | |
| occurrences (all) | 9 | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 5 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | | |
| occurrences (all) | 15 | | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | | |
| occurrences (all) | 6 | | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | | |
| occurrences (all) | 10 | | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 14 / 36 (38.89%) | | |
| occurrences (all) | 49 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 10 / 36 (27.78%) | | |
| occurrences (all) | 14 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 5 | | |

| | | | |
|-----------------------------|------------------|--|--|
| Hypomagnesaemia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | | |
| occurrences (all) | 9 | | |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | | |
| occurrences (all) | 7 | | |
| Sodium retention | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 3 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 18 / 36 (50.00%) | | |
| occurrences (all) | 27 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 18 December 2020 | The primary purpose of this amendment was to change the level of AST/ALT from $> 8 \times \text{ULN}$ to $> 5 \times \text{ULN}$ and to change the recommended action from "dose interruption" to "treatment discontinuation" in Table 6-7 of protocol, 'Guidelines for eltrombopag dose modification based on liver function abnormalities and thrombosis/embolism' in response to concerns raised by Korean Health Authority. |
| 22 December 2021 | The purpose of this amendment was to harmonize and clarify several inconsistencies in the protocol and add risk mitigation procedures during public health emergency declared by local or regional authorities. The updates were not triggered by any safety issues or new safety data becoming available. The assessment of the Benefit/Risk identified no additional risks related to COVID 19 and no changes have been made as a result. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Notes: