Clinical trial results:
SOAR, Interventional phase II single-arm study to assess efficacy and safety of eltrombopag combined with cyclosporine as first-line therapy in adult patients with severe acquired aplastic anemia

Summary

EudraCT number	2016-002814-29
Trial protocol	ES NL HU IT
Global end of trial date	30 May 2022

Results information

Result version number	v1 (current)
This version publication date	12 March 2023
First version publication date	12 March 2023

Trial information

Trial identification

Sponsor protocol code	CETB115E2403

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02998645
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 May 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of eltrombopag + cyclosporine as first-line therapy on overall hematologic response (partial response (PR) and complete response (CR)) by 6 months

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	11 May 2017
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	Brazil: 6
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	India: 4
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Turkey: 5
Worldwide total number of subjects	54
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	37
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted across 20 centers in 9 countries.

Pre-assignment

Screening details:

Participants received a combination of eltrombopag and cyclosporine for 6 months (Treatment period 1). Participants who were responders at 6 months were followed-up for cyclosporine tapering until relapse or Month 24 whichever was earlier (Treatment period 2)

Period 1

Period 1 title	Treatment period 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Eltrombopag + cyclosporine

Arm description:

Participants received eltrombopag (orally, 100 mg once daily for East/Southeast Asian participants / 150 mg once daily for all other participants) in combination with cyclosporine (orally, 10.0 mg/kg/day in divided doses every 12 hours) for up to 6 months. Thereafter, 6-month responders were treated with cyclosporine for up to Month 24.

Arm type	Experimental
Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

The starting dose was based on body weight at 10.0 mg/kg/day (acceptable rounding range was from 9.5 to 10.5 mg/kg/day) in divided doses every 12 hours. After Day 1, dosing was titrated individually according to therapeutic trough level between 200 and 400 µg/L for 6 months. After 6 months (for responders), tapering of cyclosporine was done as follows:
- 6 to 9 months: at the 6 months visit, the dose was reduced by 25% for 3 months
- 9 to 12 months: at the 9 months visit, the dose was further reduced by 25% for another 3 months
- 12 to2 4 months: dose was maintained

Investigational medicinal product name	Eltrombopag
Investigational medicinal product code	ETB115
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Film-coated tablets (12.5 mg, 25 mg, 50 mg and 75 mg) administered orally, once daily for up to 6 months. East and Southeast Asian participants were treated with 100 mg once daily, to adjust for the lower apparent clearance of eltrombopag. All other participants were treated with 150 mg once daily.

Number of subjects in period 1	Eltrombopag + cyclosporine
Started	54
Completed	35
Not completed	19
Adverse event, serious fatal	5
Adverse event, non-fatal	6
Technical Problems	4
Progressive disease	1
Subject/guardian decision	1
Lack of efficacy	2

Period 2

Period 2 title	Treatment period 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Eltrombopag + cyclosporine

Arm description:

Participants received eltrombopag (orally, 100 mg once daily for East/Southeast Asian participants / 150 mg once daily for all other participants) in combination with cyclosporine (orally, 10.0 mg/kg/day in divided doses every 12 hours) for up to 6 months. Thereafter, 6-month responders were treated with cyclosporine for up to Month 24.

Arm type	Experimental
Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

The starting dose was based on body weight at 10.0 mg/kg/day (acceptable rounding range was from 9.5 to 10.5 mg/kg/day) in divided doses every 12 hours. After Day 1, dosing was titrated individually according to therapeutic trough level between 200 and 400 µg/L for 6 months. After 6 months (for responders), tapering of cyclosporine was done as follows:
- 6 to 9 months: at the 6 months visit, the dose was reduced by 25% for 3 months
- 9 to 12 months: at the 9 months visit, the dose was further reduced by 25% for another 3 months
- 12 to2 4 months: dose was maintained

Number of subjects in period 2[1]	Eltrombopag + cyclosporine
Started	21
Completed	11
Not completed	10
Physician decision	1
Adverse event, non-fatal	2
Progressive disease	2
Lack of efficacy	5

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only participants who were responders at Month 6 entered the treatment period 2

Baseline characteristics

Reporting groups	
Reporting group title	Eltrombopag + cyclosporine
Reporting group description:	
Participants received eltrombopag (orally, 100 mg once daily for East/Southeast Asian participants / 150 mg once daily for all other participants) in combination with cyclosporine (orally, 10.0 mg/kg/day in divided doses every 12 hours) for up to 6 months. Thereafter, 6-month responders were treated with cyclosporine for up to Month 24.	

Reporting group values	Eltrombopag + cyclosporine	Total	
Number of subjects	54	54	
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)	37	37	
From 65-84 years	17	17	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	52.0		
standard deviation	± 17.88	-	
Sex: Female, Male Units: Participants			
Female	20	20	
Male	34	34	
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	22	22	
Southeast Asian	11	11	
East Asian	7	7	
West Asian	5	5	
Other	4	4	
South Asian	3	3	
Mixed ethnicity	1	1	
Not reported	1	1	

End points

End points reporting groups

Reporting group title	Eltrombopag + cyclosporine

Reporting group description:

Participants received eltrombopag (orally, 100 mg once daily for East/Southeast Asian participants / 150 mg once daily for all other participants) in combination with cyclosporine (orally, 10.0 mg/kg/day in divided doses every 12 hours) for up to 6 months. Thereafter, 6-month responders were treated with cyclosporine for up to Month 24.

Reporting group title	Eltrombopag + cyclosporine

Reporting group description:

Participants received eltrombopag (orally, 100 mg once daily for East/Southeast Asian participants / 150 mg once daily for all other participants) in combination with cyclosporine (orally, 10.0 mg/kg/day in divided doses every 12 hours) for up to 6 months. Thereafter, 6-month responders were treated with cyclosporine for up to Month 24.

Primary: Overall hematologic response rate by 6 months

End point title	Overall hematologic response rate by 6 months[1]

End point description:

Overall hematologic response rate by 6 months was defined as the percentage of participants with complete response (CR) or partial response (PR) any time on or before 6 months.
PR was defined as any two of the following parameters at two consecutive measurements at least 7 days apart and no platelet transfusion within 7 days of platelet measurement:
- Absolute neutrophil count (ANC) >500/µL
- Platelet count >20 000/µL
- Reticulocyte count >60 000/µL

CR was defined as all three parameters meet the following criteria at two consecutive measurements at least 7 days apart and no platelet transfusions within 7 days of platelet measurement and no red blood cell transfusion with 14 days of the hemoglobin measurements:
- ANC > 1 000/µL
- Platelet count >100 000/µL
- Hemoglobin >10 g/L

End point type	Primary

End point timeframe:

Up to 6 months

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 analyses were planned for the primary endpoint

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Percentage of participants				
number (confidence interval 95%)	46.3 (32.6 to 60.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall hematologic response rate by 3 months

End point title	Overall hematologic response rate by 3 months

End point description:

Overall hematologic response rate by 3 months was defined as the percentage of participants with CR or PR any time on or before 3 months.
PR was defined as any two of the following parameters at two consecutive measurements at least 7 days apart and no platelet transfusion within 7 days of platelet measurement:
● ANC >500/µL
● Platelet count >20 000/µL
● Reticulocyte count >60 000/µL
CR was defined as all three parameters meet the following criteria at two consecutive measurements at least 7 days apart and no platelet transfusions within 7 days of platelet measurement and no red blood cell transfusion with 14 days of the hemoglobin measurements:
● ANC > 1 000/µL
● Platelet count >100 000/µL
● Hemoglobin >10 g/L

End point type	Secondary

End point timeframe:

Up to 3 months

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Percentage of participants				
number (confidence interval 95%)	40.7 (27.6 to 55.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall hematologic response rate at 12 and 24 months

End point title	Overall hematologic response rate at 12 and 24 months

End point description:

Overall hematologic response rate at 12 and 24 months was defined as the percentage of participants with CR or PR at 12 and 24 months respectively.
PR was defined as any two of the following parameters at two consecutive measurements at least 7 days apart and no platelet transfusion within 7 days of platelet measurement:
● ANC>500/µL
● Platelet count >20 000/µL
● Reticulocyte count >60 000/µL
CR was defined as all three parameters meet the following criteria at two consecutive measurements at least 7 days apart and no platelet transfusions within 7 days of platelet measurement and no red blood cell transfusion with 14 days of the hemoglobin measurements:
● ANC > 1 000/µL
● Platelet count >100 000/µL
● Hemoglobin >10 g/L

End point type	Secondary

End point timeframe:

12 and 24 months

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Percentage of participants				
number (confidence interval 95%)				
At 12 months	18.5 (9.3 to 31.4)			
At 24 months	18.5 (9.3 to 31.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of first hematologic response

End point title	Duration of first hematologic response

End point description:

Duration of first hematologic response is the time from the date of the start of first response to the date of first relapse. Relapse is defined as no longer meeting definition of PR or CR. Kaplan-Meier method was used for the analysis. If no relapse occurred, the participant was censored at the date of last contact. Only participants who achieved hematologic response of CR or PR at Month 6 were followed up until Month 24. PR was defined as any 2 of the following parameters at 2 consecutive measurements at least 7 days apart and no platelet transfusion within 7 days of platelet measurement:
●ANC >500/µL
●Platelet count >20 000/µL
●Reticulocyte count >60 000/µL.
CR was defined as all 3 parameters meet the following criteria at 2 consecutive measurements at least 7 days apart and no platelet transfusions within 7 days of platelet measurement and no red blood cell transfusion with 14 days of the hemoglobin measurements:
●ANC >1 000/µL
●Platelet count >100 000/µL
●Hemoglobin >10 g/L

End point type	Secondary

End point timeframe:

Up to 6 months (non-responders at Month 6) and up to 24 months (responders at Month 6)

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Days				
median (confidence interval 95%)	351.0 (99.0 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with evolution to myelodysplasia, paroxysmal nocturnal hemoglobinuria (PNH) and leukemia

End point title	Percentage of participants with evolution to myelodysplasia, paroxysmal nocturnal hemoglobinuria (PNH) and leukemia

End point description:

The percentage of participants with evolution to myelodysplasia, PNH and acute leukemia occurring at any time during the study. Clonal evolution to myelodysplasia was defined as a new marrow cytogenic abnormality with or without characteristic dysplastic marrow findings. Clonal evolution to leukemia was defined as greater than 20% peripheral blood and/or marrow blasts. Clonal evolution to paroxysmal nocturnal hemoglobinuria (PNH) was defined as a clone at baseline < 10% that rose to greater than 50% on study.
Only participants who achieved hematologic response of CR or PR at Month 6 were followed up until Month 24

End point type	Secondary

End point timeframe:

Up to 6 months (non-responders at Month 6) and up to 24 months (responders at Month 6)

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Percentage of participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse rate by 6 and 24 months

End point title	Relapse rate by 6 and 24 months

End point description:

Relapse was defined as no longer meeting the definition of PR (and not CR). Relapse rate by 6 months and 24 was defined as the percentage of responders by 6 months who relapsed prior to 6 months or prior to 24 months respectively. Responders by 6 months were participants who achieved CR or PR any time on or before 6 months. Only participants who achieved hematologic response of CR or PR at Month 6 were followed up until Month 24.
PR: any 2 of the following parameters at 2 consecutive measurements at least 7 days apart and no platelet transfusion within 7 days of platelet measurement:
●ANC>500/µL
●Platelet count>20 000/µL
●Reticulocyte count>60 000/µL.
CR: all 3 parameters meet the following criteria at 2 consecutive measurements at least 7 days apart and no platelet transfusions within 7 days of platelet measurement and no red blood cell transfusion with 14 days of the hemoglobin measurements:
●ANC>1 000/µL
●Platelet count>100 000/µL
●Hemoglobin>10 g/L

End point type	Secondary

End point timeframe:

Up to 6 months (non-responders at Month 6) and up to 24 months (responders at Month 6)

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Percentage of participants				
number (confidence interval 95%)				
By 6 months	32.0 (14.9 to 53.5)			
By 24 months	44.0 (24.4 to 65.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who were red blood cells (RBC) transfusion independent

End point title	Percentage of participants who were red blood cells (RBC) transfusion independent

End point description:

Percentage of participants who were RBC transfusion independent at least once by 6 months and by 24 months (responders only). Independence was defined as no RBC transfusion for at least 56 days. Results are presented for responders and non-responders. If any participant achieved hematologic response (either CR or PR) any time on or before 6 months, they were considered as responders, else they were considered as non-responders.
Only participants who achieved hematologic response of CR or PR at Month 6 were followed up until Month 24.

End point type	Secondary

End point timeframe:

Up to 6 months (non-responders at Month 6) and up to 24 months (responders at Month 6)

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Participants				
Day 1 to 6 months- Responders	17			
Day 1 to 24 months- Responders	20			
Day 1 to 6 months- Non-Responders	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Longest duration of transfusion independence (platelet or RBC)

End point title	Longest duration of transfusion independence (platelet or RBC)

End point description:

Longest duration of transfusion independence (platelet or RBC) by 6 months and by 24 months (responders only). Transfusion independence was defined as no transfusions required in at least a 28-day period for platelet transfusion and at least 56-day period for RBC transfusion. The duration of the longest interval with transfusion independence was summarized using Kaplan-Meier analysis.
Results are presented for responders and non-responders. If any participant achieved hematologic response (either CR or PR) any time on or before 6 months, they were considered as responders, else they were considered as non-responders.
Only participants who achieved hematologic response of CR or PR at Month 6 were followed up until Month 24

End point type	Secondary

End point timeframe:

Up to 6 months (non-responders at Month 6) and up to 24 months (responders at Month 6)

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Days				
median (confidence interval 95%)				
Day 1 to 6 months- Responders	9999 (-9999 to 9999)			
Day 1 to 24 months- Responders	9999 (498.0 to 9999)			
Day 1 to 6 months- Non-Responders	87.0 (48.0 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who were platelet transfusion independent

End point title	Percentage of participants who were platelet transfusion independent

End point description:

Percentage of participants who were platelet transfusion independent at least once by 6 months and by 24 months (responders only). Independence was defined as no platelet transfusion for at least 28 days.
Results are presented for responders and non-responders. If any participant achieved hematologic response (either CR or PR) any time on or before 6 months, they were considered as responders, else they were considered as non-responders.
Only participants who achieved hematologic response of CR or PR at Month 6 were followed up until Month 24.

End point type	Secondary

End point timeframe:

Up to 6 months (non-responders at Month 6) and up to 24 months (responders at Month 6)

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Participants				
Day 1 to 6 months- Responders	25			
Day 1 to 24 months- Responders	25			
Day 1 to 6 months- Non-responders	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in scores of Functional Assessment of Cancer Therapy - General (FACT-G) Patient Reported Outcome

End point title	Change from baseline in scores of Functional Assessment of Cancer Therapy - General (FACT-G) Patient Reported Outcome

End point description:

The FACT-G consists of 27-items divided into 4 domains (physical well-being, social well-being, emotional and functional well-being). All items of the FACT-G use a 5 point scale ranging from 0 to 4 with a 0 rating being "not at all" and a 4 rating being "very much". Total FACT-G score is the sum of physical well-being score, social well-being score, emotional well-being score and functional well-being score. Score ranges from 0 to 108, with higher scores indicating better quality of life (QoL). A positive change from baseline indicates improvement in the QoL.
Results are presented for responders and non-responders. If any participant achieved hematologic response (either CR or PR) any time on or before 6 months, they were considered as responders, else they were considered as non-responders.
Only participants who achieved hematologic response of CR or PR at Month 6 were followed up until Month 24.

End point type	Secondary

End point timeframe:

Baseline, every 2 weeks from Week 2 to Week 24 or End of Treatment Period 1 (for all participants); and at Week 38, Week 53, Month 24 or End of Treatment Period 2 (for responders at Month 6 only)

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Score on a scale				
median (full range (min-max))				
Week 2 (Treatment period 1) - Responders	-2.0 (-26 to 30)			
Week 4 (Treatment period 1) - Responders	-3.0 (-22 to 23)			
Week 6 (Treatment period 1) - Responders	-0.3 (-48 to 30)			
Week 8 (Treatment period 1) - Responders	0.0 (-25 to 30)			
Week 10 (Treatment period 1) - Responders	-1.3 (-43 to 33)			
Week 12 (Treatment period 1) - Responders	0.8 (-40 to 30)			

Week 14 (Treatment period 1) - Responders	1.0 (-44 to 29)			
Week 16 (Treatment period 1) - Responders	-2.0 (-51 to 35)			
Week 18 (Treatment period 1) - Responders	3.0 (-41 to 37)			
Week 20 (Treatment period 1) - Responders	-1.0 (-46 to 41)			
Week 22 (Treatment period 1) - Responders	1.0 (-43 to 39)			
Week 24 (Treatment period 1) - Responders	1.8 (-46 to 35)			
Week 26 (Treatment period 1) - Responders	1.0 (-51 to 38)			
End of treatment period 1 - Responders	-1.0 (-51 to 38)			
Week 38 (Treatment period 2)- Responders	5.7 (-43 to 47)			
Week 53 (Treatment period 2)- Responders	4.0 (-46 to 42)			
Month 24 (Treatment period 2)- Responders	22.0 (-50 to 84)			
End of treatment period 2 - Responders	13.5 (-5 to 47)			
Week 2 (Treatment period 1) - Non-Responders	-0.3 (-34 to 21)			
Week 4 (Treatment period 1) - Non-Responders	-1.0 (-42 to 22)			
Week 6 (Treatment period 1) - Non-Responders	-3.6 (-45 to 17)			
Week 8 (Treatment period 1) - Non-Responders	1.5 (-36 to 99)			
Week 10 (Treatment period 1) - Non-Responders	-0.9 (-27 to 25)			
Week 12 (Treatment period 1) - Non-Responders	-0.3 (-54 to 26)			
Week 14 (Treatment period 1) - Non-Responders	-0.3 (-39 to 28)			
Week 16 (Treatment period 1) - Non-Responders	0.3 (-50 to 23)			
Week 18 (Treatment period 1) - Non-Responders	-2.6 (-45 to 19)			
Week 20 (Treatment period 1) - Non-Responders	-1.5 (-44 to 22)			
Week 22 (Treatment period 1) - Non-Responders	-1.0 (-45 to 12)			
Week 24 (Treatment period 1) - Non-Responders	2.7 (-30 to 18)			
Week 26 (Treatment period 1) - Non-Responders	-2.7 (-25 to 24)			
End of treatment period 1 - Non-Responders	-2.0 (-30 to 24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in scores of FACT - Thrombocytopenia 18 (FACT-TH18) Patient Reported Outcome

End point title	Change from baseline in scores of FACT - Thrombocytopenia 18 (FACT-TH18) Patient Reported Outcome

End point description:

The FACT-TH18 is comprised of FACT-G and a thrombocytopenia specific questionnaire. FACT-G consists of 27-items divided into 4 domains (physical, social, emotional and functional well-being). FACT-TH18 has 18 additional items which asks the patient to rate degree of thrombocytopenia. All items of the FACT-TH18 use a 5 point scale ranging from 0 to 4, with 0 = "not at all" and 4 = "very much". Total FACT-TH18 score is the sum of physical, social, emotional and functional well-being scores, and thrombocytopenia subscale. Score ranges from 0 to 180, with higher scores indicating better QoL. A positive change from baseline indicates improvement in the QoL. Results are presented for responders and non-responders. If any participant achieved hematologic response (CR or PR) any time on or before 6 months, they were considered as responders, else they were considered as non-responders. Only participants who achieved hematologic response of CR or PR at Month 6 were followed up until Month 24.

End point type	Secondary

End point timeframe:

Baseline, every 2 weeks from Week 2 to Week 24 or End of Treatment Period 1 (for all participants); and at Week 38, Week 53, Month 24 or End of Treatment Period 2 (for responders at Month 6 only)

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Score on a scale				
median (full range (min-max))				
Week 2 (Treatment period 1) - Responders	2.3 (-43 to 43)			
Week 4 (Treatment period 1) - Responders	-1.5 (-37 to 54)			
Week 6 (Treatment period 1) - Responders	8.4 (-62 to 70)			
Week 8 (Treatment period 1) - Responders	9.0 (-34 to 66)			
Week 10 (Treatment period 1) - Responders	3.4 (-44 to 73)			
Week 12 (Treatment period 1) - Responders	9.3 (-45 to 69)			
Week 14 (Treatment period 1) - Responders	6.4 (-45 to 63)			
Week 16 (Treatment period 1) - Responders	7.8 (-47 to 68)			
Week 18 (Treatment period 1) - Responders	13.9 (-46 to 77)			
Week 20 (Treatment period 1) - Responders	11.8 (-48 to 81)			
Week 22 (Treatment period 1) - Responders	13.5 (-46 to 81)			
Week 24 (Treatment period 1) - Responders	14.5 (-48 to 72)			
Week 26 (Treatment period 1) - Responders	18.2 (-57 to 72)			
End of treatment period 1 - Responders	13.9 (-57 to 72)			
Week 38 (Treatment period 2)- Responders	21.7 (-50 to 88)			
Week 53 (Treatment period 2)- Responders	22.0 (-50 to 84)			

Month 24 (Treatment period 2)-Responders	35.7 (5 to 95)			
End of treatment period 2 - Responders	6.9 (-55 to 35)			
Week 2 (Treatment period 1) - Non-Responders	0.6 (-78 to 39)			
Week 4 (Treatment period 1) - Non-Responders	2.1 (-77 to 45)			
Week 6 (Treatment period 1) - Non-Responders	-1.5 (-97 to 42)			
Week 8 (Treatment period 1) - Non-Responders	2.0 (-54 to 43)			
Week 10 (Treatment period 1) - Non-Responders	5.2 (-22 to 41)			
Week 12 (Treatment period 1) - Non-Responders	1.8 (-101 to 49)			
Week 14 (Treatment period 1) - Non-Responders	2.8 (-64 to 41)			
Week 16 (Treatment period 1) - Non-Responders	2.1 (-98 to 38)			
Week 18 (Treatment period 1) - Non-Responders	0.5 (-78 to 27)			
Week 20 (Treatment period 1) - Non-Responders	2.4 (-68 to 43)			
Week 22 (Treatment period 1) - Non-Responders	-1.3 (-67 to 39)			
Week 24 (Treatment period 1) - Non-Responders	0.7 (-31 to 43)			
Week 26 (Treatment period 1) - Non-Responders	-1.4 (-24 to 41)			
End of treatment period 1 - Non-Responders	-1.4 (-27 to 41)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in scores of Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT- Fatigue) Patient Reported Outcome

End point title	Change from baseline in scores of Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT- Fatigue) Patient Reported Outcome

End point description:

The FACIT- Fatigue is a 13-item fatigue subscale that asks the patient to rate their degree of tiredness, weakness and fatigue. All items of the FACIT-Fatigue use a 5-point scale ranging from 0 to 4 with a 0 rating being "not at all" and a 4 rating being "very much". Total score ranges from 0 to 52. Negatively worded items were reverse scored before summing so that higher total scores indicate less fatigue. A positive change from baseline indicates improvement.
Results are presented for responders and non-responders. If any participant achieved hematologic response (either CR or PR) any time on or before 6 months, they were considered as responders, else they were considered as non-responders.
Only participants who achieved hematologic response of CR or PR at Month 6 were followed up until Month 24.

End point type	Secondary

End point timeframe:

Baseline, every 2 weeks from Week 2 to Week 24 or End of Treatment Period 1 (for all participants); and at Week 38, Week 53, Month 24 or End of Treatment Period 2 (for responders at Month 6 only)

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Score on a scale				
median (full range (min-max))				
Week 2 (Treatment period 1) - Responders	3.0 (-13 to 34)			
Week 4 (Treatment period 1) - Responders	2.0 (-16 to 22)			
Week 6 (Treatment period 1) - Responders	4.0 (-22 to 32)			
Week 8 (Treatment period 1) - Responders	6.0 (-7 to 29)			
Week 10 (Treatment period 1) - Responders	4.5 (-11 to 30)			
Week 12 (Treatment period 1) - Responders	5.5 (-11 to 31)			
Week 14 (Treatment period 1) - Responders	6.5 (-5 to 26)			
Week 16 (Treatment period 1) - Responders	6.0 (-5 to 28)			
Week 18 (Treatment period 1) - Responders	7.0 (-5 to 28)			
Week 20 (Treatment period 1) - Responders	6.0 (-5 to 29)			
Week 22 (Treatment period 1) - Responders	6.0 (-8 to 33)			
Week 24 (Treatment period 1) - Responders	6.0 (-5 to 29)			
Week 26 (Treatment period 1) - Responders	7.0 (-9 to 32)			
End of treatment period 1 - Responders	6.0 (-9 to 32)			
Week 38 (Treatment period 2)- Responders	6.0 (-8 to 33)			
Week 53 (Treatment period 2)- Responders	8.0 (-2 to 41)			
Month 24 (Treatment period 2)- Responders	9.0 (1 to 31)			
End of treatment period 2 - Responders	11.5 (-5 to 42)			
Week 2 (Treatment period 1) - Non-Responders	-0.5 (-23 to 19)			
Week 4 (Treatment period 1) - Non-Responders	-2.0 (-38 to 20)			
Week 6 (Treatment period 1) - Non-Responders	0.0 (-43 to 18)			
Week 8 (Treatment period 1) - Non-Responders	-1.0 (-27 to 14)			
Week 10 (Treatment period 1) - Non-Responders	0.5 (-25 to 16)			
Week 12 (Treatment period 1) - Non-Responders	-1.0 (-42 to 15)			
Week 14 (Treatment period 1) - Non-Responders	-1.5 (-43 to 16)			
Week 16 (Treatment period 1) - Non-Responders	-0.5 (-46 to 15)			

Week 18 (Treatment period 1) - Non-Responders	-6.0 (-43 to 15)			
Week 20 (Treatment period 1) - Non-Responders	-6.0 (-45 to 22)			
Week 22 (Treatment period 1) - Non-Responders	-4.0 (-45 to 15)			
Week 24 (Treatment period 1) - Non-Responders	-7.0 (-19 to 12)			
Week 26 (Treatment period 1) - Non-Responders	-8.0 (-19 to 15)			
End of treatment period 1 - Non-Responders	-4.0 (-19 to 15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter- Cmax of eltrombopag when combined with cyclosporine

End point title	Pharmacokinetic parameter- Cmax of eltrombopag when combined with cyclosporine

End point description:

Cmax is the observed maximum plasma concentration following administration. The plasma samples from all participants were assayed for eltrombopag concentrations using a validated liquid chromatography – tandem mass spectrometry assay (LC-MS/MS). The lower limit of quantitation (LLOQ) was 0.1 microgram/milliliter (ug/mL). Concentration values below the LLOQ were reported as zero, and missing samples were labeled accordingly. Results are reported by ethnicity: East/Southeast Asian participants received eltrombopag planned dose of 100mg/day and all other participants received eltrombopag planned dose of 150mg/day.

End point type	Secondary

End point timeframe:

Week 2 at pre-dose and 2, 4, 6 and 8 hours post-dose.

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: microgram/milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
East/Southeast Asian ethnicity	29.1 (± 43.5)			
Non-East/Southeast Asian ethnicity	38.7 (± 38.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter-AUClast of eltrombopag when combined with cyclosporine

End point title	Pharmacokinetic parameter-AUClast of eltrombopag when combined with cyclosporine

End point description:

AUClast is the area under the curve calculated to the last quantifiable concentration point (Tlast). The plasma samples from all participants were assayed for eltrombopag concentrations using a validated liquid chromatography – tandem mass spectrometry assay (LC-MS/MS). The lower limit of quantitation (LLOQ) was 0.1 ug/mL. Concentration values below the LLOQ were reported as zero, and missing samples were labeled accordingly. Results are reported by ethnicity: East/Southeast Asian participants received eltrombopag planned dose of 100mg/day and all other participants received eltrombopag planned dose of 150mg/day.

End point type	Secondary

End point timeframe:

Week 2 at pre-dose and 2, 4, 6 and 8 hours post-dose

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: hour*microgram/milliliter (h*ug/mL)				
geometric mean (geometric coefficient of variation)				
East/Southeast Asian ethnicity	583 (± 38.3)			
Non-East/Southeast Asian ethnicity	702 (± 59.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter- AUCtau of eltrombopag when combined with cyclosporine

End point title	Pharmacokinetic parameter- AUCtau of eltrombopag when combined with cyclosporine

End point description:

AUCtau is the area under the curve calculated to the end of the dosing interval (tau). The plasma samples from all participants were assayed for eltrombopag concentrations using a validated liquid chromatography – tandem mass spectrometry assay (LC-MS/MS). The lower limit of quantitation (LLOQ) was 0.1 ug/mL. Concentration values below the LLOQ were reported as zero, and missing samples were labeled accordingly. Results are reported by ethnicity: East/Southeast Asian participants received eltrombopag planned dose of 100mg/day and all other participants received eltrombopag planned dose of 150mg/day.

End point type	Secondary

End point timeframe:

Week 2 at pre-dose and 2, 4, 6 and 8 hours post-dose

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: hour*microgram/milliliter (h*ug/mL)				
geometric mean (geometric coefficient of variation)				
East/Southeast Asian ethnicity	686 (± 32.4)			
Non-East/Southeast Asian ethnicity	727 (± 33.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter- Ctrough of eltrombopag when combined with cyclosporine

End point title	Pharmacokinetic parameter- Ctrough of eltrombopag when combined with cyclosporine

End point description:

Ctrough is the pre-dose plasma concentration. The plasma samples from all participants were assayed for eltrombopag concentrations using a validated liquid chromatography – tandem mass spectrometry assay (LC-MS/MS). The lower limit of quantitation (LLOQ) was 0.1 ug/mL. Concentration values below the LLOQ were reported as zero, and missing samples were labeled accordingly. Results are reported by ethnicity: East/Southeast Asian participants received eltrombopag planned dose of 100mg/day and all other participants received eltrombopag planned dose of 150mg/day.

End point type	Secondary

End point timeframe:

Week 2 at pre-dose

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: microgram/milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
East/Southeast Asian ethnicity	19.3 (± 45.3)			
Non-East/Southeast Asian ethnicity	27.2 (± 44.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter- Tmax of eltrombopag when combined with cyclosporine

End point title	Pharmacokinetic parameter- Tmax of eltrombopag when combined with cyclosporine

End point description:

Tmax is the time to reach peak or maximum concentration. The plasma samples from all participants were assayed for eltrombopag concentrations using a validated liquid chromatography – tandem mass spectrometry assay (LC-MS/MS). The lower limit of quantitation (LLOQ) was 0.1 ug/mL. Concentration values below the LLOQ were reported as zero, and missing samples were labeled accordingly. Results are reported by ethnicity: East/Southeast Asian participants received eltrombopag planned dose of 100mg/day and all other participants received eltrombopag planned dose of 150mg/day.

End point type	Secondary

End point timeframe:

Week 2 at pre-dose and 2, 4, 6 and 8 hours post-dose

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Hours				
median (full range (min-max))				
East/Southeast Asian ethnicity	5.79 (1.93 to 8.00)			
Non-East/Southeast Asian ethnicity	3.75 (0.00 to 8.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter- CLss/F of eltrombopag when combined with cyclosporine

End point title	Pharmacokinetic parameter- CLss/F of eltrombopag when combined with cyclosporine

End point description:

CLss/F is the apparent systemic (or total body) clearance at steady state from plasma. The plasma samples from all participants were assayed for eltrombopag concentrations using a validated liquid chromatography – tandem mass spectrometry assay (LC-MS/MS). The lower limit of quantitation (LLOQ) was 0.1 ug/mL. Concentration values below the LLOQ were reported as zero, and missing samples were labeled accordingly. Results are reported by ethnicity: East/Southeast Asian participants received eltrombopag planned dose of 100mg/day and all other participants received eltrombopag planned dose of 150mg/day.

End point type	Secondary

End point timeframe:

Week 2 at pre-dose and 2, 4, 6 and 8 hours post-dose

End point values	Eltrombopag + cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: milliliter/hour (mL/h)				
geometric mean (geometric coefficient of variation)				
East/Southeast Asian ethnicity	146 (± 32.4)			
Non-East/Southeast Asian ethnicity	206 (± 33.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From day of first dose of study medication to 30 days after last dose of study medication, assessed up to 25 months

Adverse event reporting additional description:

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	25.0

Reporting groups

Reporting group title	Eltrombopag + cyclosporine

Reporting group description:

Participants received eltrombopag (orally, 100 mg once daily for East/Southeast Asian participants / 150 mg once daily for all other participants) in combination with cyclosporine (orally, 10.0 mg/kg/day in divided doses every 12 hours) for up to 6 months. Thereafter, 6-month responders were treated with cyclosporine for up to Month 24

Serious adverse events	Eltrombopag + cyclosporine		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 54 (50.00%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Organising pneumonia				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				

Depression			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Incisional hernia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	10 / 54 (18.52%)		
occurrences causally related to treatment / all	0 / 22		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric dysplasia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dental caries			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral pain			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal haemorrhage			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Haematochezia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			

subjects affected / exposed	2 / 54 (3.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Sepsis				

subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostatic abscess			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia fungal			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 54 (1.85%)		
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 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Eltrombopag + cyclosporine		
Total subjects affected by non-serious adverse events subjects affected / exposed	47 / 54 (87.04%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	8 / 54 (14.81%) 10		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all)	 4 / 54 (7.41%) 4 8 / 54 (14.81%) 13 8 / 54 (14.81%) 8		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	 5 / 54 (9.26%) 7 4 / 54 (7.41%) 5		
Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Alanine aminotransferase increased subjects affected / exposed occurrences (all) Blood alkaline phosphatase increased	 10 / 54 (18.52%) 17 12 / 54 (22.22%) 18 		

subjects affected / exposed occurrences (all) Blood bilirubin increased subjects affected / exposed occurrences (all) SARS-CoV-2 test positive subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 11 22 / 54 (40.74%) 46 3 / 54 (5.56%) 3 3 / 54 (5.56%) 6 10 / 54 (18.52%) 12		
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all)	 3 / 54 (5.56%) 3 4 / 54 (7.41%) 5		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	 3 / 54 (5.56%) 3		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	 6 / 54 (11.11%) 7 10 / 54 (18.52%) 30 3 / 54 (5.56%) 3		
Eye disorders			

Retinal haemorrhage			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	12 / 54 (22.22%)		
occurrences (all)	19		
Abdominal pain			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	5		
Gingival bleeding			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	11		
Gastritis			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	8		
Gingival hypertrophy			
subjects affected / exposed	6 / 54 (11.11%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	16 / 54 (29.63%)		
occurrences (all)	21		
Mouth ulceration			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Mouth haemorrhage			

subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	4		
Odynophagia			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	11 / 54 (20.37%)		
occurrences (all)	25		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Ecchymosis			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Petechiae			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	7		
Rash			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	5		
Muscle spasms			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	5		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 5			
Oral candidiasis subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 5			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 54 (9.26%) 8			
Oral herpes subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3			
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3			
Hyperglycaemia subjects affected / exposed occurrences (all)	6 / 54 (11.11%) 7			
Hyperkalaemia subjects affected / exposed occurrences (all)	5 / 54 (9.26%) 7			
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	7 / 54 (12.96%) 7			
Hyperuricaemia subjects affected / exposed occurrences (all)	5 / 54 (9.26%) 6			
Iron overload subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3			
Hypomagnesaemia subjects affected / exposed occurrences (all)	10 / 54 (18.52%) 21			
Hypokalaemia				

subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2017	The scope of this amendment was to lower the upper limit of exclusion criterion 6 (renal function) and to further clarify wording and improve consistency in the document.
26 February 2019	Rationale for this amendment was based on findings in the study that identified the need to clarify patient selection and dose management. The occurrence of 6 fatal cases (four on treatment, one post treatment and one additional death in screening) warranted a thorough assessment by Novartis. In order to accurately investigate these findings, assess their causalities, identify and implement any necessary corrective actions, Novartis voluntarily put the study on a partial/temporary clinical hold (hold of recruitment of new patients), effective 05-Oct-2018. Health Authorities were notified in all participating countries. In summary, none of these fatal cases were suspected to be related to study treatment (eltrombopag and cyclosporine) by the Investigators. Novartis and the Steering Committee determined that the six fatal cases reported in this study were due to known complications of the underlying SAA, compounded by high-risk baseline demographics (notably age, frailty and comorbidities), low adherence to study treatment and worse severity of disease. Likewise all six deaths were considered by the Investigators to be due to the underlying disease. Novartis therefore considered the events that led to the fatal outcomes did not alter the established safety profile of eltrombopag and that the benefit-risk profile for eltrombopag remained positive. Based on the findings identified, changes were implemented in this protocol amendment to some inclusion, exclusion criteria and dose management sections. The enrollment was re-started after approval of this amendment by the local HA/ECs. Of note, in this amendment, the study duration was shortened from 60 months to 24 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 October 2018	Novartis voluntarely put the recruitment on hold to accurately investigate 6 fatal cases (four on treatment, one post treatment and one additional death in screening), assess their causalities, identify and implement any necessary corrective actions	26 February 2019

Notes:

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/ for complete trial results

Notes: