Clinical trial results:
A phase II, open-label, non-controlled, intra-patient dose-escalation study to characterize the pharmacokinetics after oral administration of eltrombopag in pediatric patients with refractory, relapsed or treatment-naive severe aplastic anemia or recurrent aplastic anemia.

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.

Summary

EudraCT number	2015-003166-91
Trial protocol	GB PT NL
Global end of trial date	27 January 2025

Results information

Result version number	v2 (current)
This version publication date	09 August 2025
First version publication date	11 April 2025
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CETB115E2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03025698
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	Lichtstrasse 35, Basel, Switzerland, 4056
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000170-PIP03-13
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	22 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2022
Global end of trial reached?	Yes
Global end of trial date	27 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the PK of eltrombopag at the highest dose after oral administration in pediatric patients with SAA.

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	30 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Thailand: 9
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	51
EEA total number of subjects	1

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)	30
Adolescents (12-17 years)	21
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted in 19 sites in 6 countries

Pre-assignment

Screening details:

Participants received 25 mg daily (ages 1–6) or 50 mg daily (ages 6–<18) for up to 6 years. Doses were adjusted biweekly based on platelet counts, up to 150 mg max. Study included a 26-week treatment, 52-week follow-up, and 3-year long-term follow-up.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A: Regimen 1

Arm description:

Participants received hATG (ATGAM®), CsA and eltrombopag beginning on Day 1.

Arm type	Experimental
Investigational medicinal product name	Eltrombopag
Investigational medicinal product code	ETB115
Other name	
Pharmaceutical forms	Film-coated tablet, Powder for oral solution
Routes of administration	Other use , Oral use

Dosage and administration details:

Dose strengths of 12.5 mg, 25 mg, 50 mg, and 75 mg for film-coated tablet and 25 mg powder for oral soution

Arm title	Cohort A: Regimen 2

Arm description:

Participants received CsA and eltrombopag beginning on Day 1.

Arm type	Experimental
Investigational medicinal product name	Eltrombopag
Investigational medicinal product code	ETB115
Other name	
Pharmaceutical forms	Film-coated tablet, Powder for oral solution
Routes of administration	Other use , Oral use

Dosage and administration details:

Dose strengths of 12.5 mg, 25 mg, 50 mg, and 75 mg for film-coated tablet and 25 mg powder for oral soution

Arm title	Cohort B

Arm description:

Participants who previously had untreated SAA received hATG, CsA and eltrombopag beginning on Day 1.

Arm type	Experimental

Investigational medicinal product name	Eltrombopag
Investigational medicinal product code	ETB115
Other name	
Pharmaceutical forms	Film-coated tablet, Powder for oral solution
Routes of administration	Other use , Oral use

Dosage and administration details:

Dose strengths of 12.5 mg, 25 mg, 50 mg, and 75 mg for film-coated tablet and 25 mg powder for oral soution

Number of subjects in period 1	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B
Started	10	4	37
Subjs who entered 26-wk treatment phase	10	4	37
Completed 26-wk treatment	7	4	25
Entered 52-wk post-trtment f/u Ph 1	9	4	26
Did not enter 52-wk post-trtmnt f/u Ph	1 [1]	0 [2]	11
Entered 3-yr post-trtmnt f/u 2	6	3	19
Did not complete PTFU2	1 [3]	1 [4]	9 [5]
Completed	5	2	10
Not completed	5	2	27
Adverse event, serious fatal	-	1	-
Physician decision	3	-	8
Participant/Guardian Decision	2	1	11
Adverse event, non-fatal	-	-	2
Progressive Disease	-	-	3
Treatment done/study exit unclear	-	-	2
Lost to follow-up	-	-	1

Notes:

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

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

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

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

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

completed, minus those who left.
Justification: Data provided for clarification

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A: Regimen 1
Reporting group description:	
Participants received hATG (ATGAM®), CsA and eltrombopag beginning on Day 1.	
Reporting group title	Cohort A: Regimen 2
Reporting group description:	
Participants received CsA and eltrombopag beginning on Day 1.	
Reporting group title	Cohort B
Reporting group description:	
Participants who previously had untreated SAA received hATG, CsA and eltrombopag beginning on Day 1.	

Reporting group values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B
Number of subjects	10	4	37
Age categorical Units: Subjects			
Children (2-11 years)	5	3	22
Adolescents (12-17 years)	5	1	15
Age Continuous Units: Years			
median	12.0	10.0	10.0
full range (min-max)	4.0 to 17.0	7.0 to 12.0	2.0 to 17.0
Sex: Female, Male Units: Participants			
Female	5	1	17
Male	5	3	20
Race/Ethnicity, Customized Units: Subjects			
Caucasian	4	2	24
Black	2	1	4
Asian	3	1	9
Unknown	1	0	0

Reporting group values	Total		
Number of subjects	51		
Age categorical Units: Subjects			
Children (2-11 years)	30		
Adolescents (12-17 years)	21		
Age Continuous Units: Years			
median			
full range (min-max)	-		
Sex: Female, Male Units: Participants			
Female	23		
Male	28		

Race/Ethnicity, Customized Units: Subjects			
Caucasian	30		
Black	7		
Asian	13		
Unknown	1		

End points

End points reporting groups

Reporting group title	Cohort A: Regimen 1
Reporting group description: Participants received hATG (ATGAM®), CsA and eltrombopag beginning on Day 1.	
Reporting group title	Cohort A: Regimen 2
Reporting group description: Participants received CsA and eltrombopag beginning on Day 1.	
Reporting group title	Cohort B
Reporting group description: Participants who previously had untreated SAA received hATG, CsA and eltrombopag beginning on Day 1.	
Subject analysis set title	Cohort A: Regimen 1 (1 to <6 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received hATG (ATGAM®), CsA and eltrombopag beginning on Day 1.	
Subject analysis set title	Cohort A: Regimen 1 (6 to <18 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received hATG (ATGAM®), CsA and eltrombopag beginning on Day 1.	
Subject analysis set title	Cohort A: Regimen 2 (6 to <18 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received CsA and eltrombopag beginning on Day 1.	
Subject analysis set title	Cohort B (1 to < 6 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Previously untreated SAA, hATG (ATGAM®), CsA and eltrombopag begin on Day 1 and all patients will be treated with the same regimen	
Subject analysis set title	Cohort B (6 to <18 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who previously had untreated SAA received hATG, CsA and eltrombopag beginning on Day 1.	
Subject analysis set title	Cohort A: Regimen 1 (1 to <6 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received hATG (ATGAM®), CsA and eltrombopag beginning on Day 1.	
Subject analysis set title	Cohort A: Regimen 1 (6 to <18 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received hATG (ATGAM®), CsA and eltrombopag beginning on Day 1.	
Subject analysis set title	Cohort A: Regimen 2 (6 to <18 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received CsA and eltrombopag beginning on Day 1.	
Subject analysis set title	Cohort B (6 to <18 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who previously had untreated SAA received hATG, CsA and eltrombopag beginning on Day 1.	

Subject analysis set title	Cohort A: Regimen 1
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received hATG (ATGAM®), CsA and eltrombopag beginning on Day 1.	
Subject analysis set title	Cohort B (1 to <6 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Previously untreated SAA, hATG (ATGAM®), CsA and eltrombopag begin on Day 1 and all patients will be treated with the same regimen	
Subject analysis set title	Cohort B (6 to <18 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Previously untreated SAA, hATG (ATGAM®), CsA and eltrombopag begin on Day 1 and all patients will be treated with the same regimen	
Subject analysis set title	Cohort A: Regimen 1 (6 to <18 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received hATG (ATGAM®), CsA and eltrombopag beginning on Day 1.	
Subject analysis set title	Cohort B (1 to <6 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Previously untreated SAA, hATG (ATGAM®), CsA and eltrombopag begin on Day 1 and all patients will be treated with the same regimen	
Subject analysis set title	Cohort B (6 to <18 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Previously untreated SAA, hATG (ATGAM®), CsA and eltrombopag begin on Day 1 and all patients will be treated with the same regimen	
Subject analysis set title	Cohort A: Regimen 2 (6 to <18 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received CsA and eltrombopag beginning on Day 1.	
Subject analysis set title	Cohort B (6 to <18 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Previously untreated SAA, hATG (ATGAM®), CsA and eltrombopag begin on Day 1 and all patients will be treated with the same regimen	
Subject analysis set title	Cohort A: Regimen 2
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received CsA and eltrombopag beginning on Day 1	
Subject analysis set title	Cohort A: Regimen 1
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received hATG (ATGAM®), CsA and eltrombopag beginning on Day 1.	
Subject analysis set title	Total (Cohorts A (Regimen 1 & 2) and B
Subject analysis set type	Per protocol
Subject analysis set description:	
All participants in Cohort A Regimen 1, Cohort A Regimen 2 and B.	

Primary: Eltrombopag PK parameters: AUCtau, AUClast

End point title	Eltrombopag PK parameters: AUCtau, AUClast[1]

End point description:

AUC tau: Area under the curve calculated to the end of the dosing interval (tau) (mass*time/volume)
AUC last: Area under the curve calculated to the last quantifiable concentration point (Tlast) (mass*time/volume)

End point type	Primary

End point timeframe:

at least 11 weeks after dose initiation or later when patients are taking the highest dose, up to Week 78

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 analysis was done for this endpoint

End point values	Cohort A: Regimen 1 (1 to <6 years)	Cohort A: Regimen 1 (6 to <18 years)	Cohort A: Regimen 2 (6 to <18 years)	Cohort B (1 to < 6 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	7	3	8
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
AUCtau (n = 1, 4, 1, 6, 10)	272000 (± 999)	285000 (± 72.4)	406000 (± 999)	502000 (± 65.6)
AUClast (n = 1,5, 3, 8, 15)	272000 (± 999)	300000 (± 60.2)	166000 (± 196)	477000 (± 52.5)

End point values	Cohort B (6 to <18 years)			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
AUCtau (n = 1, 4, 1, 6, 10)	275000 (± 52.6)			
AUClast (n = 1,5, 3, 8, 15)	259000 (± 75.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Eltrombopag PK parameter: Cmax

End point title	Eltrombopag PK parameter: Cmax[2]

End point description:

Cmax is the observed maximum plasma concentration following administration (mass/volume)

End point type	Primary

End point timeframe:

at least 11 weeks after dose initiation or later when patients are taking the highest dose, up to Week 78

Notes:

[2] - 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 analysis was done for this endpoint

End point values	Cohort B (1 to < 6 years)	Cohort A: Regimen 1 (1 to <6 years)	Cohort A: Regimen 1 (6 to <18 years)	Cohort A: Regimen 2 (6 to <18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	1	5	2
Units: ng/mL				
geometric mean (geometric coefficient of variation)	27100 (± 40.6)	16100 (± 999)	14500 (± 66.7)	14300 (± 56.7)

End point values	Cohort B (6 to <18 years)			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	15600 (± 47.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Eltrombopag PK parameter: Ctrough at the highest dose level

End point title	Eltrombopag PK parameter: Ctrough at the highest dose level[3]

End point description:

Ctrough is the pre-dose plasma concentration (mass/volume).

End point type	Primary

End point timeframe:

at least 11 weeks after dose initiation or later when patients are taking the highest dose, up to Week 78

Notes:

[3] - 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 analysis was done for this endpoint

End point values	Cohort A: Regimen 1 (1 to <6 years)	Cohort B (1 to < 6 years)	Cohort A: Regimen 1 (6 to <18 years)	Cohort A: Regimen 2 (6 to <18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	8	5	2
Units: ng/mL				
geometric mean (geometric coefficient of variation)	5470 (± 999)	13400 (± 113)	9930 (± 68.7)	9900 (± 32.3)

End point values	Cohort B (6 to <18 years)			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	9670 (± 64.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with an overall response and percentage of participants with a platelet response

End point title	Percentage of participants with an overall response and percentage of participants with a platelet response

End point description:

Overall response rate (ORR) is defined as the percentage of participants who have achieved a complete response (CR) or partial response (PR) by the Investigator.
CR criteria: Platelet (PLT) and red blood cell (RBC) transfusion independence, Normal age-adjusted Hgb, PLT >100 × 10^9/L and absolute neutrophil count (ANC) >1.5 × 10^9/L.
PR: PLT and RBC Transfusion independence and at least 2 of the following criteria: Reticulocytes >30 × 10^9/L, PLT >30 × 10^9/L, ANC >1.5 x 10^9L.
PLT transfusion independence is defined as a period for at least 28 days without PLT transfusion.
Platelet response rate (PRR): Platelet response is comprised of CR + PR based on the following criteria: CR: PLT >100 × 10^9/L; PR: PLT >30 × 10^9/L

End point type	Secondary

End point timeframe:

Week 12, Week 26, Week 52, Week 78

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	4	37	
Units: Percentage of participants				
number (confidence interval 95%)				
ORR: Week 12	30.0 (6.7 to 65.2)	50.0 (6.8 to 93.2)	13.5 (4.5 to 28.8)	
ORR: Week 26	70.0 (34.8 to 93.3)	75.0 (19.4 to 99.4)	45.9 (29.5 to 63.1)	
ORR: Week 52	50.0 (18.7 to 81.3)	50.0 (6.8 to 93.2)	43.2 (27.1 to 60.5)	
ORR: Week 78	50.0 (18.7 to 81.3)	75.0 (19.4 to 99.4)	40.5 (24.8 to 57.9)	
PRR: Week 12	70.0 (34.8 to 93.3)	75.0 (19.4 to 99.4)	67.6 (50.2 to 82.0)	
PRR: Week 26	60.0 (26.2 to 87.8)	100 (39.8 to 100.0)	70.3 (53.0 to 84.1)	

PRR: Week 52	50.0 (18.7 to 81.3)	75.0 (19.4 to 99.4)	48.6 (31.9 to 65.6)	
PRR: Week 78	50.0 (18.7 to 81.3)	75.0 (19.4 to 99.4)	45.9 (29.5 to 63.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Hematologic counts (platelets (blood), neutrophils (blood))

End point title	Hematologic counts (platelets (blood), neutrophils (blood))

End point description:

Individual Platelets (PLT) and neutrophil counts were summarized for all participants.

End point type	Secondary

End point timeframe:

Week 12, Week 26, Week 52, Week 78, Week 130, Week 182, Week 234

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	4	37	
Units: x 10^9 cells/L				
median (full range (min-max))				
Week 12: Platelets (blood) (n = 10, 4, 35)	40.500 (5.00 to 260.00)	73.500 (17.00 to 172.00)	50.000 (3.00 to 338.00)	
Week 26: Platelets (blood) (n = 10, 4, 31)	60.500 (3.00 to 222.00)	122.500 (49.00 to 182.00)	106.000 (3.00 to 230.00)	
Week 52: Platelets (blood) (n = 7, 4, 19)	147.000 (7.00 to 164.00)	160.500 (22.00 to 240.00)	163.000 (28.00 to 318.00)	
Week 78: Platelets (blood) (n = 6, 3, 18)	133.500 (6.00 to 308.00)	140.000 (88.00 to 273.00)	152.500 (28.00 to 278.00)	
Week 130: Platelets (blood) (n = 6, 2, 9)	155.000 (43.00 to 195.00)	138.500 (128.00 to 149.00)	139.000 (31.00 to 245.00)	
Week 182: Platelets (blood) (n = 6, 2, 5)	173.000 (9.00 to 221.00)	149.000 (127.00 to 171.00)	182.000 (104.00 to 223.00)	
Week 234: Platelets (blood) (n = 5, 1, 6)	176.000 (110.00 to 196.00)	129.000 (129.00 to 129.00)	189.000 (147.00 to 264.00)	
Week 12: Neutrophils (blood)	1.795 (0.72 to 11.72)	1.555 (1.01 to 4.15)	1.100 (0.00 to 8.10)	
Week 26: Neutrophils (blood) (n = 10, 4, 31)	2.495 (0.52 to 4.60)	1.258 (0.78 to 1.63)	1.640 (0.40 to 4.47)	
Week 52: Neutrophils (blood) (n = 7, 4, 19)	3.110 (0.17 to 4.29)	1.721 (1.11 to 3.47)	2.600 (0.83 to 5.75)	
Week 78: Neutrophils (blood) (n = 6, 3, 18)	3.617 (1.02 to 4.91)	1.234 (0.56 to 1.34)	2.292 (0.69 to 5.41)	
Week 130: Neutrophils (blood) (n = 6, 2, 9)	2.732 (1.04 to 6.72)	0.892 (0.57 to 1.21)	1.690 (1.30 to 2.67)	

Week 182: Neutrophils (blood) (n = 6, 2, 5)	3.014 (1.00 to 6.09)	1.471 (0.61 to 2.33)	3.100 (2.07 to 4.30)	
Week 234: Neutrophils (blood) (n = 5, 1, 6)	2.630 (2.04 to 4.40)	1.200 (1.20 to 1.20)	2.078 (1.02 to 4.70)	

Statistical analyses

No statistical analyses for this end point

Secondary: Hematologic counts (hemoglobin (blood))

End point title	Hematologic counts (hemoglobin (blood))

End point description:

Individual hemoglobin (Hgb) counts were summarized for all participants.

End point type	Secondary

End point timeframe:

Week 12, Week 26, Week 52, Week 78, Week 130, Week 182, Week 234

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	4	37	
Units: g/L				
median (full range (min-max))				
Week 12 (n = 10, 4, 35)	89.5 (64 to 131)	87.0 (81 to 94)	88.0 (57 to 130)	
Week 26 (n = 10, 4, 31)	101.0 (59 to 128)	98.5 (93 to 102)	95.0 (44 to 125)	
Week 52 (n = 7, 4, 19)	116.0 (52 to 138)	104.5 (95 to 117)	110.0 (92 to 133)	
Week 78 (n = 6, 3, 18)	118.5 (67 to 138)	92.0 (89 to 119)	117.0 (97 to 148)	
Week 130 (n = 6, 2, 9)	119.5 (88 to 141)	125.5 (122 to 129)	126.0 (109 to 142)	
Week 182 (n = 6, 2, 5)	126.0 (96 to 138)	125.5 (115 to 136)	127.0 (66 to 129)	
Week 234 (n = 5, 1, 6)	126.0 (116 to 147)	128.0 (128 to 128)	125.0 (110 to 144)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total duration of Red Blood Cell (RBC) transfusion independence during the treatment period

End point title	Total duration of Red Blood Cell (RBC) transfusion independence during the treatment period

End point description:

RBC transfusion independence is defined as a period of time of at least 56 days without RBC transfusion.

Duration of RBC transfusion independence is defined as a period of time of at least 56 days without RBC transfusion. First transfusion duration was calculated as the date of the day before the first transfusion after baseline minus the date of first exposure eltrombopag + 1.

End point type	Secondary

End point timeframe:

From date of first dose to approx. 4.5 years

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	3	25	
Units: days				
median (full range (min-max))				
approx. 3 years	355.0 (185 to 860)	430.0 (262 to 558)	267.0 (58 to 1074)	
approx. 4.5 years	355.0 (185 to 1637)	430.0 (262 to 558)	267.0 (58 to 1296)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total duration of Platelet (PLT) transfusion independence during the treatment period

End point title	Total duration of Platelet (PLT) transfusion independence during the treatment period

End point description:

Platelet transfusion independence during the treatment period is defined as the duration from the first day of the 28-day period without PLT transfusion until the occurrence of a PLT transfusion after the period free from any PLT transfusion.
Duration of PLT transfusion independence is defined as a period of time of at least 28 days without platelet transfusion. First transfusion duration was calculated as the date of the day before the first transfusion after baseline minus the date of first exposure eltrombopag + 1.

End point type	Secondary

End point timeframe:

From date of first dose to approx. 4.5 years

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	4	28	
Units: days				
median (full range (min-max))				
approx. 3 years	252.0 (36 to 860)	360.5 (139 to 560)	268.0 (34 to 1100)	
approx. 4.5 years	252.0 (36 to 1637)	360.5 (139 to 560)	268.0 (34 to 1322)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum duration of Red Blood Cell (RBC) transfusion independence

End point title	Maximum duration of Red Blood Cell (RBC) transfusion independence

End point description:

RBC transfusion independence is defined as a period of time of at least 56 days without RBC transfusion. Maximum duration of RBC transfusion independence is defined as the maximum duration among the durations of RBC transfusion independence. First transfusion duration was calculated as the date of first transfusion after baseline minus the date of first exposure eltrombopag + 1.

End point type	Secondary

End point timeframe:

From date of first dose to approx. 4.5 years

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	3	25	
Units: days				
median (full range (min-max))				
approx. 3 years	355.0 (185 to 860)	321.0 (262 to 430)	259.0 (58 to 1074)	
approx. 4.5 years	355.0 (185 to 1637)	321.0 (262 to 430)	262.0 (58 to 1296)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum duration of platelet (PLT) transfusion independence

End point title	Maximum duration of platelet (PLT) transfusion independence

End point description:

Maximum duration of PLT transfusion independence is defined as the maximum duration among the durations of PLT transfusion independence. First transfusion duration was calculated as the date of first transfusion after baseline minus the date of first exposure eltrombopag + 1.

End point type	Secondary

End point timeframe:

From date of first dose to approx. 4.5 years

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	4	28	
Units: days				
median (full range (min-max))				
approx. 3 years	252.0 (36 to 860)	360.5 (64 to 560)	249.5 (34 to 1067)	
approx. 4.5 years	252.0 (36 to 1637)	360.5 (64 to 560)	249.5 (34 to 1289)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Bone marrow cellularity

End point title	Overall Bone marrow cellularity

End point description:

Percentage of cells in bone marrow biopsy - a comprehensive diagnostic evaluation to distinguish between the various bone marrow disorders.

End point type	Secondary

End point timeframe:

Screening, Week 26, Week 52, Week 78, Week 130, Week 184, Week 234

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	4	33	
Units: Percentage of cells				
median (full range (min-max))				
Overall cellularity (OC): Screening (n=10, 4, 26)	11.5 (5.0 to 30.0)	32.5 (20.0 to 50.0)	4.0 (2.0 to 40.0)	
OC: Week 26 (n = 8, 3, 30)	30.0 (10.0 to 50.0)	30.0 (20.0 to 50.0)	22.5 (2.0 to 55.0)	
OC: Week 52 (n = 5, 3, 16)	35.0 (5.0 to 45.0)	50.0 (50.0 to 65.0)	35.0 (3.0 to 55.0)	
OC: Week 78 (n = 6, 1, 15)	32.5 (5.0 to 50.0)	50.0 (50.0 to 50.0)	35.0 (3.0 to 70.0)	
OC: Week 130 (n = 4, 1, 10)	40.0 (40.0 to 50.0)	45.0 (45.0 to 45.0)	42.5 (10.0 to 60.0)	
OC: Week 182 (n = 3, 1, 8)	60.0 (30.0 to 60.0)	45.0 (45.0 to 45.0)	45.0 (40.0 to 60.0)	
OC: Week 234 (n = 4, 0, 4)	52.5 (30.0 to 55.0)	999 (999 to 999)	47.5 (25.0 to 60.0)	
Hematologic cellularity (HC): Screening(n=10,4,26)	5.0 (1.0 to 25.0)	22.5 (10.0 to 45.0)	1.5 (1.0 to 25.0)	

HC: Week 26 (n = 8, 3, 30)	21.0 (5.0 to 45.0)	25.0 (15.0 to 40.0)	17.5 (1.0 to 50.0)	
HC: Week 52 (n = 5, 3, 16)	30.0 (30.0 to 40.0)	45.0 (45.0 to 45.0)	27.5 (2.0 to 50.0)	
HC: Week 78 (n = 6, 1, 15)	25.0 (3.0 to 40.0)	40.0 (40.0 to 40.0)	30.0 (2.0 to 50.0)	
HC: Week 130 (n = 4, 1, 10)	30.0 (30.0 to 40.0)	35.0 (35.0 to 35.0)	37.5 (8.0 to 50.0)	
HC: Week 182 (n = 3, 1, 8)	50.0 (25.0 to 50.0)	35.0 (35.0 to 35.0)	40.0 (25.0 to 80.0)	
HC: Week 234 (n = 4, 0, 4)	45.0 (25.0 to 50.0)	999 (999 to 999)	37.5 (20.0 to 50.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Bone marrow morphology

End point title	Bone marrow morphology[4]

End point description:

Percentage of morphology (erythropoiesis, granulopoiesis, megakaryopoiesis, CD34+ (blast cells) cells in bone marrow aspirate - a comprehensive diagnostic evaluation to distinguish between the various bone marrow disorders.

End point type	Secondary

End point timeframe:

Screening, Week, 26, Week 52, Week 78, Week 130, Week 182, Week 234

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No analysis was done for this endpoint

End point values	Cohort A: Regimen 2	Cohort B	Cohort A: Regimen 1	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	4	37	10	
Units: Percentage of cells				
median (full range (min-max))				
Erythroid cells: Screening (n = 10, 4, 26)	27.0 (19.0 to 39.0)	5.0 (0.0 to 38.0)	11.5 (0.0 to 28.0)	
Erythroid cells: Week 26 (n = 9, 3, 30)	12.0 (2.0 to 22.0)	18.0 (0.0 to 55.0)	10.0 (1.0 to 25.0)	
Erythroid cells: Week 52 (n = 6, 3, 16)	12.0 (2.0 to 17.0)	14.5 (1.0 to 28.0)	13.0 (4.0 to 37.0)	
Erythroid cells: Week 78 (n = 6, 1, 14)	15.0 (15.0 to 15.0)	20.5 (4.0 to 26.0)	14.0 (5.0 to 20.0)	
Erythroid cells: Week 130 (n = 3, 1, 10)	15.0 (15.0 to 15.0)	17.0 (4.0 to 32.0)	19.0 (11.0 to 22.0)	
Erythroid cells: Week 182 (n = 3, 1, 8)	24.0 (24.0 to 24.0)	16.5 (7.0 to 32.0)	26.0 (8.0 to 33.0)	
Erythroid cells: Week 234 (n = 4, 0, 4)	999 (999 to 999)	18.0 (13.0 to 33.0)	13.0 (5.0 to 20.0)	
Neutrophil: Screening (n = 10, 4, 26)	29.5 (19.0 to 48.0)	8.0 (0.0 to 45.0)	33.0 (1.0 to 48.0)	
Neutrophil cells: Week 26 (n = 9, 3, 30)	47.0 (29.0 to 66.0)	50.0 (17.0 to 78.0)	52.0 (34.0 to 63.0)	

Neutrophil: Week 52 (n = 6, 3, 16)	62.0 (57.0 to 67.0)	52.5 (20.0 to 76.0)	48.5 (32.0 to 59.0)	
Neutrophil: Week 78 (n = 6, 1, 14)	53.0 (53.0 to 53.0)	52.0 (34.0 to 67.0)	43.0 (4.0 to 54.0)	
Neutrophil cells: Week 130 (n = 3, 1, 10)	51.0 (51.0 to 51.0)	53.0 (39.0 to 65.0)	50.0 (44.0 to 50.0)	
Neutrophil cells: Week 182 (n = 3, 1, 8)	51.0 (51.0 to 51.0)	32.5 (5.0 to 59.0)	40.0 (25.0 to 56.0)	
Neutrophil cells: Week 234 (n = 4, 0, 4)	999 (999 to 999)	33.5 (25.0 to 36.0)	43.5 (30.0 to 56.0)	
Blast cells: Screening (n = 10, 4, 26)	1.0 (0.0 to 5.0)	0.0 (0.0 to 3.0)	0.00 (0.0 to 1.0)	
Blast cells: Week 26 (n = 9, 3, 30)	1.0 (0.0 to 2.0)	0.0 (0.0 to 1.0)	0.0 (0.0 to 2.0)	
Blast cells: Week 52 (n = 6, 3, 16)	1.0 (0.0 to 2.0)	0.0 (0.0 to 1.0)	0.0 (0.0 to 1.0)	
Blast cells: Week 78 (n = 6, 1, 14)	0.0 (0.0 to 0.0)	1.0 (0.0 to 2.0)	0.0 (0.0 to 1.0)	
Blast cells: Week 130 (n = 3, 1, 10)	0.0 (0.0 to 0.0)	0.5 (0.0 to 2.0)	0.0 (0.0 to 1.0)	
Blast cells: Week 182 (n = 3, 1, 8)	0.0 (0.0 to 0.0)	1.0 (0.0 to 26.0)	0.0 (0.0 to 1.0)	
Blast cells: Week 234 (n = 4, 0, 4)	999 (999 to 999)	1.0 (0.0 to 2.0)	0.0 (0.0 to 2.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Bone marrow cytogenetics

End point title	Bone marrow cytogenetics

End point description:

Number of bone marrow cytogenetics (chromosomal structure) by kryotyping and Fluorescence in situ hybridization (FISH). This is a comprehensive diagnostic evaluation to distinguish between the various bone marrow disorders.

End point type	Secondary

End point timeframe:

Screening, Week 12, Week 26, Week 52, Week 78, Week 130, Week 182, Week 234

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	4	37	
Units: Participants				
FISH Chr 7 @ Screening: Normal	10	4	26	
FISH Chr 7 @ Screening: Abnormal	0	0	0	
FISH Chr 7@ Screening: Not Available	0	0	2	
FISH Chr 7 @ Week 12: Normal	9	2	26	
FISH Chr 7 @ Week 12: Abnormal	0	0	0	
FISH Chr 7 @ Week 12: Not Available	0	0	1	
FISH Chr 7 @ Week 26: Normal	8	3	28	
FISH Chr 7 @ Week 26: Abnormal	0	0	0	
FISH Chr 7 @ Week 26: Not Available	1	0	1	
FISH Chr 7 @ Week 52: Normal	6	3	15	

FISH Chr 7 @ Week 52: Abnormal	0	0	0	
FISH Chr 7 @ Week 52: Not Available	0	0	1	
FISH Chr 7 @ Week 78: Normal	6	1	13	
FISH Chr 7 @ Week 78: Abnormal	0	0	0	
FISH Chr 7 @ Week 78: Not Available	0	0	2	
FISH Chr 7 @ Week 130: Normal	2	1	9	
FISH Chr 7 @ Week 130: Abnormal	0	0	0	
FISH Chr 7 @ Week 130: Not Available	1	0	1	
FISH Chr 7 @ Week 182: Normal	3	1	8	
FISH Chr 7 @ Week 182: Abnormal	0	0	0	
FISH Chr 7 @ Week 182: Not Available	0	0	0	
FISH Chr 7 @ Week 234: Normal	4	0	4	
FISH Chr 7 @ Week 234: Abnormal	0	0	0	
FISH Chr 7 @ Week 234: Not Available	0	0	0	
Karyotype @ Screening: Normal	8	4	19	
Karyotype @ Screening: Abnormal	0	0	0	
Karyotype @ Screening: Not Available	2	0	8	
Karyotype @ Week 12: Normal	8	2	25	
Karyotype @ Week 12: Abnormal	1	0	0	
Karyotype @ Week 12: Not Available	0	0	6	
Karyotype @ Week 26: Normal	7	3	25	
Karyotype @ Week 26: Abnormal	1	0	1	
Karyotype @ Week 26: Not Available	1	0	5	
Karyotype @ Week 52: Normal	5	3	15	
Karyotype @ Week 52: Abnormal	1	0	0	
Karyotype @ Week 52: Not Available	0	0	2	
Karyotype @ Week 78: Normal	4	1	13	
Karyotype @ Week 78: Abnormal	1	0	0	
Karyotype @ Week 78: Not Available	1	0	2	
Karyotype @ Week 130: Normal	2	1	8	
Karyotype @ Week 130: Abnormal	0	0	0	
Karyotype @ Week 130: Not Available	2	0	2	
Karyotype @ Week 182: Normal	3	1	7	
Karyotype @ Week 182: Abnormal	0	0	1	
Karyotype @ Week 182: Not Available	0	0	0	
Karyotype @ Week 234: Normal	4	0	4	
Karyotype @ Week 234: Abnormal	0	0	0	
Karyotype @ Week 234: Not Available	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability and palatability for both tablets and powder formulation for oral solution (PfOS)

End point title	Acceptability and palatability for both tablets and powder formulation for oral solution (PfOS)

End point description:

Standardized (total) summary score, ranged from 0-100, (where 0 means worst and 100 means the best), was derived from all items from the questionnaire based on a scoring matrix. The questionnaire

was completed by parents and caregivers of patients under 12 years of age (ObsRO) and a questionnaire completed by patients 12 years and older (PRO).

End point type	Secondary

End point timeframe:

any day from Day 1 of drug initiation up to Week 78

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	4	16	
Units: scores on a scale (of acceptability)				
median (full range (min-max))				
Acceptability (including palatability) - Tablet	71.0 (58.0 to 96.0)	75.0 (58.0 to 88.0)	71.0 (46.0 to 96.0)	
Acceptability (incl. palatability)- PfOS (n=0,0,8)	999 (999 to 999)	999 (999 to 999)	71.0 (32.0 to 82.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clonal evolution to Paroxysmal Nocturnal Hemoglobinuria (PNH)

End point title	Clonal evolution to Paroxysmal Nocturnal Hemoglobinuria (PNH)

End point description:

Percentage of participants with clonal evolution to Paroxysmal Nocturnal Hemoglobinuria (PNH).

End point type	Secondary

End point timeframe:

Baseline, Week (W) 26 Day (D) 1, W52D1, W78D1, W130D1, W182D1, W234D1

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	4	37	
Units: Percentage of participants				
number (not applicable)				
Baseline: Positive clonal evolution	20.0	25.0	29.7	
Baseline: Negative clonal evolution	80.0	75.0	64.9	
Baseline: Missing	0.0	0.0	5.4	
W26D1: Positive clonal evolution	10.0	50.0	8.1	
W26D1: Negative clonal evolution	80.0	25.0	64.9	
W26D1: Missing	10.0	25.0	27.0	
W52D1: Positive clonal evolution	0	25.0	2.7	
W52D1: Negative clonal evolution	30.0	25.0	29.7	
W52D1: Missing	70.0	50.0	67.6	

W78D1: Positive clonal evolution	0	25.0	0	
W78D1: Negative clonal evolution	40.0	25.0	21.6	
W78D1: Missing	60.0	50.0	78.4	
W130D1: Positive clonal evolution	0	0	0	
W130D1: Negative clonal evolution	30.0	0	8.1	
W130D1: Missing	70.0	100.0	91.9	
W182D1: Positive clonal evolution	10.0	0	2.7	
W182D1: Negative clonal evolution	20.0	0	8.1	
W182D1: Missing	70.0	100.0	89.2	
W234D1: Positive clonal evolution	0	0	2.7	
W234D1: Negative clonal evolution	30.0	0	2.7	
W234D1: Missing	70.0	100.0	94.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Alternate overall response rate (aORR)

End point title	Alternate overall response rate (aORR)

End point description:

Alternate overall responses were derived using hematological parameters (i.e., hemoglobin, platelet, reticulocyte, and ANC). aORR is defined as the percentage of participants who achieved an alternate complete response (aCR) or an alternate partial response (aPR)

End point type	Secondary

End point timeframe:

Week 12, Week 26, Week 52, Week 78

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	4	37	
Units: Percentage of participants				
number (confidence interval 95%)				
Week 12	90.0 (55.5 to 99.7)	100 (39.8 to 100.0)	64.9 (47.5 to 79.8)	
Week 26	90.0 (55.5 to 99.7)	100 (39.8 to 100.0)	75.7 (58.8 to 88.2)	
Week 52	60.0 (26.2 to 87.8)	100 (39.8 to 100.0)	40.5 (24.8 to 57.9)	
Week 78	50.0 (18.7 to 81.3)	75.0 (19.4 to 99.4)	48.6 (31.9 to 65.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) of eltrombopag at the starting dose (AUCtau)

End point title	Pharmacokinetics (PK) of eltrombopag at the starting dose (AUCtau)

End point description:

PK parameter, AUCtau.

AUC tau: Area under the curve calculated to the end of the dosing interval (tau) (mass*time/volume)

End point type	Secondary

End point timeframe:

Week 3 Day 1

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	3	12	
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	367000 (± 35.6)	350000 (± 47.7)	441000 (± 55.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: PK of eltrombopag at the starting dose (Ctrough)

End point title	PK of eltrombopag at the starting dose (Ctrough)[5]

End point description:

PK parameter, Ctrough
Ctrough is the pre-dose plasma concentration (mass/volume).

End point type	Secondary

End point timeframe:

Week 3 Day 1

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No analysis was done for this endpoint

End point values	Cohort A: Regimen 1	Cohort B	Cohort A: Regimen 2	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	16	3	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	8760 (± 72.9)	13200 (± 52.2)	10900 (± 66.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: PK of eltrombopag at the starting dose (Cmax)

End point title	PK of eltrombopag at the starting dose (Cmax)

End point description:

PK parameter, Cmax
Cmax is the observed maximum plasma concentration following administration (mass/volume)

End point type	Secondary

End point timeframe:

Week 3 Day 1

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	3	16	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	19700 (± 46.5)	21000 (± 24.5)	24000 (± 51.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Red Blood Cells (RBC) transfusions

End point title	Number of Red Blood Cells (RBC) transfusions

End point description:

Number of transfusions during the treatment period refers to total number of RBC transfusions participants have received while on treatment.

End point type	Secondary

End point timeframe:

From date of first dose to approx. 4.5 years

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	4	37	
Units: RBC transfusions				
median (full range (min-max))				
approx. 3 years (n = 8, 3, 33)	7.0 (1 to 17)	3.0 (1 to 34)	7.0 (1 to 26)	
approx. 4.5 years (n =8, 3, 33)	7.0 (1 to 17)	3.0 (1 to 34)	7.0 (1 to 26)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Platelet (PLT) transfusions

End point title	Number of Platelet (PLT) transfusions

End point description:

Number of transfusions during the treatment period refers to total number of PLT transfusions participants have received while on treatment.

End point type	Secondary

End point timeframe:

From date of first dose to approx. 4.5 years

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	4	37	
Units: Platelet transfusions				
median (full range (min-max))				
approx. 3 years (n = 8, 1, 34)	13.0 (3 to 48)	53.0 (53 to 53)	13.0 (2 to 65)	
approx. 4.5 years (n =)	13.0 (3 to 48)	53.0 (53 to 53)	13.0 (2 to 65)	

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Red Blood Cell (RBC) transfusions

End point title	Frequency of Red Blood Cell (RBC) transfusions

End point description:

Frequency of transfusions during the treatment period refers to number of RBC transfusions during the treatment period divided by number of months of treatment duration.

End point type	Secondary

End point timeframe:

From date of first dose to approx. 4.5 years

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	4	37	
Units: RBC transfusions per month				
median (full range (min-max))				
approx. 3 years (n = 8, 3, 33)	1.5 (0 to 4)	0.2 (0 to 3)	0.9 (0 to 5)	
approx. 4.5 years (n = 8, 3, 33)	1.5 (0 to 4)	0.2 (0 to 3)	0.9 (0 to 5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure (AUCtau) - response relationship of eltrombopag and overall response rate by age groups

End point title	Exposure (AUCtau) - response relationship of eltrombopag and overall response rate by age groups

End point description:

Pharmacokinetic parameter (AUCtau) of eltrombopag at the highest dose in relationship to overall response rate in regard to complete response (CR), partial response (PR) and no response (NR).
AUC tau: Area under the curve calculated to the end of the dosing interval (tau)
(mass*time/volume)

End point type	Secondary

End point timeframe:

at least 11 weeks after dose initiation or later when patients are taking the highest dose, up to Week 78

End point values	Cohort A: Regimen 1 (1 to <6 years)	Cohort A: Regimen 1 (6 to <18 years)	Cohort A: Regimen 2 (6 to <18 years)	Cohort B (6 to <18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	7	3	19
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
No response (NR):	816000 (± 0)	390000 (± 0)	999 (± 999)	999 (± 999)
Complete response (CR):	999 (± 999)	769000 (± 87.3)	999 (± 999)	503000 (± 57.4)
Partial response (PR):	999 (± 999)	999 (± 999)	1220000 (± 0)	963000 (± 80.6)

End point values	Cohort B (1 to <6 years)			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
No response (NR):	1260000 (± 27.0)			
Complete response (CR):	2260000 (± 0)			
Partial response (PR):	671000 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Platelet (PLT) transfusions

End point title	Frequency of Platelet (PLT) transfusions

End point description:

Frequency of transfusions during the treatment period refers to number of PLT transfusions during the treatment period divided by number of months of treatment duration.

End point type	Secondary

End point timeframe:

From date of first dose to approx. 4.5 years

End point values	Cohort A: Regimen 1	Cohort A: Regimen 2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	4	37	
Units: Platelet transfusions per month				
median (full range (min-max))				
approx. 3 years (n = 8, 1, 34)	2.0 (0 to 14)	4.2 (4.2 to 4.2)	2.0 (0 to 13)	
approx. 4.5 years (n = 8, 1, 34)	2.0 (0 to 14)	4.2 (4.2 to 4.2)	1.9 (0 to 13)	

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure (Cmax, Ctrough) - response relationship of eltrombopag and overall response rate by age groups

End point title	Exposure (Cmax, Ctrough) - response relationship of eltrombopag and overall response rate by age groups

End point description:

Pharmacokinetic parameters (Cmax and Ctrough) of eltrombopag at the highest dose in relationship to overall response rate in regard to complete response (CR), partial response (PR) and no response (NR).

Cmax is the observed maximum plasma concentration following administration (mass/volume).
Ctrough is the pre-dose plasma concentration (mass/volume).

End point type	Secondary

End point timeframe:

at least 11 weeks after dose initiation or later when patients are taking the highest dose, up to Week 78

End point values	Cohort A: Regimen 1 (1 to <6 years)	Cohort A: Regimen 2 (6 to <18 years)	Cohort A: Regimen 1 (6 to <18 years)	Cohort B (1 to <6 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	2	3	4
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cmax: No Response (n = 1, 2, 0, 4, 2)	48400 (± 0)	999 (± 999)	33900 (± 115)	84900 (± 32.6)
Cmax: Complete Response (n = 0, 3, 0, 1, 9)	999 (± 999)	999 (± 999)	35700 (± 88.3)	112000 (± 0)
Cmax: Partial Response (n = 0, 0, 2, 3, 4)	999 (± 999)	24800 (± 212)	999 (± 999)	60500 (± 26.6)
Ctrough: No Response (n = 1, 2, 0, 4, 2)	16400 (± 0)	999 (± 999)	19900 (± 106)	37800 (± 32.6)
Ctrough: Complete Response (n = 0, 3, 0, 1, 9)	999 (± 999)	999 (± 999)	27000 (± 104)	84700 (± 0)
Ctrough: Partial Response (n = 0, 0, 2, 3, 4)	999 (± 999)	17100 (± 151)	999 (± 999)	23800 (± 194)

End point values	Cohort B (6 to <18 years)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cmax: No Response (n = 1, 2, 0, 4, 2)	39200 (± 33.1)			
Cmax: Complete Response (n = 0, 3, 0, 1, 9)	31200 (± 63.7)			
Cmax: Partial Response (n = 0, 0, 2, 3, 4)	54000 (± 54.4)			
Ctrough: No Response (n = 1, 2, 0, 4, 2)	18500 (± 43.6)			
Ctrough: Complete Response (n = 0, 3, 0, 1, 9)	20100 (± 72.8)			
Ctrough: Partial Response (n = 0, 0, 2, 3, 4)	35300 (± 65.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure (AUCtau) - response relationship of eltrombopag and platelet response rate by age groups

End point title	Exposure (AUCtau) - response relationship of eltrombopag and platelet response rate by age groups

End point description:

Pharmacokinetic parameter (AUCtau) of eltrombopag at the highest dose in relationship to platelet response rate.
AUC tau: Area under the curve calculated to the end of the dosing interval (tau)
(mass*time/volume)

End point type	Secondary

End point timeframe:

at least 11 weeks after dose initiation or later when patients are taking the highest dose, up to Week 78

End point values	Cohort A: Regimen 1 (1 to <6 years)	Cohort A: Regimen 1 (6 to <18 years)	Cohort B (1 to <6 years)	Cohort B (6 to <18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	4	9
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
No Response	816000 (± 0)	999 (± 999)	999 (± 999)	1280000 (± 0)
Complete Response	999 (± 999)	769000 (± 87.3)	1670000 (± 45.2)	563000 (± 67.3)
Partial Response	999 (± 999)	390000 (± 0)	1090000 (± 43.5)	999 (± 999)

End point values	Cohort A: Regimen 2 (6 to <18 years)			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
No Response	999 (± 999)			
Complete Response	1220000 (± 0)			
Partial Response	999 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure (Cmax, Ctrough) - response relationship of eltrombopag and platelet response rate by age groups

End point title	Exposure (Cmax, Ctrough) - response relationship of eltrombopag and platelet response rate by age groups

End point description:

Pharmacokinetic parameters (Cmax and Ctrough) of eltrombopag at the highest dose in relationship to platelet response rate.
Cmax is the observed maximum plasma concentration following administration (mass/volume).
Ctrough is the pre-dose plasma concentration (mass/volume).

End point type	Secondary

End point timeframe:

at least 11 weeks after dose initiation or later when patients are taking the highest dose, up to Week 78

End point values	Cohort A: Regimen 1 (1 to <6 years)	Cohort A: Regimen 1 (6 to <18 years)	Cohort B (1 to <6 years)	Cohort A: Regimen 2 (6 to <18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	4	1
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cmax: No Response (n = 1, 1, 0, 0, 2)	48400 (± 0)	64900 (± 0)	999 (± 999)	999 (± 999)
Cmax: Complete Response (n = 0, 3, 1, 4, 12)	999 (± 999)	35700 (± 88.3)	80900 (± 31.7)	62400 (± 0)
Cmax: Partial Response n = 0, 1, 0, 4, 1)	999 (± 999)	17700 (± 0)	74000 (± 42.1)	999 (± 999)
Ctrough: No Response (n = 1, 3, 0, 0, 1)	16400 (± 0)	1 (± 36800)	999 (± 999)	999 (± 999)
Ctrough: Complete Response (n = 0, 3, 1, 4, 12)	999 (± 999)	27000 (± 104)	50100 (± 48.6)	37100 (± 0)
Ctrough: Partial Response (n = 0, 1, 0, 4, 12)	999 (± 999)	10800 (± 0)	24600 (± 132)	999 (± 999)

End point values	Cohort B (6 to <18 years)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cmax: No Response (n = 1, 1, 0, 0, 2)	39200 (± 33.1)			
Cmax: Complete Response (n = 0, 3, 1, 4, 12)	35200 (± 65.8)			
Cmax: Partial Response n = 0, 1, 0, 4, 1)	66600 (± 0)			
Ctrough: No Response (n = 1, 3, 0, 0, 1)	45000 (± 0)			
Ctrough: Complete Response (n = 0, 3, 1, 4, 12)	22700 (± 75.3)			
Ctrough: Partial Response (n = 0, 1, 0, 4, 12)	18500 (± 43.6)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: All Collected Deaths

End point title	All Collected Deaths[6]

End point description:

On-treatment deaths were collected from the first dose of study treatment up to 30 days after last dose of study medication, for a maximum duration of 234 weeks.
Post-treatment survival follow-up deaths were collected 31 days after last dose of study medication until date of the last follow-up for the primary analysis, up to 234 weeks.

End point type	Post-hoc

End point timeframe:

On-treatment deaths: from first dose of study treatment up to 30 days post treatment, approx. 234 weeks; Post-treatment survival follow-up deaths: from Day 31 to approx. 234 weeks

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No analysis was done for this endpoint

End point values	Cohort A: Regimen 2	Cohort B	Cohort A: Regimen 1	Total (Cohorts A (Regimen 1 & 2) and B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	4	37	10	51
Units: Participants				
Total deaths	1	0	0	1
On-treatment deaths	0	0	0	0
Post-treatment deaths	1	0	0	1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from first dosing (Day 1) until date of the last follow-up, up to 234 weeks.

Adverse event reporting additional description:

An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporarily or causally associated with the use of a medicinal (investigational) product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Cohort A - Regimen 1

Reporting group description:

Cohort A - Regimen 1

Reporting group title	Total Patients

Reporting group description:

Total Patients

Reporting group title	Cohort B

Reporting group description:

Cohort B

Reporting group title	Cohort A - Regimen 2

Reporting group description:

Cohort A - Regimen 2

Reporting group title	Total Cohort A

Reporting group description:

Total Cohort A

Serious adverse events	Cohort A - Regimen 1	Total Patients	Cohort B
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	29 / 51 (56.86%)	23 / 37 (62.16%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	2 / 10 (20.00%)	11 / 51 (21.57%)	8 / 37 (21.62%)
occurrences causally related to treatment / all	0 / 2	0 / 16	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Serum sickness			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Abnormal uterine bleeding			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar exudate			

subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sunburn			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 10 (10.00%)	7 / 51 (13.73%)	5 / 37 (13.51%)
occurrences causally related to treatment / all	0 / 2	0 / 14	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			

subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Azotaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute kidney injury			
subjects affected / exposed	0 / 10 (0.00%)	3 / 51 (5.88%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacillus bacteraemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			

subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metapneumovirus infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Magnesium metabolism disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort A - Regimen 2	Total Cohort A	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	6 / 14 (42.86%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	3 / 14 (21.43%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Serum sickness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Abnormal uterine bleeding			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar exudate			

subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sunburn			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Headache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 14 (14.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute kidney injury			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacillus bacteraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			

subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Magnesium metabolism disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort A - Regimen 1	Total Patients	Cohort B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	51 / 51 (100.00%)	37 / 37 (100.00%)
Vascular disorders			
Hyperaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Thrombophlebitis			

subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	3 / 51 (5.88%)	2 / 37 (5.41%)
occurrences (all)	0	3	2
Poor peripheral circulation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	4 / 10 (40.00%)	20 / 51 (39.22%)	15 / 37 (40.54%)
occurrences (all)	8	29	19
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)	14 / 51 (27.45%)	10 / 37 (27.03%)
occurrences (all)	4	22	15
Pain			
subjects affected / exposed	1 / 10 (10.00%)	3 / 51 (5.88%)	2 / 37 (5.41%)
occurrences (all)	1	3	2
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 10 (0.00%)	3 / 51 (5.88%)	2 / 37 (5.41%)
occurrences (all)	0	3	2
Feeling hot			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	5 / 51 (9.80%)	5 / 37 (13.51%)
occurrences (all)	0	7	7
Face oedema			

subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Chills			
subjects affected / exposed	1 / 10 (10.00%)	4 / 51 (7.84%)	3 / 37 (8.11%)
occurrences (all)	1	4	3
Immune system disorders			
Serum sickness			
subjects affected / exposed	2 / 10 (20.00%)	8 / 51 (15.69%)	6 / 37 (16.22%)
occurrences (all)	2	8	6
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Anaphylactic shock			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Heavy menstrual bleeding			
subjects affected / exposed	2 / 10 (20.00%)	3 / 51 (5.88%)	1 / 37 (2.70%)
occurrences (all)	3	6	3
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 10 (20.00%)	8 / 51 (15.69%)	5 / 37 (13.51%)
occurrences (all)	3	14	10
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Cough			
subjects affected / exposed	2 / 10 (20.00%)	5 / 51 (9.80%)	3 / 37 (8.11%)
occurrences (all)	3	7	4
Laryngospasm			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	2	2	0
Nasal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	2	0

Oropharyngeal pain			
subjects affected / exposed	1 / 10 (10.00%)	5 / 51 (9.80%)	3 / 37 (8.11%)
occurrences (all)	1	7	5
Rhinorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	0	5	1
Tonsillar exudate			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Nasal congestion			
subjects affected / exposed	0 / 10 (0.00%)	4 / 51 (7.84%)	3 / 37 (8.11%)
occurrences (all)	0	5	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 10 (0.00%)	5 / 51 (9.80%)	5 / 37 (13.51%)
occurrences (all)	0	5	5
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 51 (5.88%)	3 / 37 (8.11%)
occurrences (all)	0	3	3
Psychotic disorder			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 10 (70.00%)	24 / 51 (47.06%)	16 / 37 (43.24%)
occurrences (all)	14	47	32
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 10 (60.00%)	20 / 51 (39.22%)	13 / 37 (35.14%)
occurrences (all)	11	36	24
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 10 (10.00%)	3 / 51 (5.88%)	1 / 37 (2.70%)
occurrences (all)	1	3	1
Blood bilirubin increased			
subjects affected / exposed	6 / 10 (60.00%)	24 / 51 (47.06%)	18 / 37 (48.65%)
occurrences (all)	16	55	39
Blood creatinine increased			

subjects affected / exposed	5 / 10 (50.00%)	19 / 51 (37.25%)	12 / 37 (32.43%)
occurrences (all)	13	31	15
Blood folate decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Blood glucose increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Blood magnesium decreased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Blood phosphorus increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Blood pressure increased			
subjects affected / exposed	0 / 10 (0.00%)	6 / 51 (11.76%)	5 / 37 (13.51%)
occurrences (all)	0	6	5
Blood urea increased			
subjects affected / exposed	4 / 10 (40.00%)	12 / 51 (23.53%)	5 / 37 (13.51%)
occurrences (all)	7	21	6
Klebsiella test positive			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Liver function test increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
SARS-CoV-2 test negative			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	5	0
Serum ferritin increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Staphylococcus test positive			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Immunosuppressant drug level			

increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Contusion			
subjects affected / exposed	1 / 10 (10.00%)	5 / 51 (9.80%)	3 / 37 (8.11%)
occurrences (all)	1	6	4
Infusion related reaction			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Procedural pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Refractoriness to platelet transfusion			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Transfusion reaction			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 51 (5.88%)	2 / 37 (5.41%)
occurrences (all)	0	4	3
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 10 (20.00%)	10 / 51 (19.61%)	8 / 37 (21.62%)
occurrences (all)	6	16	10
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Syncope			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0

Tremor			
subjects affected / exposed	1 / 10 (10.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	1	2	1
Blood and lymphatic system disorders			
Aplastic anaemia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Febrile neutropenia			
subjects affected / exposed	2 / 10 (20.00%)	11 / 51 (21.57%)	8 / 37 (21.62%)
occurrences (all)	2	17	14
Haemolysis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 10 (10.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	2	3	1
Dry eye			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	3	3
Conjunctival haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Choroidal effusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Accommodation disorder			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			

Enterocolitis			
subjects affected / exposed	2 / 10 (20.00%)	5 / 51 (9.80%)	3 / 37 (8.11%)
occurrences (all)	3	8	5
Gastritis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	6 / 51 (11.76%)	6 / 37 (16.22%)
occurrences (all)	0	6	6
Chronic gastritis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Aphthous ulcer			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	0	4	1
Anal haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	6 / 51 (11.76%)	5 / 37 (13.51%)
occurrences (all)	0	7	5
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)	16 / 51 (31.37%)	13 / 37 (35.14%)
occurrences (all)	1	21	17
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	10 / 51 (19.61%)	9 / 37 (24.32%)
occurrences (all)	0	15	11
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	8 / 51 (15.69%)	6 / 37 (16.22%)
occurrences (all)	1	10	6
Small intestinal obstruction			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0

Periodontal disease			
subjects affected / exposed	1 / 10 (10.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	1	2	1
Oral pain			
subjects affected / exposed	1 / 10 (10.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	1	2	1
Oral blood blister			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Odynophagia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	3	0
Nausea			
subjects affected / exposed	2 / 10 (20.00%)	20 / 51 (39.22%)	17 / 37 (45.95%)
occurrences (all)	2	31	27
Mucous stools			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Haematochezia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	3	0
Gingival swelling			
subjects affected / exposed	0 / 10 (0.00%)	3 / 51 (5.88%)	3 / 37 (8.11%)
occurrences (all)	0	3	3
Gingival pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Gingival hypertrophy			
subjects affected / exposed	0 / 10 (0.00%)	7 / 51 (13.73%)	4 / 37 (10.81%)
occurrences (all)	0	8	5
Gingival bleeding			
subjects affected / exposed	0 / 10 (0.00%)	6 / 51 (11.76%)	5 / 37 (13.51%)
occurrences (all)	0	10	7

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Tongue ulceration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	21 / 51 (41.18%)	18 / 37 (48.65%)
occurrences (all)	1	38	31
Hepatobiliary disorders			
Ocular icterus			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	3	3	0
Jaundice			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Hyperbilirubinaemia			
subjects affected / exposed	1 / 10 (10.00%)	3 / 51 (5.88%)	2 / 37 (5.41%)
occurrences (all)	2	4	2
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	2 / 10 (20.00%)	4 / 51 (7.84%)	2 / 37 (5.41%)
occurrences (all)	2	5	3
Acne			
subjects affected / exposed	1 / 10 (10.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	1	2	1
Alopecia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Ecchymosis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	3	3	0
Erythema			
subjects affected / exposed	0 / 10 (0.00%)	3 / 51 (5.88%)	1 / 37 (2.70%)
occurrences (all)	0	3	1
Hirsutism			

subjects affected / exposed	0 / 10 (0.00%)	5 / 51 (9.80%)	3 / 37 (8.11%)
occurrences (all)	0	5	3
Petechiae			
subjects affected / exposed	0 / 10 (0.00%)	5 / 51 (9.80%)	3 / 37 (8.11%)
occurrences (all)	0	10	8
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	5 / 51 (9.80%)	4 / 37 (10.81%)
occurrences (all)	0	5	4
Rash			
subjects affected / exposed	1 / 10 (10.00%)	11 / 51 (21.57%)	10 / 37 (27.03%)
occurrences (all)	1	12	11
Rash maculo-papular			
subjects affected / exposed	1 / 10 (10.00%)	4 / 51 (7.84%)	2 / 37 (5.41%)
occurrences (all)	1	5	3
Rash papular			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	1 / 10 (10.00%)	7 / 51 (13.73%)	6 / 37 (16.22%)
occurrences (all)	3	9	6
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 10 (10.00%)	5 / 51 (9.80%)	3 / 37 (8.11%)
occurrences (all)	1	8	6
Azotaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Nephropathy toxic			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Paroxysmal nocturnal haemoglobinuria			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Renal failure			

subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Renal impairment			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Renal tubular acidosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	2 / 10 (20.00%)	3 / 51 (5.88%)	1 / 37 (2.70%)
occurrences (all)	2	3	1
Cushingoid			
subjects affected / exposed	1 / 10 (10.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	1	2	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	6 / 51 (11.76%)	4 / 37 (10.81%)
occurrences (all)	3	9	5
Kyphosis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 10 (10.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	1	3	2
Pain in extremity			
subjects affected / exposed	2 / 10 (20.00%)	9 / 51 (17.65%)	5 / 37 (13.51%)
occurrences (all)	3	11	6
Tendon pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	1 / 10 (10.00%)	4 / 51 (7.84%)	2 / 37 (5.41%)
occurrences (all)	2	5	2
Infections and infestations			

Bacterial disease carrier			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Vascular device infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Tonsillitis			
subjects affected / exposed	1 / 10 (10.00%)	5 / 51 (9.80%)	4 / 37 (10.81%)
occurrences (all)	1	8	7
Soft tissue infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Rhinitis			
subjects affected / exposed	2 / 10 (20.00%)	4 / 51 (7.84%)	2 / 37 (5.41%)
occurrences (all)	2	5	3
Respiratory tract infection viral			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Pharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	3 / 51 (5.88%)	2 / 37 (5.41%)
occurrences (all)	1	3	2
Paronychia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Molluscum contagiosum			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Gingivitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Fungal infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	1 / 37 (2.70%)
occurrences (all)	0	2	1

Escherichia bacteraemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Epididymitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
COVID-19			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	8 / 51 (15.69%)	7 / 37 (18.92%)
occurrences (all)	0	11	9
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 10 (10.00%)	5 / 51 (9.80%)	4 / 37 (10.81%)
occurrences (all)	1	6	5
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	6 / 51 (11.76%)	5 / 37 (13.51%)
occurrences (all)	0	6	5
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Fluid retention			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Hyperglycaemia			
subjects affected / exposed	1 / 10 (10.00%)	4 / 51 (7.84%)	3 / 37 (8.11%)
occurrences (all)	1	9	8
Hyperkalaemia			
subjects affected / exposed	2 / 10 (20.00%)	3 / 51 (5.88%)	1 / 37 (2.70%)
occurrences (all)	6	7	1
Hypermagnesaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 51 (1.96%)	0 / 37 (0.00%)
occurrences (all)	2	2	0
Hypervolaemia			

subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Hypomagnesaemia			
subjects affected / exposed	3 / 10 (30.00%)	19 / 51 (37.25%)	15 / 37 (40.54%)
occurrences (all)	7	30	21
Hyponatraemia			
subjects affected / exposed	1 / 10 (10.00%)	3 / 51 (5.88%)	1 / 37 (2.70%)
occurrences (all)	1	5	1
Iron overload			
subjects affected / exposed	2 / 10 (20.00%)	6 / 51 (11.76%)	4 / 37 (10.81%)
occurrences (all)	2	6	4
Metabolic acidosis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 51 (3.92%)	0 / 37 (0.00%)
occurrences (all)	1	3	0
Vitamin D deficiency			
subjects affected / exposed	0 / 10 (0.00%)	2 / 51 (3.92%)	2 / 37 (5.41%)
occurrences (all)	0	2	2

Non-serious adverse events	Cohort A - Regimen 2	Total Cohort A	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	14 / 14 (100.00%)	
Vascular disorders			
Hyperaemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Thrombophlebitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Poor peripheral circulation			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Hypertension			

subjects affected / exposed	1 / 4 (25.00%)	5 / 14 (35.71%)	
occurrences (all)	2	10	
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	4 / 14 (28.57%)	
occurrences (all)	3	7	
Pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Feeling hot			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Face oedema			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Chills			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Immune system disorders			
Serum sickness			
subjects affected / exposed	0 / 4 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Haemophagocytic lymphohistiocytosis			

subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Anaphylactic shock			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Heavy menstrual bleeding			
subjects affected / exposed	0 / 4 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 4 (25.00%)	3 / 14 (21.43%)	
occurrences (all)	1	4	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 4 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	3	
Laryngospasm			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Nasal obstruction			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	2	2	
Oropharyngeal pain			
subjects affected / exposed	1 / 4 (25.00%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Rhinorrhoea			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	4	4	
Tonsillar exudate			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Nasal congestion			

subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Psychotic disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	8 / 14 (57.14%)	
occurrences (all)	1	15	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	7 / 14 (50.00%)	
occurrences (all)	1	12	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)	6 / 14 (42.86%)	
occurrences (all)	0	16	
Blood creatinine increased			
subjects affected / exposed	2 / 4 (50.00%)	7 / 14 (50.00%)	
occurrences (all)	3	16	
Blood folate decreased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Blood glucose increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Blood magnesium decreased			

subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Blood phosphorus increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Blood pressure increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Blood urea increased			
subjects affected / exposed	3 / 4 (75.00%)	7 / 14 (50.00%)	
occurrences (all)	8	15	
Klebsiella test positive			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Liver function test increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
SARS-CoV-2 test negative			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	5	5	
Serum ferritin increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Staphylococcus test positive			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Immunosuppressant drug level increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Contusion			

subjects affected / exposed	1 / 4 (25.00%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Infusion related reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Procedural pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Refractoriness to platelet transfusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Transfusion reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 4 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	6	
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Aplastic anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Febrile neutropenia			

subjects affected / exposed	1 / 4 (25.00%)	3 / 14 (21.43%)	
occurrences (all)	1	3	
Haemolysis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Lymphadenopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Dry eye			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Conjunctival haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	2	2	
Choroidal effusion			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Accommodation disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	3	
Gastritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Constipation			

subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Chronic gastritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Aphthous ulcer			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	3	3	
Anal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	2	2	
Abdominal pain			
subjects affected / exposed	2 / 4 (50.00%)	3 / 14 (21.43%)	
occurrences (all)	3	4	
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	4	4	
Stomatitis			
subjects affected / exposed	1 / 4 (25.00%)	2 / 14 (14.29%)	
occurrences (all)	3	4	
Small intestinal obstruction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Periodontal disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Oral pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Oral blood blister			

subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Odynophagia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	3	3	
Nausea			
subjects affected / exposed	1 / 4 (25.00%)	3 / 14 (21.43%)	
occurrences (all)	2	4	
Mucous stools			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Mouth ulceration			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Haematochezia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	3	3	
Gingival swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Gingival pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Gingival hypertrophy			
subjects affected / exposed	3 / 4 (75.00%)	3 / 14 (21.43%)	
occurrences (all)	3	3	
Gingival bleeding			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	3	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Tongue ulceration			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	2	2	
Vomiting			

subjects affected / exposed	2 / 4 (50.00%)	3 / 14 (21.43%)	
occurrences (all)	6	7	
Hepatobiliary disorders			
Ocular icterus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	3	
Jaundice			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	0 / 4 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Acne			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Ecchymosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	3	
Erythema			
subjects affected / exposed	2 / 4 (50.00%)	2 / 14 (14.29%)	
occurrences (all)	2	2	
Hirsutism			
subjects affected / exposed	2 / 4 (50.00%)	2 / 14 (14.29%)	
occurrences (all)	2	2	
Petechiae			
subjects affected / exposed	2 / 4 (50.00%)	2 / 14 (14.29%)	
occurrences (all)	2	2	
Pruritus			

subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Rash maculo-papular			
subjects affected / exposed	1 / 4 (25.00%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Rash papular			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 4 (25.00%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Azotaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Nephropathy toxic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Paroxysmal nocturnal haemoglobinuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Renal failure			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Renal impairment			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Renal tubular acidosis			

subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 4 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Cushingoid			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 14 (14.29%)	
occurrences (all)	1	4	
Kyphosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	2 / 4 (50.00%)	4 / 14 (28.57%)	
occurrences (all)	2	5	
Tendon pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	2 / 14 (14.29%)	
occurrences (all)	1	3	
Infections and infestations			
Bacterial disease carrier			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Vascular device infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Tonsillitis			

subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Soft tissue infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Respiratory tract infection viral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Molluscum contagiosum			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Gingivitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Fungal infection			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Escherichia bacteraemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Epididymitis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
COVID-19			

subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Decreased appetite			
subjects affected / exposed	1 / 4 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Fluid retention			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	6	
Hypermagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Hypervolaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Hypomagnesaemia			
subjects affected / exposed	1 / 4 (25.00%)	4 / 14 (28.57%)	
occurrences (all)	2	9	
Hyponatraemia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 14 (14.29%)	
occurrences (all)	3	4	

Iron overload			
subjects affected / exposed	0 / 4 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Metabolic acidosis			
subjects affected / exposed	1 / 4 (25.00%)	2 / 14 (14.29%)	
occurrences (all)	2	3	
Vitamin D deficiency			
subjects affected / exposed	0 / 4 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2017	Provided further clarification of the study population in Cohort A. Provided dose modification guidelines for G3/4 AEs that are not liver related and are not AEs of special interest. Designated that selected hematology, biochemistry tests and Cyclosporine (CsA) levels could be performed by local lab to facilitate the management of the patients by the site.
16 August 2017	Modified the ECG monitoring plan to include ECG evaluations at Tmax (time of Cmax) after single dose and at steady-state with eltrombopag treatment. Updated to include additional ECG assessments.
21 December 2017	Introduced an optional consent form to allow for screening bone marrow aspirate and biopsy specimens to be sent to and analyzed by the central laboratory prior to enrollment.
05 October 2018	Provided guidance regarding the use of medications belonging to the azole class of antifungal agents. Provided guidance regarding patients already receiving CsA at the time of study entry. Provided guidance regarding appropriate follow up for patients who discontinue eltrombopag prior to completion of the 26-week Treatment Period. Clarified changes of tablets of eltrombopag used in this study, visit frequency during long-term follow up, and ECG monitoring plan.
20 August 2020	Aligned bone marrow aspirate collection with bone marrow biopsy at Week 12 and Week 78 in order to monitor clonal evolution in the early and late phases of study treatment. Clarified the secondary objectives. Clarified requirements prior to PK sampling. Modified the process of bone marrow karyotyping at screening and added additional probes to improve screening for chromosomal abnormalities. Clarified exclusion and inclusion criteria. Modified guidelines for eltrombopag dose adjustment. Clarified study treatment modifications in case of bone marrow fibrosis and cytogenetic abnormalities. Clarified which abnormalities will not be reported as AEs or SAEs. Modified clonal evolution reporting so that it is consistent across all ETB115 clinical trials. Modified treatment for eltrombopag and CsA to be permitted beyond Week 104.
16 April 2021	Aligned protocol sections 5.1 'Patient population' and 10.8 'Sample size calculation' to the Pediatric Investigation Plan (PIP) for SAA (EMEA-000170-PIP03-13-M04). Modified objective for exploratory biomarker analysis. Added, as per Novartis guidance, risk mitigation procedures during the public health emergency declared by local or regional authorities.

20 April 2022	Removed objective #14 exploratory biomarker analysis of assessing proteomics in urine samples as the sample size collected was inadequate to perform a rigorous data analysis and correlate with treatment effect. Clarified that eltrombopag re-initiation was allowed only during the Study Treatment phase until Week 26. Clarified that patients whose SAA progressed during the Follow-up and Long-term Follow-up Period were to be discontinued from the study and that they may receive any SAA therapy at the discretion of the treating physician outside this study. Clarified that any case of MDS or AML must be reported as an adverse event throughout the study, including the Follow-up Period or the Long-term Follow-up Period. Clarified that any cytogenetic abnormality detected was to be recorded in the Cytogenetics CRF, and if clinically significant, was to be reported as an adverse event. Clarified that SAA progression, as determined by the investigator, was to be reported as an adverse event throughout the study, including the Follow-up Period or the Long-term Follow-up Period. Clarified that patients who progressed to MDS/AML or receive HSCT will be discontinued from the study, and they will not to be monitored during the Follow-up and Long-term Follow-up periods.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported