Clinical trial results:
A Phase 2 Open-Label Study to Evaluate Safety and Clinical Activity of Etavopivat in Patients with Thalassemia or Sickle Cell Disease

Summary

EudraCT number	2021-005267-48
Trial protocol	IT
Global end of trial date	24 September 2025

Results information

Result version number	v1 (current)
This version publication date	09 April 2026
First version publication date	09 April 2026

Trial information

Trial identification

Sponsor protocol code	4202-HEM-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04987489
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Alle, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002924-PIP03-24
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes
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	13 November 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to assess the erythroid response of etavopivat in adolescents and adults with sickle cell disease (SCD) or thalassemia.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Oct 2013) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, including archiving of essential documents (May 1996) and EN ISO 14155 Part 1 and 2 and Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) 312.120.

Background therapy:

Not applicable

Evidence for comparator: -

Actual start date of recruitment	28 March 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Egypt: 5
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Lebanon: 4
Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	52
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	20
Adults (18-64 years)	32
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted across 20 sites in 5 countries.

Pre-assignment

Screening details:

A total of 53 subjects were enrolled, of whom 44 completed the study. Cohorts were based on haemoglobinopathy (SCD or thalassaemia) and transfusion requirements. Subjects entered a 48-week primary treatment period with an optional 60-week extension. One subject was excluded from the population description for receiving both transfusion types.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A: Simple transfusion

Arm description:

Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with sickle cell disease (SCD) underwent chronic red blood cells (RBC) transfusion therapy through simple (manual) process to prevent stroke or recurrence of stroke.

Arm type	Experimental
Investigational medicinal product name	Etavopivat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Etavopivat 400 mg was administered orally daily in the form of two tablets of 200 mg each.

Arm title	Cohort A: Exchange transfusion

Arm description:

Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with SCD underwent chronic RBC transfusion therapy through exchange transfusion process to prevent stroke or recurrence of stroke. The exchange transfusion process involved simultaneous blood removal and RBC infusion, which impacted clinical parameters, such as haemoglobin (Hb) iron levels, and volume balance, differently than the simple transfusion process.

Arm type	Experimental
Investigational medicinal product name	Etavopivat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Etavopivat 400 mg was administered orally daily in the form of two tablets of 200 mg each.

Arm title	Cohort B

Arm description:

Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with

thalassaemia underwent chronic RBC transfusion therapy to prevent symptomatic anaemia.

Arm type	Experimental
Investigational medicinal product name	Etavopivat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Etavopivat 400 mg was administered orally daily in the form of two tablets of 200 mg each.

Arm title	Cohort C

Arm description:

Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with thalassaemia did not undergo chronic RBC transfusion therapy.

Arm type	Experimental
Investigational medicinal product name	Etavopivat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Etavopivat 400 mg was administered orally daily in the form of two tablets of 200 mg each.

Number of subjects in period 1	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B
Started	5	7	20
Full analysis set (FAS)	5	7	20
Safety analysis set (SAS)	5	7	20
Efficacy evaluable set (EES)	4	7	19
Completed	4	5	18
Not completed	1	2	2
Adverse event, serious fatal	1	-	-
Adverse event, non-fatal	-	-	1
Unclassified	-	2	1

Number of subjects in period 1	Cohort C
Started	20
Full analysis set (FAS)	20
Safety analysis set (SAS)	20
Efficacy evaluable set (EES)	20
Completed	16
Not completed	4
Adverse event, serious fatal	-
Adverse event, non-fatal	1
Unclassified	3

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A: Simple transfusion
Reporting group description:	
Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with sickle cell disease (SCD) underwent chronic red blood cells (RBC) transfusion therapy through simple (manual) process to prevent stroke or recurrence of stroke.	
Reporting group title	Cohort A: Exchange transfusion
Reporting group description:	
Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with SCD underwent chronic RBC transfusion therapy through exchange transfusion process to prevent stroke or recurrence of stroke. The exchange transfusion process involved simultaneous blood removal and RBC infusion, which impacted clinical parameters, such as haemoglobin (Hb) iron levels, and volume balance, differently than the simple transfusion process.	
Reporting group title	Cohort B
Reporting group description:	
Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with thalassaemia underwent chronic RBC transfusion therapy to prevent symptomatic anaemia.	
Reporting group title	Cohort C
Reporting group description:	
Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with thalassaemia did not undergo chronic RBC transfusion therapy.	

Reporting group values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B
Number of subjects	5	7	20
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	2	4	10
Adults (18-64 years)	3	3	10
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	30.8	18.0	21.5
standard deviation	± 19.25	± 5.23	± 9.57
Gender Categorical Units: Subjects			
Female	5	1	8
Male	0	6	12

Reporting group values	Cohort C	Total	

Number of subjects	20	52	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	4	20	
Adults (18-64 years)	16	32	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	31.4		
standard deviation	± 14.77	-	
Gender Categorical Units: Subjects			
Female	15	29	
Male	5	23	

End points

End points reporting groups

Reporting group title	Cohort A: Simple transfusion

Reporting group description:

Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with sickle cell disease (SCD) underwent chronic red blood cells (RBC) transfusion therapy through simple (manual) process to prevent stroke or recurrence of stroke.

Reporting group title	Cohort A: Exchange transfusion

Reporting group description:

Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with SCD underwent chronic RBC transfusion therapy through exchange transfusion process to prevent stroke or recurrence of stroke. The exchange transfusion process involved simultaneous blood removal and RBC infusion, which impacted clinical parameters, such as haemoglobin (Hb) iron levels, and volume balance, differently than the simple transfusion process.

Reporting group title	Cohort B

Reporting group description:

Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with thalassaemia underwent chronic RBC transfusion therapy to prevent symptomatic anaemia.

Reporting group title	Cohort C

Reporting group description:

Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with thalassaemia did not undergo chronic RBC transfusion therapy.

Subject analysis set title	Total: Cohort A
Subject analysis set type	Safety analysis

Subject analysis set description:

The total arm for Cohort A includes the Cohort A – simple transfusion arm, the Cohort A – exchange transfusion arm, and one subject who received both simple and exchange transfusions during the study.

Primary: Cohorts A (Simple transfusion) and B: Percentage of subjects achieving greater than or equal to (>=) 20% reduction in RBC transfusion units over a continuous 12-week treatment period versus baseline RBC transfusion history

End point title	Cohorts A (Simple transfusion) and B: Percentage of subjects achieving greater than or equal to (>=) 20% reduction in RBC transfusion units over a continuous 12-week treatment period versus baseline RBC transfusion history[1][2]

End point description:

Percentage of subjects achieving >= 20% reduction in red blood cell (RBC) transfusion units over a continuous 12-week treatment period versus baseline RBC transfusion history in cohort A (simple transfusion) group and cohort B is presented. Responders were defined as any subject with a >=20% reduction from baseline in RBC units transfused during at least one qualifying 12-week (84 day) interval in the primary treatment period (i.e. Days 2 to 85, 3 to 86, ..., 253 to end of primary treatment period), where baseline is defined as the total number of RBC units transfused from study day -83 to study day 1. Chronically transfused was defined as >=6 RBC units in the previous 24 weeks before the first dose of study treatment and no transfusion-free period for >35 days during that period. Efficacy evaluable set included subjects in the safety set who had completed the week 12 response visit and who had a baseline record of the primary endpoint.

End point type	Primary

End point timeframe:

From baseline up to week 48 (any 12 weeks)

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: Cohort A: Prespecified one-sided exact binomial test vs 20% null response rate and corresponding Clopper–Pearson exact 95% confidence interval (CI) were performed; however, only 4

subjects were evaluable, hence formal inference was not performed. Cohort B: One-sided exact binomial statistical test vs 20% null response rate (H0: P1 ≤ 0.20 vs H1: P1 > 0.20) at significance level α = 0.025 was performed. Exact two sided 95% CIs for response proportion were calculated using Clopper–Pearson method.
[2] - 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: The endpoint is reporting data for applicable arms only.

End point values	Cohort A: Simple transfusion	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	19		
Units: Percentage of subjects				
number (confidence interval 95%)	75.0 (19.4 to 99.4)	89.5 (66.9 to 98.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Cohort C: Percentage of subjects achieving a haemoglobin (Hb) response (increase of >=1.0 grams per deciliter [g/dL] from baseline)

End point title	Cohort C: Percentage of subjects achieving a haemoglobin (Hb) response (increase of >=1.0 grams per deciliter [g/dL] from baseline)[3][4]

End point description:

Percentage of subjects achieving a Hb response in cohort C is presented. Hb response at a given timepoint is defined as a change of >=1 g/dL from the baseline Hb with no RBC transfusions received in the prior 8 weeks. Hb response rate at a given timepoint is calculated as: number of Hb responders at a given timepoint/number of subjects who have completed assessment at the given timepoint. Efficacy evaluable set included subjects in the safety set who had completed the week 12 response visit and who had a baseline record of the primary endpoint.

End point type	Primary

End point timeframe:

From baseline up to week 12

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: For Cohort C: Onesided exact binomial statistical test versus a 10% null response rate (H0: P1 ≤ 0.10 vs H1: P1 > 0.10) at significance level α = 0.025 was performed. Exact twosided 95% confidence intervals for the response proportion were calculated using the Clopper–Pearson method.
[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: The endpoint is reporting data for applicable arms only.

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Percentage of subjects				
number (confidence interval 95%)	50.0 (27.2 to 72.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment emergent serious adverse events (TESAEs)

End point title	Number of subjects with treatment emergent serious adverse events (TESAEs)

End point description:

Number of subjects with TESAEs is presented. A treatment emergent adverse event (TEAE) was defined as any adverse event (AE) that emerged or worsened in the period from the first dose of study drug to 28 days after the last dose of study drug. An SAE is any untoward medical occurrence that occurs at any dose that: results in death, is life-threatening, requires in-patient hospitalization, results in persistent or significant disability/incapacity, results in a congenital anomaly/birth defect. Chronically transfused was defined as >=6 RBC units in the previous 24 weeks before the first dose of study treatment and no transfusion-free period for >35 days during that period. Safety set consisted of all subjects who received at least one dose of etavopivat.

End point type	Secondary

End point timeframe:

From baseline up to week 152

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	20	20
Units: Subjects	1	1	2	3

End point values	Total: Cohort A			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Subjects	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with TEAEs leading to discontinuation

End point title	Number of subjects with TEAEs leading to discontinuation

End point description:

Number of subjects with TEAEs leading to discontinuation is presented. A TEAE was defined as any AE that emerged or worsened in the period from the first dose of study drug to 28 days after the last dose of study drug. Safety set consisted of all subjects who received at least one dose of etavopivat. Chronically transfused was defined as >=6 RBC units in the previous 24 weeks before the first dose of study treatment and no transfusion-free period for >35 days during that period.

End point type	Secondary

End point timeframe:

From baseline up to week 152

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	20	20
Units: Subjects	0	0	1	1

End point values	Total: Cohort A			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant laboratory parameters: Haematolysis

End point title	Number of subjects with clinically significant laboratory parameters: Haematolysis

End point description:

Number of subjects with clinically significant laboratory parameters: Haematolysis is presented. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. Severity of the parameters are graded based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5 grading scale which was used to determine grades based on the corresponding laboratory values. The 4 grades were defined as follows: Grade 1 (Mild): event is usually transient and does not interfere with subject's daily activities, Grade 2 (Moderate): event introduces low level of inconvenience to the subject and may interfere with daily activities, Grade 3 (Severe): event interrupts subject's daily activities and hospitalization may be required, Grade 4 (Life threatening): event requires urgent intervention to prevent death. Safety set consisted of all subjects who received at least one dose of etavopivat.

End point type	Secondary

End point timeframe:

From baseline up to week 152

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	20	20
Units: Subjects				
Hemoglobin decreased: Grade 2	4	3	12	9
Hemoglobin decreased: Grade 3	1	2	8	11
Lymphocyte count increased: Grade 2	5	5	5	9

Lymphocyte count decreased: Grade 2	0	0	2	0
Neutrophil count decreased: Grade 2	0	0	1	0
Neutrophil count decreased: Grade 3	0	0	1	0
White blood cell decreased: Grade 2	0	0	1	0

End point values	Total: Cohort A			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Subjects				
Hemoglobin decreased: Grade 2	7			
Hemoglobin decreased: Grade 3	3			
Lymphocyte count increased: Grade 2	10			
Lymphocyte count decreased: Grade 2	0			
Neutrophil count decreased: Grade 2	0			
Neutrophil count decreased: Grade 3	0			
White blood cell decreased: Grade 2	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant laboratory parameters: Biochemistry

End point title	Number of subjects with clinically significant laboratory parameters: Biochemistry

End point description:

Number of subjects with clinically significant laboratory parameters: biochemistry is presented. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. Severity of parameters were graded based on CTCAE v 5 grading scale which was used to determine grades based on corresponding laboratory values. The 4 grades are defined as follows: Grade 1 - (Mild): event usually transient and does not interfere with subject's daily activities, Grade 2 (Moderate): event introduces low level of inconvenience and may interfere with subject's daily activities, Grade 3 (Severe): event interrupts subject's daily activities and hospitalization may be required, Grade 4 (Life-threatening): event requires urgent intervention to prevent death. Safety set consisted of all subjects who received at least one dose of etavopivat.

End point type	Secondary

End point timeframe:

From baseline up to week 152

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	20	20
Units: Subjects				
eGFR decreased: Grade 2	1	0	0	1

Creatinine increased: Grade 2	1	1	1	0
Hypercalcemia (Calcium increased): Grade 2	1	0	0	0
Hyperkalemia (Potassium increased): Grade 2	0	1	0	1
Hypermagnesemia (Magnesium increased): Grade 3	0	0	2	1
Hypernatremia (Sodium increased): Grade 2	0	0	0	1
Hypocalcemia (Calcium decreased): Grade 4	0	0	3	1
Hypoglycemia (Glucose decreased): Grade 2	0	0	0	7
Hypoglycemia (Glucose decreased): Grade 3	0	0	0	2
Hypokalemia (Potassium decreased): Grade 2	1	0	10	3
Hypokalemia (Potassium decreased): Grade 3	0	0	1	0
Lipase increased: Grade 4	0	1	0	0
Lipase increased: Grade 2	0	0	1	3
Serum amylase increased: Grade 2	1	1	0	0
Serum amylase increased: Grade 3	0	0	1	0

End point values	Total: Cohort A			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Subjects				
eGFR decreased: Grade 2	1			
Creatinine increased: Grade 2	2			
Hypercalcemia (Calcium increased): Grade 2	1			
Hyperkalemia (Potassium increased): Grade 2	1			
Hypermagnesemia (Magnesium increased): Grade 3	0			
Hypernatremia (Sodium increased): Grade 2	0			
Hypocalcemia (Calcium decreased): Grade 4	0			
Hypoglycemia (Glucose decreased): Grade 2	0			
Hypoglycemia (Glucose decreased): Grade 3	0			
Hypokalemia (Potassium decreased): Grade 2	1			
Hypokalemia (Potassium decreased): Grade 3	0			
Lipase increased: Grade 4	1			
Lipase increased: Grade 2	0			
Serum amylase increased: Grade 2	2			
Serum amylase increased: Grade 3	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant laboratory parameters: Coagulation

End point title	Number of subjects with clinically significant laboratory parameters: Coagulation

End point description:

Number of subjects with clinically significant laboratory parameters: coagulation is presented. Data is not reported for this endpoint as there are no clinically relevant findings. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. Safety set consisted of all subjects who received at least one dose of etavopivat.

End point type	Secondary

End point timeframe:

From baseline up to week 152

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	20	20
Units: Subjects	0	0	0	0

End point values	Total: Cohort A			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant laboratory parameters: Endocrinology

End point title	Number of subjects with clinically significant laboratory parameters: Endocrinology

End point description:

Number of subjects with clinically significant laboratory parameters: endocrinology is presented. Data is not reported for this endpoint as there are no clinically relevant findings. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. Safety set consisted of all subjects who received at least one dose of etavopivat.

End point type	Secondary

End point timeframe:

From baseline up to week 152

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	20	20
Units: Subjects	0	0	0	0

End point values	Total: Cohort A			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant laboratory parameters: Urinalysis

End point title	Number of subjects with clinically significant laboratory parameters: Urinalysis

End point description:

Number of subjects with clinically significant laboratory parameters: urinalysis is presented. Data is not reported for this endpoint as there are no clinically relevant findings. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. Safety set consisted of all subjects who received at least one dose of etavopivat.

End point type	Secondary

End point timeframe:

From baseline up to week 152

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	20	20
Units: Subjects	0	0	0	0

End point values	Total: Cohort A			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant abnormal electrocardiograms (ECGs)

End point title	Number of subjects with clinically significant abnormal electrocardiograms (ECGs)

End point description:

Number of subjects with clinically significant abnormal ECGs is presented. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. Safety set consisted of all subjects who received at least one dose of etavopivat.

End point type	Secondary

End point timeframe:

From baseline up to week 152

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	20	20
Units: Subjects	2	0	2	1

End point values	Total: Cohort A			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Subjects	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinically significant laboratory parameters: Serolgy

End point title	Number of participants with clinically significant laboratory parameters: Serolgy

End point description:

Number of subjects with clinically significant laboratory parameters: serology is presented. Data is not reported for this endpoint as there are no clinically relevant findings. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. Safety set consisted of all subjects who received at least one dose of etavopivat.

End point type	Secondary

End point timeframe:

From baseline up to week 152

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	20	20
Units: Subjects	0	0	0	0

End point values	Total: Cohort A			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant laboratory parameters: Iron studies, folate and Vitamin B12

End point title	Number of subjects with clinically significant laboratory parameters: Iron studies, folate and Vitamin B12

End point description:

Number of subjects with clinically significant laboratory parameters: iron studies, folate and vitamin B12 is presented. Data is not reported for this endpoint as there are no clinically relevant findings. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. Safety set consisted of all subjects who received at least one dose of etavopivat.

End point type	Secondary

End point timeframe:

From baseline up to week 152

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	20	20
Units: Subjects	0	0	0	0

End point values	Total: Cohort A			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts A (Simple transfusion) and B: Relative reduction from baseline in RBC transfusion burden from baseline to week 12

End point title	Cohorts A (Simple transfusion) and B: Relative reduction from baseline in RBC transfusion burden from baseline to week 12[5]

End point description:

Relative reduction from baseline in RBC transfusion burden in cohorts A (simple transfusion) and cohort B is presented. Relative reduction from expected units transfused was derived as -100 x (actual RBC units transfused during interval-expected RBC units transfused)/expected RBC units transfused, where the expected RBC units transfused were defined as interval duration (Weeks)/12 x baseline RBC transfusion units. Baseline RBC transfusion units were defined as the summed RBC units transfused for 12 weeks prior to study start (Study Day -83 to 1). Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. Efficacy evaluable set included subjects in the safety set who had completed the week 12 response visit and who had a baseline record of the primary endpoint.

End point type	Secondary

End point timeframe:

From baseline to week 12

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: The endpoint is reporting data for applicable arms only.

End point values	Cohort A: Simple transfusion	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	19		
Units: Percentage of RBC transfusion units				
arithmetic mean (standard deviation)	35.994 (± 38.2914)	15.277 (± 20.9685)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts A (Simple transfusion) and B: Relative reduction from baseline in RBC transfusion burden from baseline to week 24

End point title	Cohorts A (Simple transfusion) and B: Relative reduction from baseline in RBC transfusion burden from baseline to week 24[6]

End point description:

Relative reduction from baseline in RBC transfusion burden in cohorts A (simple transfusion) and cohort B is presented. Relative reduction from expected units transfused was derived as -100 x (actual RBC units transfused during interval-expected RBC units transfused)/expected RBC units transfused, where the expected RBC units transfused were defined as interval duration (Weeks)/12 x baseline RBC transfusion units. Baseline RBC transfusion units were defined as the summed RBC units transfused for 12 weeks prior to study start (Study Day -83 to 1). Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. Efficacy evaluable set included subjects in the safety set who had completed the week 12 response visit and who had a baseline record of the primary endpoint. Number of subjects analysed = Subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to week 24

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: The endpoint is reporting data for applicable arms only.

End point values	Cohort A: Simple transfusion	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	18		
Units: Percentage of RBC transfusion units				
arithmetic mean (standard deviation)	23.494 (± 32.6929)	11.874 (± 18.1068)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts A (Simple transfusion) and B: Number of subjects achieving >= 33% reduction in RBC transfusion units over a continuous 12-week treatment

period versus baseline RBC transfusion history

End point title	Cohorts A (Simple transfusion) and B: Number of subjects achieving >= 33% reduction in RBC transfusion units over a continuous 12-week treatment period versus baseline RBC transfusion history[7]

End point description:

Number of subjects achieving >= 33% reduction in RBC transfusion units over a continuous 12-week treatment period versus baseline RBC transfusion history in cohorts A (simple transfusion) and B is presented. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. Efficacy evaluable set included subjects in the safety set who had completed the week 12 response visit and who had a baseline record of the primary endpoint.

End point type	Secondary

End point timeframe:

From baseline up to week 48 (any 12 weeks)

Notes:

[7] - 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: The endpoint is reporting data for applicable arms only.

End point values	Cohort A: Simple transfusion	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	19		
Units: Subjects	3	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: Mean change from baseline to week 12 in Hb

End point title	Cohort C: Mean change from baseline to week 12 in Hb[8]

End point description:

Mean change from baseline to week 12 in Hb in cohort C is presented. FAS was defined as all subjects who completed informed consent and received at least one dose of etavopivat (including partial dosing).

End point type	Secondary

End point timeframe:

From baseline to week 12

Notes:

[8] - 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: The endpoint is reporting data for applicable arms only.

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: grams per deciliter (g/dL)				
least squares mean (confidence interval 95%)	1.12 (0.81 to 1.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts A (Simple transfusion) and B: Relative reduction from baseline in RBC transfusion burden from baseline to end of extension treatment period (week 108)

End point title	Cohorts A (Simple transfusion) and B: Relative reduction from baseline in RBC transfusion burden from baseline to end of extension treatment period (week 108)[9]

End point description:

Relative reduction from baseline in RBC transfusion burden in cohorts A (simple transfusion) and cohort B is presented. Relative reduction from expected units transfused was derived as -100 x (actual RBC units transfused during interval-expected RBC units transfused)/expected RBC units transfused, where the expected RBC units transfused were defined as interval duration (Weeks)/12 x baseline RBC transfusion units. Baseline RBC transfusion units were defined as the summed RBC units transfused for 12 weeks prior to study start (Study Day -83 to 1). Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. Efficacy evaluable set included subjects in the safety set who had completed the week 12 response visit and who had a baseline record of the primary endpoint. Number of subjects analysed = Subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to end of extension treatment period (week 108)

Notes:

[9] - 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: The endpoint is reporting data for applicable arms only.

End point values	Cohort A: Simple transfusion	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	14		
Units: Percentage of RBC transfusion units				
arithmetic mean (standard deviation)	()	4.573 (± 20.5664)		

Notes:

[10] - No subjects were analysed for this arm in this particular timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts A (Simple transfusion) and B: Relative reduction from baseline in RBC transfusion burden from baseline to week 48

End point title	Cohorts A (Simple transfusion) and B: Relative reduction from baseline in RBC transfusion burden from baseline to week 48[11]

End point description:

Relative reduction from baseline in RBC transfusion burden from cohorts A (simple transfusion) and cohort B is presented. Relative reduction from expected units transfused was derived as -100 x (actual RBC units transfused during interval-expected RBC units transfused)/expected RBC units transfused, where the expected RBC units transfused were defined as interval duration (Weeks)/12 x baseline RBC transfusion units. Baseline RBC transfusion units were defined as the summed RBC units transfused for 12 weeks prior to study start (Study Day -83 to 1). Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. Efficacy evaluable set included subjects in the safety set who had completed the week 12 response visit and who had a baseline record of the primary endpoint. Number of subjects analysed = Subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to week 48

Notes:

[11] - 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: The endpoint is reporting data for applicable arms only.

End point values	Cohort A: Simple transfusion	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	18		
Units: Percentage of RBC transfusion units				
arithmetic mean (standard deviation)	22.315 (± 23.6839)	10.855 (± 15.7686)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: Number of subjects achieving a Hb response (increase of >=1.0 g/dL from baseline) at week 48

End point title	Cohort C: Number of subjects achieving a Hb response (increase of >=1.0 g/dL from baseline) at week 48[12]

End point description:

Number of subjects achieving a Hb response in cohort C is presented. Hb response at a given timepoint is defined as a change of >=1 g/dL from the baseline Hb with no RBC transfusions received in the prior 8 weeks. Hb response rate at a given timepoint is calculated as: number of Hb responders at a given timepoint/number of subjects who have completed assessment at the given timepoint. Efficacy evaluable set included subjects in the safety set who had completed the week 12 response visit and who had a baseline record of the primary endpoint. Number of subjects analysed = Subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to week 48

Notes:

[12] - 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: The endpoint is reporting data for applicable arms only.

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Subjects	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: Number of subjects achieving a Hb response (increase of >=1.0 g/dL from baseline) at end of extension treatment period (week 108)

End point title	Cohort C: Number of subjects achieving a Hb response (increase of >=1.0 g/dL from baseline) at end of extension treatment period (week 108)[13]

End point description:

Number of subjects achieving a Hb response in cohort C is presented. Hb response at a given timepoint is defined as a change of >=1 g/dL from the baseline Hb with no RBC transfusions received in the prior 8 weeks. Hb response rate at end of extension treatment (EOET) was defined as number of Hb responders at EOET/number of subjects continuing into the extension treatment period who have completed assessment or dropped out. Efficacy evaluable set included subjects in the safety set who had completed the week 12 response visit and who had a baseline record of the primary endpoint. Number of subjects analysed = Subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to end of extension treatment period (week 108)

Notes:

[13] - 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: The endpoint is reporting data for applicable arms only.

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Subjects	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: Number of subjects achieving a Hb response (increase of >=1.0 g/dL from baseline) at week 24

End point title	Cohort C: Number of subjects achieving a Hb response (increase of >=1.0 g/dL from baseline) at week 24[14]

End point description:

Number of subjects achieving a Hb response in cohort C is presented. Hb response at a given timepoint is defined as a change of >=1 g/dL from the baseline Hb with no RBC transfusions received in the prior 8 weeks. Hb response rate at a given timepoint is calculated as: number of Hb responders at a given timepoint/number of subjects who have completed assessment at the given timepoint. Efficacy evaluable set included subjects in the safety set who had completed the week 12 response visit and who had a baseline record of the primary endpoint. Number of subjects analysed = Subjects with available

data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to week 24

Notes:

[14] - 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: The endpoint is reporting data for applicable arms only.

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Subjects	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: Mean change from baseline to end of extension treatment period (week 108) in Hb

End point title	Cohort C: Mean change from baseline to end of extension treatment period (week 108) in Hb[15]

End point description:

Mean change from baseline to end of extension treatment period (week 108) in Hb in cohort C is presented. FAS was defined as all subjects who completed informed consent and received at least one dose of etavopivat (including partial dosing).

End point type	Secondary

End point timeframe:

From baseline to end of extension treatment period (week 108)

Notes:

[15] - 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: The endpoint is reporting data for applicable arms only.

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: g/dL				
least squares mean (confidence interval 95%)	0.92 (0.33 to 1.51)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: Mean change from baseline to week 48 in Hb

End point title	Cohort C: Mean change from baseline to week 48 in Hb[16]

End point description:

Mean change from baseline to week 48 in Hb in cohort C is presented. FAS was defined as all subjects who completed informed consent and received at least one dose of etavopivat (including partial dosing). Number of subjects analysed = Subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to week 48

Notes:

[16] - 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: The endpoint is reporting data for applicable arms only.

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: g/dL				
least squares mean (confidence interval 95%)	0.91 (0.56 to 1.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: Mean change from baseline to week 24 in Hb

End point title	Cohort C: Mean change from baseline to week 24 in Hb[17]

End point description:

Mean change from baseline to week 24 in Hb in cohort C is presented. FAS was defined as all subjects who completed informed consent and received at least one dose of etavopivat (including partial dosing). Number of subjects analysed = Subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to week 24

Notes:

[17] - 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: The endpoint is reporting data for applicable arms only.

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: g/dL				
least squares mean (confidence interval 95%)	0.88 (0.56 to 1.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A and B and C: Change from baseline to week 12 in serum ferritin levels

End point title	Cohort A and B and C: Change from baseline to week 12 in serum ferritin levels

End point description:

Change from baseline to week 12 in serum ferritin levels in cohort A, cohort B and cohort C is presented. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. FAS was defined as all subjects who completed informed consent and received at least one dose of etavopivat (including partial dosing). Number of subjects analysed = Subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to week 12

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	7	18	18
Units: picomoles per liter (pmol/L)				
least squares mean (confidence interval 95%)	952.0 (-716.5 to 2620.5)	1085.7 (-937.5 to 3108.9)	-101.8 (-652.6 to 448.9)	113.7 (-32.9 to 260.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A and B and C: Change from baseline to week 24 in serum ferritin levels

End point title	Cohort A and B and C: Change from baseline to week 24 in serum ferritin levels

End point description:

Change from baseline to week 24 in serum ferritin levels in cohort and B and C is presented. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. FAS was defined as all subjects who completed informed consent and received at least one dose of etavopivat (including partial dosing). Number of subjects analysed = Subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to week 24

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	17	16
Units: pmol/L				
least squares mean (confidence interval 95%)	832.8 (-835.8 to 2501.3)	-188.6 (-2393.2 to 2016.0)	-344.1 (-903.9 to 215.7)	18.6 (-136.0 to 173.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A and B and C: Change from baseline to week 48 in serum ferritin levels

End point title	Cohort A and B and C: Change from baseline to week 48 in serum ferritin levels

End point description:

Change from baseline to week 48 in serum ferritin levels in cohort A and B and C is presented. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. FAS was defined as all subjects who completed informed consent and received at least one dose of etavopivat (including partial dosing). Number of subjects analysed = Subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to week 48

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	17	16
Units: pmol/L				
least squares mean (confidence interval 95%)	1249.5 (-419.0 to 2918.0)	585.2 (-1835.7 to 3006.1)	-359.0 (-922.0 to 204.0)	-56.4 (-213.0 to 100.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A and B and C: Change from baseline to end of extension treatment period (week 108) in serum ferritin levels

End point title	Cohort A and B and C: Change from baseline to end of extension treatment period (week 108) in serum ferritin levels

End point description:

Change from baseline to end of extension treatment period (week 108) in serum ferritin levels in cohort A and B and C is presented. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. FAS

was defined as all subjects who completed informed consent and received at least one dose of etavopivat (including partial dosing). Number of subjects analysed = Subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to end of extension treatment period (week 108)

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[18]	1	6	2
Units: pmol/L				
least squares mean (confidence interval 95%)	(to)	6335.6 (723.9 to 11947.4)	-127.1 (-1015.2 to 761.1)	-129.4 (-562.0 to 303.1)

Notes:

[18] - No subjects were analysed for this arm in this particular timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A and B and C: Change from baseline to week 48 in liver iron concentration (LIC)

End point title	Cohort A and B and C: Change from baseline to week 48 in liver iron concentration (LIC)

End point description:

Change from baseline to week 48 in LIC is presented. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. FAS was defined as all subjects who completed informed consent and received at least one dose of etavopivat (including partial dosing). Number of subjects analysed = Subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to week 48

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	17	13
Units: milligrams iron per gram (mgFe/g)				
arithmetic mean (standard deviation)	1.553 (± 2.3951)	-1.645 (± 2.5148)	0.337 (± 2.4807)	-1.588 (± 2.7642)

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A and B and C: Change from baseline to week 96 in LIC

End point title	Cohort A and B and C: Change from baseline to week 96 in LIC

End point description:

Change from baseline to week 96 in LIC is presented. Chronically transfused was defined as >=6 RBC units in previous 24 weeks before first dose of study treatment and no transfusion-free period for >35 days during that period. FAS was defined as all subjects who completed informed consent and received at least one dose of etavopivat (including partial dosing). Number of subjects analysed = Subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

From baseline to week 96

End point values	Cohort A: Simple transfusion	Cohort A: Exchange transfusion	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[19]	1	12	6
Units: mgFe/g				
arithmetic mean (standard deviation)	()	-5.800 (± 0.0)	0.525 (± 3.7794)	-1.512 (± 2.0428)

Notes:

[19] - No subjects were analysed for this arm in this particular timepoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to week 152

Adverse event reporting additional description:

All presented AEs are TEAEs. TEAE: an AE if they emerge or worsen in the period from first dose of study drug (Day 1) to 28 days after last dose of study drug. Safety set: all subjects who received at least one dose of etavopivat. Planned duration of study was up to 120 weeks. However, some subjects duration was longer due to operational reasons.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Cohort A: Simple Transfusion

Reporting group description:

Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with sickle cell disease (SCD) underwent chronic red blood cells (RBC) transfusion therapy through simple (manual) process to prevent stroke or recurrence of stroke.

Reporting group title	Cohort A: Exchange Transfusion

Reporting group description:

Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with SCD underwent chronic RBC transfusion therapy through exchange transfusion process to prevent stroke or recurrence of stroke. The exchange transfusion process involved simultaneous blood removal and RBC infusion, which impacted clinical parameters, such as haemoglobin (Hb) iron levels, and volume balance, differently than the simple transfusion process.

Reporting group title	Cohort C

Reporting group description:

Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with thalassaemia did not undergo chronic RBC transfusion therapy.

Reporting group title	Cohort B

Reporting group description:

Subjects received etavopivat 400 mg (2 tablets of 200mg each) daily orally for 48-week primary treatment period followed by an optional 60-week extension treatment period. In this arm, subjects with thalassaemia underwent chronic RBC transfusion therapy to prevent symptomatic anaemia.

Reporting group title	Total: Cohort A

Reporting group description:

The total arm for cohort A includes subjects in the cohort A - simple transfusion arm and cohort A - exchange transfusion arm and one subject who underwent both simple and exchange transfusion procedures throughout the duration of the study. This subject was included in the Cohort A Total column in this and all other Cohort A summaries.

Serious adverse events	Cohort A: Simple Transfusion	Cohort A: Exchange Transfusion	Cohort C
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	3 / 20 (15.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0

Investigations			
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Portal vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hypersplenism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sickle cell anaemia with crisis			

subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 20 (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
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Haemorrhagic ovarian cyst			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			

subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Tonsillitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort B	Total: Cohort A	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	2 / 13 (15.38%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Investigations			
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (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			
Allergic transfusion reaction			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Portal vein thrombosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardiac arrest			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypersplenism			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (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			
Haemorrhagic ovarian cyst			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Tonsillitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (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: Simple Transfusion	Cohort A: Exchange Transfusion	Cohort C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	6 / 7 (85.71%)	20 / 20 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign hepatic neoplasm			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Portal vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	4 / 20 (20.00%)
occurrences (all)	1	0	4
Influenza like illness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	5 / 20 (25.00%)
occurrences (all)	0	1	13
Peripheral swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	3 / 20 (15.00%)
occurrences (all)	0	0	3

Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	3 / 20 (15.00%)
occurrences (all)	0	0	3
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hypersensitivity			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	2
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	4 / 20 (20.00%)
occurrences (all)	0	0	5
Dyspnoea exertional			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dry throat			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	3 / 20 (15.00%)
occurrences (all)	0	0	4
Throat irritation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Amylase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Blood uric acid increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood testosterone decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram T wave abnormal			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Haemoglobin S increased			

subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Lipase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Pancreatic enzymes increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Thyroxine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Vitamin B12 decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Foot fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Limb injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Neck injury			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Thermal burn			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Road traffic accident			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Transfusion reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Extrasystoles			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Supraventricular extrasystoles			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ventricular extrasystoles			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Ventricular arrhythmia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			

subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	9 / 20 (45.00%)
occurrences (all)	1	5	14
Migraine			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Parosmia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hyperviscosity syndrome			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Leukocytosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Splenomegaly			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 5 (20.00%)	2 / 7 (28.57%)	0 / 20 (0.00%)
occurrences (all)	1	4	0
Eye disorders			
Dry eye			

subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Eye disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Aphthous ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	5 / 20 (25.00%)
occurrences (all)	1	1	6
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Food poisoning			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	4 / 20 (20.00%)
occurrences (all)	0	2	5

Mouth cyst			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	3
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Cholecystitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gallbladder polyp			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hepatic lesion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hyperbilirubinaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Acne			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Rash maculo-papular			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	3
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Urticaria			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	3
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Haematuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hypercalciuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hypocitraturia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nephrolithiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Bone pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	2 / 5 (40.00%)	1 / 7 (14.29%)	2 / 20 (10.00%)
occurrences (all)	2	1	2
Fibromyalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Limb discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	3
Tendon pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	3
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Beta haemolytic streptococcal infection			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	3 / 20 (15.00%)
occurrences (all)	0	0	4
Nasopharyngitis			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	1 / 20 (5.00%)
occurrences (all)	1	3	1
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	11 / 20 (55.00%)
occurrences (all)	1	1	18
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	3
Tonsillitis			

subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	3 / 20 (15.00%)
occurrences (all)	1	0	3
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gout			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hypoglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Iron overload			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Vitamin C deficiency			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Vitamin B6 deficiency			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 20 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Cohort B	Total: Cohort A	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 20 (95.00%)	12 / 13 (92.31%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign hepatic neoplasm			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Portal vein thrombosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Discomfort			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	3 / 20 (15.00%)	1 / 13 (7.69%)	
occurrences (all)	5	1	
Influenza like illness			
subjects affected / exposed	1 / 20 (5.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Peripheral swelling			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			

subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hypersensitivity			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Dyspnoea exertional			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Dry throat			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	2 / 20 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	3 / 20 (15.00%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Throat irritation			

subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 20 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Amylase increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 20 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Blood uric acid increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Blood testosterone decreased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Blood phosphorus decreased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram abnormal			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram T wave abnormal			

subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Haemoglobin S increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Pancreatic enzymes increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Prothrombin time prolonged			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Thyroxine increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Vitamin B12 decreased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Foot fracture			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Limb injury			

subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Neck injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Road traffic accident			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Transfusion reaction			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Extrasystoles			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Palpitations			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Supraventricular extrasystoles			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Ventricular arrhythmia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	

Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	5 / 20 (25.00%)	2 / 13 (15.38%)	
occurrences (all)	6	6	
Migraine			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Parosmia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Paraesthesia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hyperviscosity syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Leukocytosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Splenomegaly			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 20 (0.00%)	4 / 13 (30.77%)	
occurrences (all)	0	6	
Eye disorders			

Dry eye			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Eye disorder			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Aphthous ulcer			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	2 / 20 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 20 (5.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Gastritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Food poisoning			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nausea			

subjects affected / exposed	2 / 20 (10.00%)	1 / 13 (7.69%)	
occurrences (all)	3	2	
Mouth cyst			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Cholecystitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Gallbladder polyp			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Hepatic lesion			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Acne			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Eczema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Rash papular			

subjects affected / exposed	2 / 20 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Rash maculo-papular			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Urticaria			
subjects affected / exposed	2 / 20 (10.00%)	1 / 13 (7.69%)	
occurrences (all)	5	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Haematuria			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hypercalciuria			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hypocitraturia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Nephrolithiasis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Arthralgia			

subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Bone pain			
subjects affected / exposed	1 / 20 (5.00%)	1 / 13 (7.69%)	
occurrences (all)	3	2	
Back pain			
subjects affected / exposed	2 / 20 (10.00%)	3 / 13 (23.08%)	
occurrences (all)	2	3	
Fibromyalgia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Limb discomfort			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Tendon pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

Beta haemolytic streptococcal infection				
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)		
occurrences (all)	1	0		
Gastrointestinal viral infection				
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)		
occurrences (all)	0	0		
Gastroenteritis				
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)		
occurrences (all)	1	0		
Hordeolum				
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)		
occurrences (all)	1	0		
Influenza				
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)		
occurrences (all)	0	0		
Nasopharyngitis				
subjects affected / exposed	0 / 20 (0.00%)	2 / 13 (15.38%)		
occurrences (all)	0	4		
Pneumonia				
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)		
occurrences (all)	0	0		
Pharyngitis				
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)		
occurrences (all)	1	0		
Otitis media				
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)		
occurrences (all)	0	0		
Rhinitis				
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)		
occurrences (all)	0	0		
Upper respiratory tract infection				
subjects affected / exposed	10 / 20 (50.00%)	2 / 13 (15.38%)		
occurrences (all)	14	2		
Urinary tract infection				

subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Tonsillitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Dehydration			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Gout			
subjects affected / exposed	0 / 20 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Hypoglycaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Iron deficiency			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Iron overload			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 20 (5.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	0 / 20 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

Vitamin C deficiency subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 13 (0.00%) 0	
Vitamin B6 deficiency subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 13 (7.69%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2021	The changes included were as follows: i) Study visit nomenclature and visit windows were adjusted to clarify visit structure and better accommodate individual subject's transfusion schedules. ii) The risk/benefit assessment language and dose justification text was updated to provide current supportive data from the ongoing first-in-human phase 1 study (4202-HVS-101). iii) Study assessments, exploratory objectives, and endpoints were modified to include the 36-Item Short Form Health Survey (SF-36) quality of life instrument. iv) Adverse event dose interruption/stopping criteria were updated and clarified to address regulatory authority feedback. v) Liver chemistry dose interruption/stopping criteria were updated and clarified to address regulatory authority feedback. vi) Text was added to provide guidelines for determination of whether a subject's worsening alanine transaminase (ALT) is related or unrelated to the subject's underlying disease. vii) Study assessment text was reorganized to improve presentation and consolidate text across the assessment and statistical consideration sections. viii) Text was added to describe the statistical analysis of change from baseline in serum ferritin and liver iron concentration. ix) The Appendices were updated as needed to reflect changes to the protocol.
10 March 2022	The changes included were as follows: i) Respective sections were updated to remove text regarding the replacement of subjects who drop out prior to week 12 for consistency with other sections of the protocol. ii) Respective sections were updated to reflect that subjects who discontinue the study prior to 24 weeks of treatment should complete the early discontinuation visit.
21 November 2022	The changes included were as follows: i) The study's medical lead and associated contact infor-mation was updated. ii) Etavopivat, the international nonproprietary name for FT-4202, was in-corporated throughout the protocol iii) The screening period was extended to 8 weeks to better align with subject transfusion schedules which tend to occur every 4 weeks, thus allowing sites additional screening time iv) The allowed range for post-transfusion Hb values for patients with SCD (Cohort A) was expanded to allow for subjects with values of ~9 to 12 g/dL to align with cur-rent clinical practice. v) Risk/benefit text was updated to reflect currently available information based on Investigator's Brochure (Version 4.0, dated 06 Jan 2022). vi) Dose justification text was updated to provide a more complete and current assessment of available information supporting the etavopivat dose of 400 mg once daily as the selected dose for the study. vii) Contraception language was updated throughout the protocol to align with guidelines provided in the current etavopivat Investigator's Brochure (Version 4.0, dated 06 Jan 2022). viii) Cohort-specific inclusion and exclusion criteria were updated to clarify procedures and adjust requirements to improve enrollment. ix) Exclusion criteria were updated to remove restrictions on subjects receiving con-comitant medications that were moderate or strong inhibitors of CYP3A4/5 based on currently available drug-drug interaction data. x) A new section was added to provide guidelines for study drug administration that was inadvertently missed in the previous version of the protocol. x) The Schedule of Events and Appendices were updated as needed to reflect the above changes to the protocol. xi) The Schedule of Events was also updated to expand the safety visit windows and the time between safety visits to close potential gaps surrounding the safety visits which are situated between the response and EOT visits.

24 August 2023	The changes included were as follows: i) An optional 60-week extension treatment period was added to the study. Impacted sections included: study endpoints, study design, treatment/study duration, end of study and study/treatment discontinuation. ii) Study endpoints were clarified to align with the Statistical Analysis Plan (SAP) and current clinical guidance. iii) Study drug administration text was updated to clarify that actions taken in relation to study drug administration (dose hold, dose reduction, rechallenge) must be recorded on an ongoing basis during the entire duration of the study, including the time between study visits. iv) Statistical considerations text was clarified to align with the SAP and current clinical guidance, and to correct typographical errors. v) The Schedule of Events and Appendices were updated as needed to reflect the above changes to the protocol.
11 December 2023	The changes included were as follows: i) Update of the contraception guidance based on the safety profile agreed for etavopivat. ii) Update of the safety reporting information as Novo Nordisk Global Safety is now responsible for safety surveillance in the study. Safety text has been added throughout the document to reflect the Novo Nordisk Safety Surveillance practice. iii) Inclusion of an appendix for country specific considerations in alignment with Novo Nordisk protocol process and to prevent separate country specific amendments. iv) Update to ensure alignment with the Statistical Analysis Plan. v) Implementation of wording allowing transition into a future roll-over study after completion of the primary treatment period or while on the extension treatment period vi) The Schedule of Events table (Table 1 and Table 2) and associated footnotes have been updated to reflect the described changes.
28 October 2024	The changes included were as follows: i) New potential risk (Histiocytic sarcomas) added. Based on a signal from a non-clinical study. ii) Drug-drug interaction with CYP3A4 inducers. Based on a clinical evaluation. iii) An End of Study visit will not be performed in case subjects were enrolled in the roll-over study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported