



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Investigating the Efficacy and Safety of Roxadustat (FG-4592) for Treatment of Anemia in Patients with Lower Risk Myelodysplastic Syndrome (MDS) with Low Red Blood Cell (RBC) Transfusion Burden (LTB)

Summary

EudraCT number	2017-001773-17
Trial protocol	DE ES GB BE DK IT
Global end of trial date	20 June 2023

Results information

Result version number	v1
This version publication date	29 June 2024
First version publication date	29 June 2024

Trial information

Trial identification

Sponsor protocol code	FGCL-4592-082
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03263091
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	FibroGen, Inc.
Sponsor organisation address	409 Illinois Street, San Francisco, United States, CA 94158
Public contact	Clinical Trial Information Desk, FibroGen, Inc., 082MDSstudy@fibrogen.com
Scientific contact	Clinical Trial Information Desk, FibroGen, Inc., 082MDSstudy@fibrogen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 June 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine whether FG-4592 is safe and effective in the treatment of anemia in participants with lower risk MDS and low red blood cell transfusion burden.

Protection of trial subjects:

This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), the International Council for Harmonisation (ICH) E6 Guidance for GCP, any other applicable local health and regulatory requirements and Institutional Ethics Committee (IEC) requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	India: 7
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 15
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Türkiye: 16
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	184
EEA total number of subjects	73

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	45
From 65 to 84 years	126
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

The study included 3 components: Open-label (OL) Lead-in, Double-blind (DB), and OL High-erythropoietin (High-EPO) component. Participants were enrolled in sequential dose level cohorts in OL lead-in component prior to the start of DB component.

Pre-assignment

Screening details:

Concurrent with enrollment in DB component, participants with high serum EPO levels (>400 milli-international units [mIU]/milliliter [mL]), exclusionary for DB component, were enrolled in an OL high-EPO component. Participants with lower-risk myelodysplastic syndrome (MDS) with LTB were randomized 3:2 to roxadustat or placebo in DB component.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	OL Component (Cohort 1): Roxadustat 1.5 mg/kg

Arm description:

Participants received roxadustat 1.5 milligrams (mg)/kilograms (kg), three times a week (TIW) for 52 weeks.

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

Dosage and administration details:

Roxadustat was administered per schedule specified in the arm description.

Arm title	OL Component (Cohort 2): Roxadustat 2.0 mg/kg
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Arm description:

Participants received roxadustat 2.0 mg/kg, TIW for 52 weeks.

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

Dosage and administration details:

Roxadustat was administered per schedule specified in the arm description.

Arm title	OL Component (Cohort 3): Roxadustat 2.5 mg/kg
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Arm description:

Participants received roxadustat 2.5 mg/kg, TIW for 52 weeks.

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

Dosage and administration details:

Roxadustat was administered per schedule specified in the arm description.

Arm title	OL High-EPO Component: Roxadustat 2.5 mg/kg
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Arm description:

Participants with high serum EPO levels (>400 mIU/mL) received roxadustat 2.5 mg/kg TIW for 52 weeks.

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

Dosage and administration details:

Roxadustat was administered per schedule specified in the arm description.

Arm title	DB Component: Roxadustat
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Arm description:

Participants received roxadustat 2.5 mg/kg TIW for 52 weeks.

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

Dosage and administration details:

Roxadustat was administered per schedule specified in the arm description.

Arm title	DB Component: Placebo
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Arm description:

Participants received placebo matched to roxadustat for 52 weeks.

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

Dosage and administration details:

Placebo matched to roxadustat was administered per schedule specified in the arm description.

Number of subjects in period 1	OL Component (Cohort 1): Roxadustat 1.5 mg/kg	OL Component (Cohort 2): Roxadustat 2.0 mg/kg	OL Component (Cohort 3): Roxadustat 2.5 mg/kg
Started	8	8	8
Received at least 1 dose of study drug	8	8	8
Completed	6	6	6
Not completed	2	2	2
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	1	1	-
Physician decision	-	1	2
Adverse event, non-fatal	-	-	-
Other than specified	-	-	-
Lost to follow-up	-	-	-

Number of subjects in period 1	OL High-EPO Component: Roxadustat 2.5 mg/kg	DB Component: Roxadustat	DB Component: Placebo
Started	20	82	58
Received at least 1 dose of study drug	20	82	58
Completed	10	38	37
Not completed	10	44	21
Adverse event, serious fatal	3	7	4
Consent withdrawn by subject	6	22	8
Physician decision	1	3	1
Adverse event, non-fatal	-	2	1
Other than specified	-	8	6
Lost to follow-up	-	2	1

Baseline characteristics

Reporting groups

Reporting group title	OL Component (Cohort 1): Roxadustat 1.5 mg/kg
Reporting group description: Participants received roxadustat 1.5 milligrams (mg)/kilograms (kg), three times a week (TIW) for 52 weeks.	
Reporting group title	OL Component (Cohort 2): Roxadustat 2.0 mg/kg
Reporting group description: Participants received roxadustat 2.0 mg/kg, TIW for 52 weeks.	
Reporting group title	OL Component (Cohort 3): Roxadustat 2.5 mg/kg
Reporting group description: Participants received roxadustat 2.5 mg/kg, TIW for 52 weeks.	
Reporting group title	OL High-EPO Component: Roxadustat 2.5 mg/kg
Reporting group description: Participants with high serum EPO levels (>400 mIU/mL) received roxadustat 2.5 mg/kg TIW for 52 weeks.	
Reporting group title	DB Component: Roxadustat
Reporting group description: Participants received roxadustat 2.5 mg/kg TIW for 52 weeks.	
Reporting group title	DB Component: Placebo
Reporting group description: Participants received placebo matched to roxadustat for 52 weeks.	

Reporting group values	OL Component (Cohort 1): Roxadustat 1.5 mg/kg	OL Component (Cohort 2): Roxadustat 2.0 mg/kg	OL Component (Cohort 3): Roxadustat 2.5 mg/kg
Number of subjects	8	8	8
Age Categorical Units: participants			
<65 Years	3	0	2
≥65 Years	5	8	6
Sex: Female, Male Units: participants			
Female	3	3	6
Male	5	5	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	7	8	8
More than one race	0	0	0
Unknown or Not Reported	1	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	0
Not Hispanic or Latino	7	7	6

Unknown or Not Reported	0	0	2
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Reporting group values	OL High-EPO Component: Roxadustat 2.5 mg/kg	DB Component: Roxadustat	DB Component: Placebo
Number of subjects	20	82	58
Age Categorical Units: participants			
<65 Years	8	18	14
≥65 Years	12	64	44
Sex: Female, Male Units: participants			
Female	6	36	21
Male	14	46	37
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	14	7
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	17	63	49
More than one race	0	0	0
Unknown or Not Reported	0	5	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	19	78	55
Unknown or Not Reported	0	3	1

Reporting group values	Total		
Number of subjects	184		
Age Categorical Units: participants			
<65 Years	45		
≥65 Years	139		
Sex: Female, Male Units: participants			
Female	75		
Male	109		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	24		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	152		
More than one race	0		
Unknown or Not Reported	8		

Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	6		
Not Hispanic or Latino	172		
Unknown or Not Reported	6		

End points

End points reporting groups

Reporting group title	OL Component (Cohort 1): Roxadustat 1.5 mg/kg
Reporting group description: Participants received roxadustat 1.5 milligrams (mg)/kilograms (kg), three times a week (TIW) for 52 weeks.	
Reporting group title	OL Component (Cohort 2): Roxadustat 2.0 mg/kg
Reporting group description: Participants received roxadustat 2.0 mg/kg, TIW for 52 weeks.	
Reporting group title	OL Component (Cohort 3): Roxadustat 2.5 mg/kg
Reporting group description: Participants received roxadustat 2.5 mg/kg, TIW for 52 weeks.	
Reporting group title	OL High-EPO Component: Roxadustat 2.5 mg/kg
Reporting group description: Participants with high serum EPO levels (>400 mIU/mL) received roxadustat 2.5 mg/kg TIW for 52 weeks.	
Reporting group title	DB Component: Roxadustat
Reporting group description: Participants received roxadustat 2.5 mg/kg TIW for 52 weeks.	
Reporting group title	DB Component: Placebo
Reporting group description: Participants received placebo matched to roxadustat for 52 weeks.	

Primary: DB Component: Number of Participants who Achieved RBC TI ≥56 Consecutive Days Since First Dose in the First 28 Weeks of Treatment

End point title	DB Component: Number of Participants who Achieved RBC TI ≥56 Consecutive Days Since First Dose in the First 28 Weeks of Treatment ^[1]
End point description: RBC TI was defined as the absence of any IV RBC transfusion (packed cell or whole blood) during any consecutive 56 days during the treatment period. Data presented is for number of participants with RBC TI ≥56 consecutive days since first dose in the first 28 weeks of treatment. FAS included all enrolled participants who received at least 1 dose of study medication, and at least 1 corresponding on-treatment Hb assessment.	
End point type	Primary
End point timeframe: 28 weeks	

Notes:

[1] - 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 end point is reporting statistics for the specified arms only.

End point values	DB Component: Roxadustat	DB Component: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	57		
Units: participants	38	19		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The odds ratio along with its 95% confidence interval (CI) were calculated based on the Cochran-Mantel-Haenszel (CMH) chi-square test adjusting for the stratification factors (EPO level, International Prognostic Scoring System – Revised [IPSS-R] risk category and RBC transfusion burden).	
Comparison groups	DB Component: Roxadustat v DB Component: Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.217
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.582
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.761
upper limit	3.29

Primary: OL and OL High-EPO Components: Number of Participants who Achieved Red Blood Cell (RBC) Transfusion Independence (TI) ≥8 Weeks (≥56 Consecutive Days) Since First Dose in the First 28 weeks of Treatment

End point title	OL and OL High-EPO Components: Number of Participants who Achieved Red Blood Cell (RBC) Transfusion Independence (TI) ≥8 Weeks (≥56 Consecutive Days) Since First Dose in the First 28 weeks of Treatment ^{[2][3]}
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End point description:

The RBC TI was defined as the absence of any intravenous (IV) RBC transfusion (packed cell or whole blood) during any consecutive 56 days during the treatment period. Data presented is for number of participants with RBC TI ≥8 weeks (≥56 consecutive days) since first dose in the first 28 weeks of treatment. The full analysis set (FAS) included all enrolled participants who received at least 1 dose of study medication, and at least 1 corresponding on-treatment hemoglobin (Hb) assessment.

End point type	Primary
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End point timeframe:

28 weeks

Notes:

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

Justification: The end point is reporting statistics for the specified arms only.

[3] - 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 end point is reporting statistics for the specified arms only.

End point values	OL Component (Cohort 1): Roxadustat 1.5 mg/kg	OL Component (Cohort 2): Roxadustat 2.0 mg/kg	OL Component (Cohort 3): Roxadustat 2.5 mg/kg	OL High-EPO Component: Roxadustat 2.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	20
Units: participants	3	1	5	3

Statistical analyses

No statistical analyses for this end point

Secondary: DB Component: Number of Participants who Achieved $\geq 50\%$ Reduction From Baseline in Number of pRBC Transfusions Over 8 Weeks

End point title	DB Component: Number of Participants who Achieved $\geq 50\%$ Reduction From Baseline in Number of pRBC Transfusions Over 8 Weeks ^[4]
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End point description:

Baseline number of transfusions (pRBC/8-weeks) = total number of packs of rRBCs within 16 weeks prior to first dose/2. A pRBC transfusion reduction responder was defined as a participant who achieved $\geq 50\%$ reduction in number of pRBC transfusions over 8 weeks compared to their baseline for any 8 week period in the duration beginning with the first dose date (Day 1) and ending with the end of study or treatment discontinuation due to adverse event (AE)/serious adverse event (SAE) or death, whichever came earlier. FAS included all enrolled participants who received at least 1 dose of study medication, and at least 1 corresponding on-treatment Hb assessment.

End point type	Secondary
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End point timeframe:

Baseline up to Week 8

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point is reporting statistics for the specified arms only.

End point values	DB Component: Roxadustat	DB Component: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	57		
Units: participants	59	37		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Component: Number of Participants who Achieved TI ≥ 56 Consecutive Days Anytime During the Study

End point title	DB Component: Number of Participants who Achieved TI ≥ 56 Consecutive Days Anytime During the Study ^[5]
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End point description:

RBC TI was defined as the absence of any IV RBC transfusion (packed cell or whole blood) during any consecutive 56 days anytime during the study (up to Week 56). FAS included all enrolled participants who received at least 1 dose of study medication, and at least 1 corresponding on-treatment Hb

assessment.

End point type	Secondary
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End point timeframe:

Baseline up to Week 56

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 end point is reporting statistics for the specified arms only.

End point values	DB Component: Roxadustat	DB Component: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	57		
Units: participants	52	29		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Component: Number of Participants who Achieved TI ≥ 56 Consecutive Days Since First Dose in 52 Weeks of Treatment

End point title	DB Component: Number of Participants who Achieved TI ≥ 56 Consecutive Days Since First Dose in 52 Weeks of Treatment ^[6]
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End point description:

RBC TI was defined as the absence of any IV RBC transfusion (packed cell or whole blood) during any consecutive 56 days during the treatment period. Data presented is for number of participants with RBC TI ≥ 56 consecutive days since first dose in the 52 weeks of treatment. FAS included all enrolled participants who received at least 1 dose of study medication, and at least 1 corresponding on-treatment Hb assessment.

End point type	Secondary
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End point timeframe:

52 weeks

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point is reporting statistics for the specified arms only.

End point values	DB Component: Roxadustat	DB Component: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	57		
Units: participants	44	23		

Statistical analyses

No statistical analyses for this end point

Secondary: OL and OL High-EPO Components: Number of Participants who Achieved

TI ≥50% Reduction From Baseline in Number of Packs of Red Blood Cells (pRBC) Transfusions over 8 Weeks

End point title	OL and OL High-EPO Components: Number of Participants who Achieved TI ≥50% Reduction From Baseline in Number of Packs of Red Blood Cells (pRBC) Transfusions over 8 Weeks ^[7]
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End point description:

Number of pRBC transfusions at baseline was defined as pRBC transfusions requirement during 8-week period prior to the start of first study medication. Responders were defined as participants with at least a 50% reduction in the number of pRBC transfusions over any 8-week (56 consecutive days) period during the study as compared with the baseline. FAS included all enrolled participants who received at least 1 dose of study medication, and at least 1 corresponding on-treatment Hb assessment.

End point type	Secondary
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End point timeframe:

Baseline up to Week 8

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 end point is reporting statistics for the specified arms only.

End point values	OL Component (Cohort 1): Roxadustat 1.5 mg/kg	OL Component (Cohort 2): Roxadustat 2.0 mg/kg	OL Component (Cohort 3): Roxadustat 2.5 mg/kg	OL High-EPO Component: Roxadustat 2.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	20
Units: participants	5	3	7	8

Statistical analyses

No statistical analyses for this end point

Secondary: DB Component: Cumulative Number of Participant Exposure Weeks (PEW) of TI Over the First 28 Weeks of Treatment

End point title	DB Component: Cumulative Number of Participant Exposure Weeks (PEW) of TI Over the First 28 Weeks of Treatment ^[8]
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End point description:

The PEW of TI periods over the first 28 weeks was added up to a cumulative number of weeks. For a participant with at least 1 TI response period over the first 28 weeks, the last TI response period was ended with the date of a subsequent RBC transfusion, visit date at Week 28, date of the end of study or treatment discontinuation due to AE/SAE or death, whichever came earlier. For a participant with no TI response period over the first 28 weeks, the cumulative number of PEW was set to zero. FAS included all enrolled participants who received at least 1 dose of study medication, and at least 1 corresponding on-treatment Hb assessment.

End point type	Secondary
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End point timeframe:

28 weeks

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 end point is reporting statistics for the specified arms only.

End point values	DB Component: Roxadustat	DB Component: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	57		
Units: weeks				
arithmetic mean (standard deviation)	9.60 (\pm 11.537)	7.60 (\pm 11.557)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Component: Mean Change from Baseline in the European Quality of Life Five Dimensional Five Level Health Questionnaire (EQ-5D-5L) Visual Analogue Scale Score at Week 9

End point title	DB Component: Mean Change from Baseline in the European Quality of Life Five Dimensional Five Level Health Questionnaire (EQ-5D-5L) Visual Analogue Scale Score at Week 9 ^[9]
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End point description:

The EQ-5D questionnaire is designed for self-completion by participants. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problem, moderate problems, severe problems, and unable to/extreme problems. The questionnaire also included a visual analogue scale, where the participant was asked to rate current health status on a scale of 0-100, with 0 being the worst imaginable health state and 100 being the best imaginable health. FAS included all enrolled participants who received at least 1 dose of study medication, and at least 1 corresponding on-treatment Hb assessment. Here, 'Overall number of participants analyzed' = participants evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Baseline, Week 9

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 end point is reporting statistics for the specified arms only.

End point values	DB Component: Roxadustat	DB Component: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	55		
Units: units on a scale				
arithmetic mean (standard deviation)	-1.7 (\pm 20.31)	1.6 (\pm 16.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Component: Number of Participants who Achieved TI \geq 20 Consecutive Weeks During the Study

End point title	DB Component: Number of Participants who Achieved TI \geq 20
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End point description:

≥20 consecutive weeks TI was defined as the absence of any IV RBC transfusion (packed cell or whole blood) during any consecutive 140 days anytime during the study (up to 56 weeks). TI was estimated between the first dose date (Day 1) and the end of study (Week 56) or treatment discontinuation due to AE/SAE or death, whichever came earlier. FAS included all enrolled participants who received at least 1 dose of study medication, and at least 1 corresponding on-treatment Hb assessment.

End point type

Secondary

End point timeframe:

Baseline up to Week 56

Notes:

[10] - 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 end point is reporting statistics for the specified arms only.

End point values	DB Component: Roxadustat	DB Component: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	57		
Units: participants	23	15		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Component: Mean Change from Baseline in the Patient-Reported Outcomes Measurement Information System-Short Form (PROMIS-SF) v2.0 Physical Function (PF) 10b Score at Week 9

End point title

DB Component: Mean Change from Baseline in the Patient-Reported Outcomes Measurement Information System-Short Form (PROMIS-SF) v2.0 Physical Function (PF) 10b Score at Week 9^[11]

End point description:

The PROMIS physical function item measures self-reported, current capability to carry out activities that require physical actions. PF 10-item short form which contains 10 questions was used in this study, and each item was scored on a 5-point rating scale (1 [unable to do] to 5 [without any difficulty]), with higher scores indicating better functioning. Total raw score was the sum of response to each question, with the lowest possible raw score 10 (poor physical function) and the highest possible raw score 50 (better physical function). T-score rescaled the total raw score into a standardized score using PROMIS-SF v2.0 Physical Function 10b score conversion table. T-score ranged from 13.8 to 61.3 with higher scores indicating better physical functioning. FAS = all enrolled participants who received at least 1 dose of study medication, and at least 1 corresponding on-treatment Hb assessment. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type

Secondary

End point timeframe:

Baseline, Week 9

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 end point is reporting statistics for the specified arms only.

End point values	DB Component: Roxadustat	DB Component: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	52		
Units: T-score				
arithmetic mean (standard deviation)	-1.9 (± 7.29)	-0.4 (± 6.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Component: Change From Baseline in Number of pRBC Packs Transfused Over the First 28 Weeks of Treatment

End point title	DB Component: Change From Baseline in Number of pRBC Packs Transfused Over the First 28 Weeks of Treatment ^[12]
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End point description:

Number of pRBC transfusions at baseline was defined as pRBC transfusions requirement during 8-week period prior to the start of first study medication. FAS included all enrolled participants who received at least 1 dose of study medication, and at least 1 corresponding on-treatment Hb assessment.

End point type	Secondary
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End point timeframe:

Baseline, Week 28

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 end point is reporting statistics for the specified arms only.

End point values	DB Component: Roxadustat	DB Component: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	57		
Units: pRBC packs				
arithmetic mean (standard deviation)	-0.13 (± 2.314)	0.44 (± 1.833)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Component: Mean Change from Baseline in the PROMIS-SF v1.0 Fatigue 13a Score at Week 9

End point title	DB Component: Mean Change from Baseline in the PROMIS-SF v1.0 Fatigue 13a Score at Week 9 ^[13]
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End point description:

Fatigue was measured using the 13-item fatigue scale of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System, each item was scored on a 5-point rating scale ranging from 1 "not at all" to 5 "very much", with lower scores indicating better functioning. Total raw score was the sum of the response to each question, with the lowest possible raw score 13 (lowest level of fatigue)

and the highest possible raw score 65 (highest level of fatigue), with lower scores indicating better functioning. The T-score rescaled the total raw score into a standardized score using PROMIS-SF v1.0 Fatigue 13a score conversion table. T-score ranged from 30.3 to 83.5 with lower scores indicating better functioning. FAS included all enrolled participants who received at least 1 dose of study medication, and at least 1 corresponding on-treatment Hb assessment. Here, 'Overall number of participants analyzed' = participants evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Baseline, Week 9

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 end point is reporting statistics for the specified arms only.

End point values	DB Component: Roxadustat	DB Component: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	52		
Units: T-score				
arithmetic mean (standard deviation)	1.9 (\pm 7.61)	-0.6 (\pm 7.36)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 56

Adverse event reporting additional description:

The safety analysis set included all participants who received at least 1 dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	OL Component (Cohort 1): Roxadustat 1.5 mg/kg
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Reporting group description:

Participants received roxadustat 1.5 mg/kg, TIW for 52 weeks.

Reporting group title	OL Component (Cohort 2): Roxadustat 2.0 mg/kg
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Reporting group description:

Participants received roxadustat 2.0 mg/kg, TIW for 52 weeks.

Reporting group title	DB Component: Placebo
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Reporting group description:

Participants received placebo matched to roxadustat for 52 weeks.

Reporting group title	OL High-EPO Component: Roxadustat 2.5 mg/kg
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Reporting group description:

Participants with high serum EPO levels (>400 mIU/mL) received roxadustat 2.5 mg/kg TIW for 52 weeks.

Reporting group title	DB Component: Roxadustat
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Reporting group description:

Participants received roxadustat 2.5 mg/kg TIW for 52 weeks.

Reporting group title	OL Component (Cohort 3): Roxadustat 2.5 mg/kg
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Reporting group description:

Participants received roxadustat 2.5 mg/kg, TIW for 52 weeks.

Serious adverse events	OL Component (Cohort 1): Roxadustat 1.5 mg/kg	OL Component (Cohort 2): Roxadustat 2.0 mg/kg	DB Component: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)	3 / 8 (37.50%)	10 / 58 (17.24%)
number of deaths (all causes)	1	0	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
General physical health deterioration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (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
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (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
Pulmonary oedema			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (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
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Fall			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Head injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Humerus fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Pelvic fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haemorrhage			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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 failure			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Acute myocardial infarction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (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
Acute left ventricular failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Syncope			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (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
Ischaemic stroke			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Brain oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenomegaly			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Pancytopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Inguinal hernia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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 function abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Hyperbilirubinaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Portal hypertension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Cholecystitis acute			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric stenosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (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
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spinal stenosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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

Appendicitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Diverticulitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Pyelonephritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (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
Urosepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (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
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (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

Serious adverse events	OL High-EPO Component: Roxadustat 2.5 mg/kg	DB Component: Roxadustat	OL Component (Cohort 3): Roxadustat 2.5 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 20 (30.00%)	22 / 82 (26.83%)	1 / 8 (12.50%)
number of deaths (all causes)	3	7	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (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
General physical health deterioration			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Pyrexia			

subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 20 (0.00%)	2 / 82 (2.44%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Pulmonary oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Pleural effusion			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
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			
Femoral neck fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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

Fall			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Head injury			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Humerus fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Limb injury			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Pelvic fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Traumatic haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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			
Atrial fibrillation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Cardiac failure			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Cardiac failure congestive			

subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 20 (0.00%)	2 / 82 (2.44%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (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
Syncope			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Ischaemic stroke			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Brain oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Transient ischaemic attack			

subjects affected / exposed	1 / 20 (5.00%)	2 / 82 (2.44%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 82 (2.44%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splénomegaly			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (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
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Colitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Inguinal hernia			

subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Hepatic function abnormal			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (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
Portal hypertension			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Ureteric stenosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Haematuria			

subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Cervical spinal stenosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Pneumonia			
subjects affected / exposed	1 / 20 (5.00%)	4 / 82 (4.88%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Gastroenteritis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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
Diverticulitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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

Pyelonephritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Influenza			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Urosepsis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Septic shock			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Sepsis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (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
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (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
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (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

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

Non-serious adverse events	OL Component (Cohort 1): Roxadustat 1.5 mg/kg	OL Component (Cohort 2): Roxadustat 2.0 mg/kg	DB Component: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	8 / 8 (100.00%)	46 / 58 (79.31%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Acute myeloid leukaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Basal cell carcinoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Sweat gland tumour			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Pituitary tumour benign			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	2	0	2
Orthostatic hypotension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	2
Pallor			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
General physical health deterioration			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	6 / 58 (10.34%)
occurrences (all)	0	0	9
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	7 / 58 (12.07%)
occurrences (all)	0	0	10
Generalised oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	1 / 58 (1.72%)
occurrences (all)	0	2	1
Oedema peripheral			
subjects affected / exposed	2 / 8 (25.00%)	1 / 8 (12.50%)	4 / 58 (6.90%)
occurrences (all)	3	2	4
Non-cardiac chest pain			
subjects affected / exposed	3 / 8 (37.50%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	3	1	0
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 58 (3.45%)
occurrences (all)	0	1	2
Pleuritic pain			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Nasal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Hypoventilation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	1 / 58 (1.72%)
occurrences (all)	2	1	1
Cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	2 / 8 (25.00%)	2 / 8 (25.00%)	1 / 58 (1.72%)
occurrences (all)	2	2	1
Dyspnoea exertional			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	3 / 58 (5.17%)
occurrences (all)	0	1	3
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	1	1	0
Depression			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	7 / 58 (12.07%)
occurrences (all)	1	0	9
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	4 / 58 (6.90%)
occurrences (all)	1	1	5
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 58 (3.45%)
occurrences (all)	0	1	2
Lymphocyte count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	4	0
Weight decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	1	0	2
Contusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
Nasal injury			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Post-traumatic pain			

subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 58 (0.00%) 0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	1	0	2
Cardiac failure congestive			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Cardiac failure chronic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Angina pectoris			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Restless legs syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	1	0	2
Neuralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Headache			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	4 / 58 (6.90%)
occurrences (all)	0	1	4
Dizziness			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	10 / 58 (17.24%)
occurrences (all)	2	0	12
Blood and lymphatic system disorders			
Haemorrhagic diathesis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	4 / 58 (6.90%)
occurrences (all)	0	0	9
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	4 / 58 (6.90%)
occurrences (all)	1	1	5
Abdominal distension			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Abdominal discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Vomiting			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 58 (3.45%)
occurrences (all)	0	4	2
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	1 / 8 (12.50%)	7 / 58 (12.07%)
occurrences (all)	3	2	8
Mouth ulceration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Mouth haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	2 / 8 (25.00%)	3 / 8 (37.50%)	9 / 58 (15.52%)
occurrences (all)	2	4	11
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	1 / 58 (1.72%)
occurrences (all)	1	1	1
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Gallbladder disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0

Jaundice subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 58 (0.00%) 0
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	1 / 8 (12.50%) 1	2 / 58 (3.45%) 2
Madarosis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 58 (0.00%) 0
Lichen planus subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 58 (0.00%) 0
Trichodynia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 58 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	2 / 58 (3.45%) 2
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	3 / 58 (5.17%) 4
Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 58 (0.00%) 0
Proteinuria subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 58 (0.00%) 0
Renal cyst subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 58 (0.00%) 0
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	2 / 8 (25.00%) 2	0 / 58 (0.00%) 0
Musculoskeletal and connective tissue			

disorders			
Oligoarthritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	4
Muscle spasms			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 58 (3.45%)
occurrences (all)	0	2	3
Muscle contracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Osteoarthritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Spinal osteoarthritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	5 / 58 (8.62%)
occurrences (all)	0	0	5
Infections and infestations			
Gingivitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
COVID-19			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	6 / 58 (10.34%)
occurrences (all)	0	0	6
Bronchitis			

subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	0 / 58 (0.00%)
occurrences (all)	1	4	0
Atypical pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Anal abscess			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	3
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	5 / 58 (8.62%)
occurrences (all)	0	0	7
Tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	1	0	2
Respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Pharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Onychomycosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			

subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 2	0 / 8 (0.00%) 0	5 / 58 (8.62%) 5
Kidney infection subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 58 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	5 / 58 (8.62%) 7
Folate deficiency subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 8 (25.00%) 2	4 / 58 (6.90%) 5
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	1 / 8 (12.50%) 1	1 / 58 (1.72%) 1
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 58 (1.72%) 1
Hypoalbuminaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	1 / 58 (1.72%) 2
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	2 / 58 (3.45%) 2
Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 58 (0.00%) 0
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 2	1 / 58 (1.72%) 1

Non-serious adverse events	OL High-EPO Component: Roxadustat 2.5 mg/kg	DB Component: Roxadustat	OL Component (Cohort 3): Roxadustat 2.5 mg/kg
Total subjects affected by non-serious adverse events subjects affected / exposed	15 / 20 (75.00%)	68 / 82 (82.93%)	6 / 8 (75.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Malignant neoplasm progression subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 82 (0.00%) 0	0 / 8 (0.00%) 0
Acute myeloid leukaemia subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	2 / 82 (2.44%) 2	0 / 8 (0.00%) 0
Basal cell carcinoma subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 82 (0.00%) 0	1 / 8 (12.50%) 1
Sweat gland tumour subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 82 (0.00%) 0	0 / 8 (0.00%) 0
Pituitary tumour benign subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 82 (0.00%) 0	0 / 8 (0.00%) 0
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	4 / 82 (4.88%) 5	0 / 8 (0.00%) 0
Orthostatic hypotension subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 82 (1.22%) 1	1 / 8 (12.50%) 1
Pallor subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 82 (0.00%) 0	1 / 8 (12.50%) 1
General disorders and administration site conditions General physical health deterioration subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	2 / 82 (2.44%) 2	0 / 8 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	15 / 82 (18.29%) 18	0 / 8 (0.00%) 0
Asthenia subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 5	11 / 82 (13.41%) 11	1 / 8 (12.50%) 2
Generalised oedema			

subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 20 (0.00%)	5 / 82 (6.10%)	0 / 8 (0.00%)
occurrences (all)	0	5	0
Oedema peripheral			
subjects affected / exposed	2 / 20 (10.00%)	9 / 82 (10.98%)	0 / 8 (0.00%)
occurrences (all)	2	13	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Malaise			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pleuritic pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Nasal inflammation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			

subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hypoventilation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	1 / 20 (5.00%)	4 / 82 (4.88%)	1 / 8 (12.50%)
occurrences (all)	1	4	1
Dyspnoea			
subjects affected / exposed	1 / 20 (5.00%)	8 / 82 (9.76%)	2 / 8 (25.00%)
occurrences (all)	1	9	2
Dyspnoea exertional			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 20 (0.00%)	2 / 82 (2.44%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Insomnia			
subjects affected / exposed	0 / 20 (0.00%)	9 / 82 (10.98%)	1 / 8 (12.50%)
occurrences (all)	0	9	1
Depression			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 20 (5.00%)	10 / 82 (12.20%)	0 / 8 (0.00%)
occurrences (all)	4	18	0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 20 (15.00%)	8 / 82 (9.76%)	0 / 8 (0.00%)
occurrences (all)	8	19	0
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			
subjects affected / exposed	1 / 20 (5.00%)	6 / 82 (7.32%)	0 / 8 (0.00%)
occurrences (all)	2	7	0
Blood creatinine increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	2 / 20 (10.00%)	7 / 82 (8.54%)	0 / 8 (0.00%)
occurrences (all)	2	7	0
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Nasal injury			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Post-traumatic pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Palpitations			

subjects affected / exposed	0 / 20 (0.00%)	2 / 82 (2.44%)	2 / 8 (25.00%)
occurrences (all)	0	3	4
Cardiac failure congestive			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Cardiac failure chronic			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Angina pectoris			
subjects affected / exposed	0 / 20 (0.00%)	3 / 82 (3.66%)	1 / 8 (12.50%)
occurrences (all)	0	3	1
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 20 (0.00%)	2 / 82 (2.44%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Presyncope			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 82 (2.44%)	0 / 8 (0.00%)
occurrences (all)	1	3	0
Headache			
subjects affected / exposed	1 / 20 (5.00%)	7 / 82 (8.54%)	2 / 8 (25.00%)
occurrences (all)	1	9	3
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)	11 / 82 (13.41%)	2 / 8 (25.00%)
occurrences (all)	1	14	3
Blood and lymphatic system disorders			
Haemorrhagic diathesis			

subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 82 (0.00%) 0	0 / 8 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	5 / 82 (6.10%) 7	0 / 8 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 3	2 / 82 (2.44%) 4	0 / 8 (0.00%) 0
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 2	0 / 82 (0.00%) 0	0 / 8 (0.00%) 0
Eye disorders Dry eye subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 82 (1.22%) 1	1 / 8 (12.50%) 1
Visual impairment subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 82 (0.00%) 0	0 / 8 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	2 / 82 (2.44%) 2	0 / 8 (0.00%) 0
Abdominal distension subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 82 (0.00%) 0	0 / 8 (0.00%) 0
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	2 / 82 (2.44%) 2	0 / 8 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 4	6 / 82 (7.32%) 12	1 / 8 (12.50%) 1
Nausea subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	19 / 82 (23.17%) 23	2 / 8 (25.00%) 4
Mouth ulceration			

subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Mouth haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	1 / 20 (5.00%)	4 / 82 (4.88%)	0 / 8 (0.00%)
occurrences (all)	1	4	0
Dry mouth			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	2 / 20 (10.00%)	6 / 82 (7.32%)	1 / 8 (12.50%)
occurrences (all)	2	7	1
Constipation			
subjects affected / exposed	3 / 20 (15.00%)	11 / 82 (13.41%)	0 / 8 (0.00%)
occurrences (all)	3	20	0
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gallbladder disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Jaundice			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	0 / 20 (0.00%)	8 / 82 (9.76%)	0 / 8 (0.00%)
occurrences (all)	0	8	0
Madarosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Lichen planus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Trichodynia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Chronic kidney disease			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Renal cyst			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 20 (0.00%)	2 / 82 (2.44%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Oligoarthritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Myalgia			

subjects affected / exposed	0 / 20 (0.00%)	3 / 82 (3.66%)	0 / 8 (0.00%)
occurrences (all)	0	3	0
Muscle spasms			
subjects affected / exposed	1 / 20 (5.00%)	5 / 82 (6.10%)	0 / 8 (0.00%)
occurrences (all)	1	8	0
Muscle contracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	1 / 20 (5.00%)	2 / 82 (2.44%)	2 / 8 (25.00%)
occurrences (all)	2	3	2
Osteoarthritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Spinal osteoarthritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	0 / 20 (0.00%)	5 / 82 (6.10%)	2 / 8 (25.00%)
occurrences (all)	0	6	2
Infections and infestations			
Gingivitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 20 (0.00%)	4 / 82 (4.88%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Bronchitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 82 (2.44%)	2 / 8 (25.00%)
occurrences (all)	0	2	3
Atypical pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Anal abscess			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	2 / 20 (10.00%)	2 / 82 (2.44%)	1 / 8 (12.50%)
occurrences (all)	4	2	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	2 / 82 (2.44%)	2 / 8 (25.00%)
occurrences (all)	0	3	2
Tonsillitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Onychomycosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 20 (0.00%)	4 / 82 (4.88%)	1 / 8 (12.50%)
occurrences (all)	0	4	1
Kidney infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 20 (0.00%)	6 / 82 (7.32%)	0 / 8 (0.00%)
occurrences (all)	0	10	0
Folate deficiency			
subjects affected / exposed	0 / 20 (0.00%)	4 / 82 (4.88%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Hyperglycaemia			
subjects affected / exposed	2 / 20 (10.00%)	2 / 82 (2.44%)	1 / 8 (12.50%)
occurrences (all)	3	2	1
Hyperkalaemia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 82 (1.22%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 82 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 82 (2.44%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hypomagnesaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 82 (1.22%)	0 / 8 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2018	It included following changes: <ul style="list-style-type: none">- Added the following sections for additional clarity and details: Blinding; Maintenance of Blinding; Planned and Unplanned Unblinding of Treatment Assignment.- Change in enrollment criteria for greater flexibility in participant enrollment.- Added 4 Weeks Post-end of treatment (EOT).- Added If Early Termination, every 8 weeks assessment from 4 Weeks Post-EOT visit. Last visit at Week 52 from first dose.- Added Point-of-care Urine Pregnancy (for females of child-bearing capabilities).
30 January 2020	It included following changes: <ul style="list-style-type: none">- Added a new open-label exploratory cohort: Open-label High-erythropoietin Component.- Exclusion criteria updated to: Participants with elevated serum erythropoietin levels (>400 mIU/mL) at Screening 1 are allowed to repeat after ≥ 7 days. If the serum erythropoietin remains elevated (>400 mIU/mL) the participant may then qualify for the OL High-erythropoietin cohort.- Exclusion criteria updated to: Participants with TBili up to 2.0 x upper limit of normal (ULN) may be allowed to participate if the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are within normal limits.- Following has been inserted as a secondary efficacy endpoint: Proportion of participants achieved TI ≥ 56 consecutive days at any time during the study.- Study centers planned has been revised to "Approximately 100".-

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Study did not meet its primary efficacy endpoint; hence, the study was terminated early.

Notes: