



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Voxelotor (GBT440) in Pediatric Participants with Sick Cell Disease (HOPE Kids 2)

Summary

EudraCT number	2017-000903-26
Trial protocol	FR GB IT
Global end of trial date	05 November 2024

Results information

Result version number	v1 (current)
This version publication date	15 August 2025
First version publication date	15 August 2025

Trial information

Trial identification

Sponsor protocol code	C5341021
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04218084
WHO universal trial number (UTN)	-
Other trial identifiers	Alias ID: GBT440-032

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	66 East Hudson boulevard, New York, United States, NY 10001
Public contact	Pfizer ClinicalTrials.gov Call Center, ClinicalTrials.gov_Inquiries@pfizer.com, 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002356-PIP02-20
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 June 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 November 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the effect of voxelotor compared to placebo on the transcranial Doppler (TCD) time-averaged mean of the maximum velocity (TAMMV) arterial cerebral blood flow at 24 weeks in sickle cell disease (SCD) participants ≥ 2 to < 15 years of age with conditional (170 to < 200 cm/sec) TCD flow velocity.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 November 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	19 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Egypt: 34
Country: Number of subjects enrolled	Ghana: 5
Country: Number of subjects enrolled	Kenya: 24
Country: Number of subjects enrolled	Nigeria: 166
Country: Number of subjects enrolled	Oman: 1
Country: Number of subjects enrolled	Saudi Arabia: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	236
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	207
Adolescents (12-17 years)	29
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 236 participants were assigned to the study treatment. Study was terminated - emerging clinical data evaluated by Pfizer and shared with regulatory authorities indicated risk profile of voxelotor in people with sickle cell disease (SCD) exceeded benefits observed in previously generated global research and required further assessment.

Pre-assignment

Screening details:

A total of 236 participants were assigned to the study treatment. Study was terminated - emerging clinical data evaluated by Pfizer and shared with regulatory authorities indicated risk profile of voxelotor in people with sickle cell disease (SCD) exceeded benefits observed in previously generated global research and required further assessment.

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

Blinding implementation details:

Blinded roles were subject, investigator, carer, assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Voxelotor

Arm description:

Participants aged greater than or equal to 12 years of age received 1500 milligrams (mg) voxelotor tablet orally once daily for 96 weeks. Participants less than 12 years of age received voxelotor at a weight based (1500 mg-equivalent) dose. Participants were followed up to 4 weeks after last dose of study drug.

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

Dosage and administration details:

Participants received 1500 mg voxelotor tablet orally once daily for 96 weeks.

Arm title	Placebo
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Arm description:

Participants received voxelotor matched placebo orally once daily for 96 weeks. Participants were followed up to 4 weeks after last dose of study drug.

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:

Participants received voxelotor matched placebo orally once daily for 96 weeks.

Number of subjects in period 1	Voxelotor	Placebo
Started	120	116
Completed	37	40
Not completed	83	76
Consent withdrawn by subject	4	5
Physician decision	1	1
Adverse event, non-fatal	10	2
Abnormal transcranial doppler (TCD)	21	26
Non-compliance with study drug	2	1
Study terminated by sponsor	24	17
Unspecified	19	22
Lost to follow-up	2	2

Baseline characteristics

Reporting groups

Reporting group title	Voxelotor
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Reporting group description:

Participants aged greater than or equal to 12 years of age received 1500 milligrams (mg) voxelotor tablet orally once daily for 96 weeks. Participants less than 12 years of age received voxelotor at a weight based (1500 mg-equivalent) dose. Participants were followed up to 4 weeks after last dose of study drug.

Reporting group title	Placebo
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Reporting group description:

Participants received voxelotor matched placebo orally once daily for 96 weeks. Participants were followed up to 4 weeks after last dose of study drug.

Reporting group values	Voxelotor	Placebo	Total
Number of subjects	120	116	236
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	7.2 ± 3.11	7.3 ± 3.22	-
Gender categorical Units: Subjects			
Male	57	57	114
Female	63	59	122
Race Units: Subjects			
African	69	80	149
Arab	12	11	23
Black or African American	8	2	10
White	2	0	2
Multi-Racial	29	23	52
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	114	113	227
Not Reported	5	3	8

End points

End points reporting groups

Reporting group title	Voxelotor
Reporting group description: Participants aged greater than or equal to 12 years of age received 1500 milligrams (mg) voxelotor tablet orally once daily for 96 weeks. Participants less than 12 years of age received voxelotor at a weight based (1500 mg-equivalent) dose. Participants were followed up to 4 weeks after last dose of study drug.	
Reporting group title	Placebo
Reporting group description: Participants received voxelotor matched placebo orally once daily for 96 weeks. Participants were followed up to 4 weeks after last dose of study drug.	

Primary: Change From Baseline in Time-Averaged Maximum of Mean Velocity (TAMMV) Arterial Cerebral Blood Flow at Week 24

End point title	Change From Baseline in Time-Averaged Maximum of Mean Velocity (TAMMV) Arterial Cerebral Blood Flow at Week 24
End point description: TAMMV was defined the time averaged maximum of the mean velocity arterial cerebral blood flow and was measured using transcranial Doppler (TCD). Analysis was performed using mixed model for repeated measures (MMRM) including treatment, study visit, treatment by visit interaction, baseline hydroxyurea (HU) use (yes; no), age group (2 to ≤ 8 years; >8 to <15 years), and baseline TAMMV value (170 centimeter per second [cm/sec] to < 185 cm/sec; 185 cm/sec to < 200 cm/sec) as fixed effect terms and used a compound symmetry covariance matrix for within-participant variability. ITT analysis population included all randomized participants. Here, "Number of Participants Analyzed" signifies number of participants evaluable for this endpoint.	
End point type	Primary
End point timeframe: Baseline, Week 24	

End point values	Voxelotor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	108		
Units: Centimeter per second (cm/sec)				
least squares mean (confidence interval 95%)	-12.06 (-15.82 to -8.31)	-4.29 (-8.17 to -0.40)		

Statistical analyses

Statistical analysis title	Week 24
Statistical analysis description: Voxelotor versus Placebo	
Comparison groups	Voxelotor v Placebo

Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0048
Method	Mixed Model Repeated Measures analysis
Parameter estimate	Difference in LS mean
Point estimate	-7.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.18
upper limit	-2.37

Secondary: Change From Baseline in Transcranial Doppler (TCD) Flow Velocity at Week 48

End point title	Change From Baseline in Transcranial Doppler (TCD) Flow Velocity at Week 48
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End point description:

Change in TCD flow velocity from baseline to week 48 was analyzed using the MMRM model including treatment, study visit, treatment by visit interaction, baseline hydroxyurea use (yes; no), age group (2 to <= 8 years; >8 to <15 years), and baseline TAMMV value (170 cm/sec to < 185 cm/sec; 185 cm/sec to < 200 cm/sec) as fixed effect terms and used a compound symmetry covariance matrix for within-subject variability. ITT analysis population included all randomized participants. Here, 'Number Analyzed' signifies participants evaluable for specified rows.

End point type	Secondary
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End point timeframe:

Baseline (value at Screening), Weeks 48

End point values	Voxelotor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	107		
Units: Centimeter per second (cm/sec)				
least squares mean (confidence interval 95%)	-10.33 (-14.14 to -6.52)	-3.86 (-7.77 to 0.05)		

Statistical analyses

Statistical analysis title	Week 48
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Statistical analysis description:

Voxelotor versus Placebo

Comparison groups	Voxelotor v Placebo
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Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0202
Method	Mixed Models for Repeated Measures
Parameter estimate	Difference in LS mean
Point estimate	-6.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.93
upper limit	-1.01

Secondary: Time to Conversion to Abnormal TCD Flow

End point title	Time to Conversion to Abnormal TCD Flow
End point description:	
Time to conversion was the number of weeks from the date of randomization to the date of TCD assessment when an abnormal TCD flow velocity (≥ 200 cm/sec) is determined. ITT analysis population included all randomized participants. '99999' indicates due to limitations of the week 96 data as a result of the early termination of the study, the time to conversion to abnormal TCD flow secondary endpoints were considered exploratory and not subject to formal hypothesis testing.	
End point type	Secondary
End point timeframe:	
Up to 96 weeks	

End point values	Voxelotor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	116		
Units: Weeks				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reversion to Normal TCD Flow

End point title	Time to Reversion to Normal TCD Flow
End point description:	
Time to first normal TCD flow was the number of weeks from randomization to the date of first normal (<170 cm/sec) TCD flow. ITT analysis population included all randomized participants. The participants were grouped according to the treatment group to which they are randomized. Here, "Number of Participants Analyzed" signifies number of participants evaluable for this outcome measure. '99999' indicates due to limitations of the week 96 data as a result of the early termination of the study, the time to reversion to normal TCD flow secondary endpoints were considered exploratory and not subject to formal hypothesis testing.	

End point type	Secondary
End point timeframe:	
Up to 96 weeks	

End point values	Voxelotor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	90		
Units: Weeks				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With TCD Flow Velocity Reduction ≥ 15 cm/sec at Weeks 24, 48 and 96

End point title	Percentage of Participants With TCD Flow Velocity Reduction ≥ 15 cm/sec at Weeks 24, 48 and 96
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End point description:

TCD flow velocity reduction from Baseline ≥ 15 cm/sec at week 24, week 48 was analyzed using an exact Cochran-Mantel-Haenszel (CMH) general association test stratified for baseline HU use (yes; no), age group (2 to ≤ 8 years; >8 to <15 years), and baseline TAMMV value (170 cm/sec to < 185 cm/sec; 185 cm/sec to < 200 cm/sec). ITT analysis population included all randomized participants. Week 96 is not reported due to limitations of the week 96 data as a result of the early termination of the study and were considered exploratory and not subject to formal hypothesis testing.

End point type	Secondary
End point timeframe:	
Weeks 24, 48, 96	

End point values	Voxelotor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	116		
Units: Percentage of participants				
number (not applicable)				
Week 24	38.3	25.9		
Week 48	39.2	27.6		

Statistical analyses

Statistical analysis title	Difference in Adjusted Rate
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Statistical analysis description:

Difference in the adjusted response rates

Comparison groups	Voxelotor v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0686
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Adjusted Rate
Point estimate	12.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	24.5

Secondary: Change From Baseline in Hemoglobin (Hb) at Weeks 24, 48 and 96

End point title	Change From Baseline in Hemoglobin (Hb) at Weeks 24, 48 and 96
End point description:	Change from baseline in hemoglobin at weeks 24, 48, 96 was analyzed using the MMRM model including treatment, study visit, treatment by visit interaction, baseline hydroxyurea use (yes; no), age group (2 to <= 8 years; >8 to <15 years) and baseline TAMMV value (170 centimeter per second [cm/sec] to < 185 cm/sec; 185 cm/sec to < 200 cm/sec) as fixed effect terms and baseline value as a co-variate and used a compound symmetry covariance matrix for within-participant variability. ITT analysis population included all randomized participants. All participants reported under 'Number of Participants Analyzed' contributed data to the table but may not have evaluable data for every row. Here, 'Number Analyzed' signifies number of participants evaluable for each row. Week 96 is not reported due to limitations of the week 96 data as a result of the early termination of the study and were considered exploratory and not subject to formal hypothesis testing.
End point type	Secondary
End point timeframe:	Baseline (value at Screening), Weeks 24, 48 and 96

End point values	Voxelotor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	115		
Units: Grams per deciliter (g/dL)				
least squares mean (confidence interval 95%)				
Week 24 (n=96,85)	0.89 (0.65 to 1.14)	0.18 (-0.08 to 0.44)		
Week 48 (n=94,86)	0.79 (0.54 to 1.04)	-0.19 (-0.45 to 0.07)		

Statistical analyses

Statistical analysis title	Week 48
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Statistical analysis description:	
Voxelotor versus Placebo	
Comparison groups	Voxelotor v Placebo
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed Model Repeated Measures analysis
Parameter estimate	Difference in LS mean
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.35

Statistical analysis title	Week 24
Statistical analysis description:	
Voxelotor versus Placebo	
Comparison groups	Voxelotor v Placebo
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001
Method	Mixed Model Repeated Measures analysis
Parameter estimate	Difference in LS mean
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.07

Secondary: Percent Change From Baseline in Unconjugated Bilirubin at Weeks 24, 48 and 96

End point title	Percent Change From Baseline in Unconjugated Bilirubin at Weeks 24, 48 and 96
End point description:	
<p>Percent change from baseline in unconjugated bilirubin at weeks 24 48, 96 was reported in this outcome measure. Analysis was performed using MMRM including treatment, study visit, treatment by visit interaction, baseline hydroxyurea use (yes; no), age group (2 to <= 8 years; >8 to <15 years), and baseline TAMMV value (170 centimeter per second [cm/sec] to < 185 cm/sec; 185 cm/sec to < 200 cm/sec) as fixed effect terms and baseline value as a co-variate and used a compound symmetry covariance matrix for within-subject variability. ITT analysis population included all randomized participants. All participants reported under 'Number of Participants Analyzed' contributed data to table but may not have evaluable data for every row. Here, 'Number Analyzed' = number of participants evaluable for each row. Week 96 is not reported due to limitations of the week 96 data as a result of early termination of study and were considered exploratory and not subject to formal hypothesis testing.</p>	
End point type	Secondary

End point timeframe:

Baseline (value at Screening), Weeks 24, 48 and 96

End point values	Voxelotor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	116		
Units: Percent change				
least squares mean (confidence interval 95%)				
Change at Week 24 (n=109, 98)	-21.83 (-30.65 to -13.01)	11.78 (2.59 to 20.98)		
Change at Week 48 (n=97,92)	-18.39 (-27.58 to -9.21)	20.25 (10.84 to 29.65)		

Statistical analyses

Statistical analysis title	Week 48
Statistical analysis description: Voxelotor versus Placebo	
Comparison groups	Voxelotor v Placebo
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-38.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.79
upper limit	-25.49

Statistical analysis title	Week 24
Statistical analysis description: Voxelotor versus Placebo	
Comparison groups	Voxelotor v Placebo
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-33.61

Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.36
upper limit	-20.86

Secondary: Percent Change From Baseline in Reticulocyte at Weeks 24, 48 and 96

End point title	Percent Change From Baseline in Reticulocyte at Weeks 24, 48 and 96
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End point description:

Percent change from baseline in reticulocyte at weeks 24, 48 and 96 was reported in this outcome measure. Analysis was performed using MMRM including treatment, study visit, treatment by visit interaction, baseline hydroxyurea use (yes; no), age group (2 to ≤ 8 years; >8 to <15 years), and baseline TAMMV value (170 centimeter per second [cm/sec] to < 185 cm/sec; 185 cm/sec to < 200 cm/sec) as fixed effect terms and baseline value as a co-variate and used a compound symmetry covariance matrix for within-participant variability. ITT analysis population included all randomized participants. All participants reported under 'Number of Participants Analyzed' contributed data to the table but may not have evaluable data for every row. Here, 'Number Analyzed' = number of participants evaluable for each row. Week 96 is not reported due to limitations of the week 96 data as a result of the early termination of study and were considered exploratory and not subject to formal hypothesis testing.

End point type	Secondary
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End point timeframe:

Baseline (value at Screening), Weeks 24, 48 and 96

End point values	Voxelotor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	115		
Units: Percent change				
least squares mean (confidence interval 95%)				
Week 24 (n=91,80)	54.36 (-1.27 to 109.99)	74.73 (18.24 to 131.22)		
Week 48 (n=89, 82)	37.75 (-18.07 to 93.57)	38.49 (-17.83 to 94.81)		

Statistical analyses

Statistical analysis title	Week 48
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Statistical analysis description:

Voxelotor versus Placebo

Comparison groups	Voxelotor v Placebo
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Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9854
Method	Mixed Model Repeated Measures analysis
Parameter estimate	Difference in LS mean
Point estimate	-0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-80.1
upper limit	78.62

Statistical analysis title	Week 24
Statistical analysis description: Voxelotor versus Placebo	
Comparison groups	Voxelotor v Placebo
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.614
Method	Mixed Models for Repeated Measures
Parameter estimate	Difference in LS mean
Point estimate	-20.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-99.72
upper limit	58.98

Secondary: Percent Change From Baseline in Absolute Reticulocyte at Weeks 24, 48 and 96

End point title	Percent Change From Baseline in Absolute Reticulocyte at Weeks 24, 48 and 96
End point description: Percent change from baseline in absolute reticulocyte at weeks 24 and 48 was reported in this outcome measure. Analysis was performed using MMRM including treatment, study visit, treatment by visit interaction, baseline hydroxyurea use (yes; no), age group (2 to <= 8 years; >8 to <15 years), and baseline TAMMV value (170 centimeter per second [cm/sec] to < 185 cm/sec; 185 cm/sec to < 200 cm/sec) as fixed effect terms and baseline value as a co-variate and used a compound symmetry covariance matrix for within-subject variability. ITT analysis population included all randomized participants. All participants reported under 'Number of Participants Analyzed' contributed data to the table but may not have evaluable data for every row. Here, 'Number Analyzed' = number of participants evaluable for each row. Week 96 is not reported due to limitations of week 96 data as a result of the early termination of study and were considered exploratory and not subject to formal hypothesis testing.	
End point type	Secondary
End point timeframe: Baseline (value at Screening), Weeks 24, 48 and 96	

End point values	Voxelotor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: Percent change				
least squares mean (confidence interval 95%)				
Week 24 (n=91,79)	60.89 (7.22 to 114.56)	67.93 (13.10 to 122.75)		
Week 48 (87, 81)	43.52 (-10.51 to 97.54)	37.74 (-16.91 to 92.40)		

Statistical analyses

Statistical analysis title	Week 24
Statistical analysis description: Voxelotor versus Placebo	
Comparison groups	Voxelotor v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8571
Method	Mixed Models for Repeated Measures
Parameter estimate	Difference in LS mean
Point estimate	-7.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-83.88
upper limit	69.8

Statistical analysis title	Week 48
Statistical analysis description: Voxelotor versus Placebo	
Comparison groups	Voxelotor v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8828
Method	Mixed Models for Repeated Measures
Parameter estimate	Difference in LS mean
Point estimate	5.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	-71.2
upper limit	82.75

Secondary: Percent Change From Baseline in Lactate Dehydrogenase (LDH) at Weeks 24, 48 and 96

End point title	Percent Change From Baseline in Lactate Dehydrogenase (LDH) at Weeks 24, 48 and 96
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End point description:

Percent change from baseline in LDH at weeks 24 and 48 was reported in this outcome measure. Analysis was performed using MMRM including treatment, study visit, treatment by visit interaction, baseline hydroxyurea use (yes; no), age group (2 to ≤ 8 years; >8 to <15 years), and baseline TAMMV value (170 centimeter per second [cm/sec] to < 185 cm/sec; 185 cm/sec to < 200 cm/sec) as fixed effect terms and baseline value as a co-variate and used a compound symmetry covariance matrix for within-subject variability. ITT analysis population included all randomized participants. All participants reported under 'Number of Participants Analyzed' contributed data to the table but may not have evaluable data for every row. Here, 'Number Analyzed' signifies number of participants evaluable for each row. Week 96 is not reported due to limitations of the week 96 data as a result of the early termination of the study and were considered exploratory and not subject to formal hypothesis testing.

End point type	Secondary
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End point timeframe:

Baseline (value at Screening), Weeks 24, 48 and 96

End point values	Voxelotor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	116		
Units: Percent change				
least squares mean (confidence interval 95%)				
Week 24 (n=109, 98)	2.62 (-3.25 to 8.49)	2.18 (-3.99 to 8.34)		
Week 48 (n=98, 92)	-2.64 (-8.80 to 3.52)	-0.03 (-6.38 to 6.32)		

Statistical analyses

Statistical analysis title	Week 48
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Statistical analysis description:

Voxelotor versus Placebo

Comparison groups	Voxelotor v Placebo
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Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5635
Method	Mixed Models for Repeated Measures
Parameter estimate	Mixed Models for Repeated Measures
Point estimate	-2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.46
upper limit	6.25

Statistical analysis title	Week 24
Statistical analysis description: Voxelotor versus Placebo	
Comparison groups	Voxelotor v Placebo
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9181
Method	Mixed Models for Repeated Measures
Parameter estimate	Difference in LS mean
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.08
upper limit	8.97

Secondary: Annualized Incidence Rate of Vaso-Occlusive Crises (VOCs)	
End point title	Annualized Incidence Rate of Vaso-Occlusive Crises (VOCs)
End point description: VOC was defined as a composite of acute painful crisis and/or acute chest syndrome (ACS). Annualized incidence rate was defined as total number of events per total person-years. Total person-years was the sum of participants treatment period in years, which included the time from randomisation to earliest of (last dose date, post-randomization HU initiation for subjects with no HU at baseline, and end of study). The 95% CI of rate displayed the exact Poisson confidence limits. ITT analysis population included all randomized participants.	
End point type	Secondary
End point timeframe: Time from randomisation to earliest of (last dose date, post-randomization HU initiation for subjects with no HU at baseline, and end of study) [maximum treatment exposure was 106 weeks]	

End point values	Voxelotor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	116		
Units: Events per total person-years				
number (confidence interval 95%)	1.098 (0.869 to 1.387)	0.580 (0.439 to 0.765)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 up to 28 days after last dose of study drug (maximum treatment exposure was 106 weeks)

Adverse event reporting additional description:

Same event may appear as both SAE and non-SAE. However, what is presented are distinct events. An event may be categorized as serious in one participant and as non-serious in another participant, or one participant may have experienced both a serious and non-serious event during the study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	v27.1
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Reporting groups

Reporting group title	Voxelotor
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Reporting group description:

Participants aged greater than or equal to 12 years of age received 1500 mg voxelotor tablet orally once daily for 96 weeks. Participants less than 12 years of age received voxelotor at a weight based (1500 mg-equivalent) dose. Participants were followed up to 4 weeks after last dose of study drug.

Reporting group title	Placebo
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Reporting group description:

Participants received voxelotor matched placebo orally once daily for 96 weeks.

Serious adverse events	Voxelotor	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 120 (52.50%)	43 / 116 (37.07%)	
number of deaths (all causes)	8	2	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertensive emergency			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	19 / 120 (15.83%)	5 / 116 (4.31%)	
occurrences causally related to treatment / all	0 / 25	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute chest syndrome			

subjects affected / exposed	8 / 120 (6.67%)	8 / 116 (6.90%)	
occurrences causally related to treatment / all	0 / 9	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Liver function test abnormal			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Eyelid ptosis congenital			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 120 (0.83%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Coronary artery thrombosis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 120 (0.00%)	2 / 116 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhagic stroke			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 120 (0.83%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	44 / 120 (36.67%)	18 / 116 (15.52%)	
occurrences causally related to treatment / all	0 / 84	0 / 26	
deaths causally related to treatment / all	0 / 6	0 / 0	
Anaemia			
subjects affected / exposed	12 / 120 (10.00%)	13 / 116 (11.21%)	
occurrences causally related to treatment / all	0 / 13	0 / 13	
deaths causally related to treatment / all	0 / 2	0 / 1	

Haemolysis			
subjects affected / exposed	1 / 120 (0.83%)	3 / 116 (2.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytosis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersplenism			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Periorbital oedema			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 120 (5.00%)	3 / 116 (2.59%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Diarrhoea			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glomerulonephritis acute			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			

subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 120 (5.00%)	2 / 116 (1.72%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaria			
subjects affected / exposed	20 / 120 (16.67%)	16 / 116 (13.79%)	
occurrences causally related to treatment / all	0 / 24	0 / 17	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis			
subjects affected / exposed	8 / 120 (6.67%)	4 / 116 (3.45%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 120 (1.67%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 120 (2.50%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 120 (1.67%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis chronic			

subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diphtheria			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 120 (0.83%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Voxelotor	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 120 (67.50%)	83 / 116 (71.55%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Pallor			
subjects affected / exposed	3 / 120 (2.50%)	1 / 116 (0.86%)	
occurrences (all)	7	2	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Gait disturbance			
subjects affected / exposed	1 / 120 (0.83%)	1 / 116 (0.86%)	
occurrences (all)	1	1	
Non-cardiac chest pain			

subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 2	1 / 116 (0.86%) 1	
Chest pain subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 2	0 / 116 (0.00%) 0	
Pain subjects affected / exposed occurrences (all)	3 / 120 (2.50%) 3	6 / 116 (5.17%) 10	
Pyrexia subjects affected / exposed occurrences (all)	20 / 120 (16.67%) 24	12 / 116 (10.34%) 16	
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	0 / 116 (0.00%) 0	
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 120 (0.00%) 0	1 / 116 (0.86%) 1	
Respiratory, thoracic and mediastinal disorders Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	1 / 116 (0.86%) 1	
Productive cough subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	0 / 116 (0.00%) 0	
Nasal congestion subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	1 / 116 (0.86%) 1	
Haemoptysis subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	0 / 116 (0.00%) 0	
Dyspnoea exertional subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	0 / 116 (0.00%) 0	
Catarrh			

subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Acute chest syndrome			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Nasal turbinate hypertrophy			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	2 / 120 (1.67%)	0 / 116 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	3 / 120 (2.50%)	0 / 116 (0.00%)	
occurrences (all)	3	0	
Tonsillar hypertrophy			
subjects affected / exposed	4 / 120 (3.33%)	4 / 116 (3.45%)	
occurrences (all)	6	6	
Cough			
subjects affected / exposed	12 / 120 (10.00%)	3 / 116 (2.59%)	
occurrences (all)	14	6	
Dyspnoea			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Urine albumin/creatinine ratio increased			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Blood lactate dehydrogenase increased			

subjects affected / exposed	1 / 120 (0.83%)	3 / 116 (2.59%)	
occurrences (all)	1	3	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 120 (2.50%)	2 / 116 (1.72%)	
occurrences (all)	3	3	
Blood bilirubin increased			
subjects affected / exposed	4 / 120 (3.33%)	0 / 116 (0.00%)	
occurrences (all)	4	0	
Alanine aminotransferase increased			
subjects affected / exposed	4 / 120 (3.33%)	3 / 116 (2.59%)	
occurrences (all)	4	3	
Cardiac murmur			
subjects affected / exposed	1 / 120 (0.83%)	1 / 116 (0.86%)	
occurrences (all)	1	1	
Vitamin D decreased			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Platelet count increased			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Heart rate irregular			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Blood albumin decreased			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Bilirubin conjugated increased			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Overdose			

subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Nail injury			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Wound			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Soft tissue injury			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Bone fissure			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Right ventricular failure			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 120 (6.67%)	4 / 116 (3.45%)	
occurrences (all)	9	8	
Dizziness			
subjects affected / exposed	1 / 120 (0.83%)	2 / 116 (1.72%)	
occurrences (all)	1	2	
Sciatica			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Seizure			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			

Sickle cell anaemia with crisis subjects affected / exposed occurrences (all)	45 / 120 (37.50%) 98	33 / 116 (28.45%) 61	
Leukocytosis subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	1 / 116 (0.86%) 2	
Thrombocytosis subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 2	2 / 116 (1.72%) 2	
Lymphadenopathy subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 2	2 / 116 (1.72%) 2	
Anaemia subjects affected / exposed occurrences (all)	4 / 120 (3.33%) 6	6 / 116 (5.17%) 8	
Splenomegaly subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	2 / 116 (1.72%) 2	
Haemolysis subjects affected / exposed occurrences (all)	0 / 120 (0.00%) 0	1 / 116 (0.86%) 1	
Leukopenia subjects affected / exposed occurrences (all)	0 / 120 (0.00%) 0	3 / 116 (2.59%) 3	
Neutrophilia subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	0 / 116 (0.00%) 0	
Neutropenia subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	1 / 116 (0.86%) 1	
Ear and labyrinth disorders Motion sickness subjects affected / exposed occurrences (all)	0 / 120 (0.00%) 0	1 / 116 (0.86%) 1	
Eye disorders			

Eye pruritus			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Night blindness			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Vernal keratoconjunctivitis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Ocular hyperaemia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Abdominal tenderness			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 120 (0.83%)	4 / 116 (3.45%)	
occurrences (all)	3	4	
Vomiting			
subjects affected / exposed	5 / 120 (4.17%)	5 / 116 (4.31%)	
occurrences (all)	7	5	
Diarrhoea			
subjects affected / exposed	5 / 120 (4.17%)	2 / 116 (1.72%)	
occurrences (all)	8	2	
Abdominal pain			
subjects affected / exposed	7 / 120 (5.83%)	5 / 116 (4.31%)	
occurrences (all)	9	5	
Gastritis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			

subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	0 / 116 (0.00%) 0	
Hepatobiliary disorders			
Ocular icterus			
subjects affected / exposed	3 / 120 (2.50%)	1 / 116 (0.86%)	
occurrences (all)	5	4	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 120 (1.67%)	1 / 116 (0.86%)	
occurrences (all)	2	1	
Jaundice			
subjects affected / exposed	2 / 120 (1.67%)	4 / 116 (3.45%)	
occurrences (all)	2	4	
Hepatosplenomegaly			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Hepatomegaly			
subjects affected / exposed	2 / 120 (1.67%)	0 / 116 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Macule			
subjects affected / exposed	1 / 120 (0.83%)	1 / 116 (0.86%)	
occurrences (all)	1	1	
Keratosis pilaris			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Rash macular			
subjects affected / exposed	2 / 120 (1.67%)	0 / 116 (0.00%)	
occurrences (all)	2	0	
Miliaria			

subjects affected / exposed occurrences (all)	0 / 120 (0.00%) 0	1 / 116 (0.86%) 1	
Urticaria subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	1 / 116 (0.86%) 1	
Rash papular subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	0 / 116 (0.00%) 0	
Rash subjects affected / exposed occurrences (all)	3 / 120 (2.50%) 3	4 / 116 (3.45%) 4	
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	0 / 120 (0.00%) 0	1 / 116 (0.86%) 1	
Sickle cell nephropathy subjects affected / exposed occurrences (all)	0 / 120 (0.00%) 0	1 / 116 (0.86%) 1	
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	0 / 120 (0.00%) 0	1 / 116 (0.86%) 1	
Dactylitis subjects affected / exposed occurrences (all)	0 / 120 (0.00%) 0	1 / 116 (0.86%) 1	
Osteonecrosis subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	0 / 116 (0.00%) 0	
Bone pain subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	0 / 116 (0.00%) 0	
Back pain subjects affected / exposed occurrences (all)	6 / 120 (5.00%) 7	2 / 116 (1.72%) 3	
Arthralgia			

subjects affected / exposed	6 / 120 (5.00%)	2 / 116 (1.72%)	
occurrences (all)	8	2	
Pain in extremity			
subjects affected / exposed	6 / 120 (5.00%)	2 / 116 (1.72%)	
occurrences (all)	10	3	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	2	0	
Malaria			
subjects affected / exposed	18 / 120 (15.00%)	16 / 116 (13.79%)	
occurrences (all)	25	21	
Conjunctivitis			
subjects affected / exposed	2 / 120 (1.67%)	3 / 116 (2.59%)	
occurrences (all)	2	3	
Pharyngotonsillitis			
subjects affected / exposed	3 / 120 (2.50%)	5 / 116 (4.31%)	
occurrences (all)	3	5	
Pharyngitis			
subjects affected / exposed	3 / 120 (2.50%)	1 / 116 (0.86%)	
occurrences (all)	3	1	
Bronchitis			
subjects affected / exposed	3 / 120 (2.50%)	2 / 116 (1.72%)	
occurrences (all)	3	2	
Tonsillitis			
subjects affected / exposed	5 / 120 (4.17%)	6 / 116 (5.17%)	
occurrences (all)	6	7	
Respiratory tract infection			
subjects affected / exposed	6 / 120 (5.00%)	6 / 116 (5.17%)	
occurrences (all)	9	7	
Nasopharyngitis			
subjects affected / exposed	7 / 120 (5.83%)	5 / 116 (4.31%)	
occurrences (all)	9	6	
Upper respiratory tract infection			
subjects affected / exposed	12 / 120 (10.00%)	7 / 116 (6.03%)	
occurrences (all)	20	8	

Urinary tract infection		
subjects affected / exposed	1 / 120 (0.83%)	2 / 116 (1.72%)
occurrences (all)	2	2
Varicella		
subjects affected / exposed	2 / 120 (1.67%)	2 / 116 (1.72%)
occurrences (all)	2	2
Acarodermatitis		
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)
occurrences (all)	1	0
Bacterial infection		
subjects affected / exposed	1 / 120 (0.83%)	1 / 116 (0.86%)
occurrences (all)	1	1
Body tinea		
subjects affected / exposed	1 / 120 (0.83%)	1 / 116 (0.86%)
occurrences (all)	1	1
COVID-19		
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)
occurrences (all)	1	0
Escherichia urinary tract infection		
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)
occurrences (all)	1	0
Metapneumovirus infection		
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)
occurrences (all)	1	0
Mumps		
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)
occurrences (all)	1	0
Osteomyelitis acute		
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)
occurrences (all)	1	0
Otitis media		
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)
occurrences (all)	1	0
Parotitis		
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)
occurrences (all)	1	0

Pneumonia			
subjects affected / exposed	1 / 120 (0.83%)	1 / 116 (0.86%)	
occurrences (all)	1	2	
Rash pustular			
subjects affected / exposed	1 / 120 (0.83%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 120 (0.83%)	1 / 116 (0.86%)	
occurrences (all)	1	2	
Carbuncle			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 120 (0.00%)	4 / 116 (3.45%)	
occurrences (all)	0	4	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 120 (1.67%)	3 / 116 (2.59%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2019	Amendment 1.0: The open-label study in infants, Part B, was removed. Primary and key secondary objectives and endpoints were changed to focus on TCD flow velocity. Secondary objectives and endpoints regarding Hb and clinical measures of hemolysis were added. Exploratory objectives and endpoints were updated to evaluate SCD-related clinical complications and SCD-associated quality of life measures and biomarkers. Inclusion/exclusion criteria were updated, including but not limited to Updated age range to 2 to < 15 years of age (from 2 to <12 years of age). Added conditional TCD flow velocity (170 cm/sec to < 200 cm/sec) during screening (no prior criteria regarding TCD flow velocity). The treatment period was extended to 96 weeks (from 48 weeks).
05 December 2019	Amendment 2.0: Added TCD flow velocity secondary objectives for consistency with secondary endpoints. Revised inclusion criteria regarding stable Hb Levels and stable dose of HU and exclusion criteria including but not limited to cerebral vasculopathy and seizure disorder. Revised stratification factors to include screening TCD flow velocity and geographic regions (MENA, rest of world).
13 September 2021	Amendment 3.0: Added dispersible tablet(s) as an optional dosage form. Revised Exclusion Criterion 1 - to increase the weight threshold from < 5 kg to < 10 kg. Added new exclusion criterion for active symptomatic COVID-19 infection.
24 April 2023	Amendment 4.0: Added a secondary endpoint for annualized incidence of VOC. Added dose recommendations for participants < 12 years of age who receive DT dosage form. Added dose modification recommendations for DT dosage form.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 May 2024	Study drug dosing was voluntarily paused on 01 May 2024 due to a potential concern related to an imbalance of participant deaths in those receiving voxelotor compared to those on placebo. The study was terminated effective 25 September 2024 when newly generated clinical data evaluated by Pfizer and shared with the regulatory authorities indicated that the risk profile of voxelotor in people living with SCD exceeded the benefits observed in previously generated global research. The benefit-risk assessment was based on preliminary data that required further analysis.	-

Notes:

Limitations and caveats

None reported