Clinical trial results:
A phase 2, multicenter, open-label study to assess appropriate dosing and to evaluate safety of crizanlizumab, with or without hydroxyurea/hydroxycarbamide, in sequential, descending age groups of pediatric sickle cell disease patients with vaso-occlusive crisis

Summary

EudraCT number	2017-001747-12
Trial protocol	GB DE ES FR BE IT
Global end of trial date	06 November 2024

Results information

Result version number	v1 (current)
This version publication date	17 May 2025
First version publication date	17 May 2025

Trial information

Trial identification

Sponsor protocol code	CSEG101B2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03474965
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 November 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 November 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-To confirm and establish appropriate dosing of crizanlizumab in participants aged 2 to <18 years at the time of study entry (Part A and B)

-To evaluate the safety of crizanlizumab in participants aged 2 to <18 years at the time of study entry (Parts A and B).

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 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	Belgium: 6
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Colombia: 9
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	India: 2
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Lebanon: 11
Country: Number of subjects enrolled	Oman: 8
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Türkiye: 6
Country: Number of subjects enrolled	United States: 32

Worldwide total number of subjects	117
EEA total number of subjects	33

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)	67
Adolescents (12-17 years)	50
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

117 participants were enrolled in the trial in total.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Age 12 to <18 years, 5 mg/kg

Arm description:

Age 12 to <18 years, 5 mg/kg

Arm type	Experimental
Investigational medicinal product name	crizanlizumab
Investigational medicinal product code	SEG101
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

SEG101 (crizanlizumab) 5 mg/kg i.v. administered on Week 1 Day 1, Week3 Day 1 and Day 1 of every 4- week cycle

Arm title	Age 6 to <12 years, 5 mg/kg

Arm description:

Age 6 to <12 years, 5 mg/kg

Arm type	Experimental
Investigational medicinal product name	crizanlizumab
Investigational medicinal product code	SEG101
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

SEG101 (crizanlizumab) 5 mg/kg or 8.5 mg/kg i.v. administered on Week 1 Day 1, Week3 Day 1 and Day 1 of every 4- week cycle

Arm title	Age 6 to <12 years, 8.5 mg/kg

Arm description:

Age 6 to <12 years, 8.5 mg/kg

Arm type	Experimental
Investigational medicinal product name	crizanlizumab
Investigational medicinal product code	SEG101
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

SEG101 (crizanlizumab) 8.5 mg/kg i.v. administered on Week 1 Day 1, Week3 Day 1 and Day 1 of every

4- week cycle

Arm title	Age 2 to <6 years, 8.5 mg/kg

Arm description:

Age 2 to <6 years, 8.5 mg/kg

Arm type	Experimental
Investigational medicinal product name	crizanlizumab
Investigational medicinal product code	SEG101
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

SEG101 (crizanlizumab) 8.5 mg/kg i.v. administered on Week 1 Day 1, Week3 Day 1 and Day 1 of every 4- week cycle

Number of subjects in period 1	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg
Started	50	13	40
Completed	33	10	29
Not completed	17	3	11
Adverse event, serious fatal	1	-	-
Participant Decision	7	-	1
Physician decision	3	1	2
Adverse event, non-fatal	1	-	-
Pregnancy	1	-	-
Guardian Decision	4	2	7
Lost to follow-up	-	-	1

Number of subjects in period 1	Age 2 to <6 years, 8.5 mg/kg
Started	14
Completed	11
Not completed	3
Adverse event, serious fatal	-
Participant Decision	-
Physician decision	-
Adverse event, non-fatal	1
Pregnancy	-
Guardian Decision	2
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	Age 12 to <18 years, 5 mg/kg
Reporting group description: Age 12 to <18 years, 5 mg/kg	
Reporting group title	Age 6 to <12 years, 5 mg/kg
Reporting group description: Age 6 to <12 years, 5 mg/kg	
Reporting group title	Age 6 to <12 years, 8.5 mg/kg
Reporting group description: Age 6 to <12 years, 8.5 mg/kg	
Reporting group title	Age 2 to <6 years, 8.5 mg/kg
Reporting group description: Age 2 to <6 years, 8.5 mg/kg	

Reporting group values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg
Number of subjects	50	13	40
Age Categorical Units: Participants			
<=18 years	50	13	40
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Age Continuous Units: Years			
arithmetic mean	15.00	8.87	9.29
standard deviation	± 1.921	± 1.745	± 1.614
Sex: Female, Male Units: Participants			
Female	29	5	17
Male	21	8	23
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	3
Asian	7	0	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	32	7	19
White	11	4	13
More than one race	0	2	2
Unknown or Not Reported	0	0	0
Age, Customized Units: Subjects			
0 - <28 d	0	0	0
28 d - <2 y	0	0	0
2 y - <12 y	0	13	40
12 y - <18 y	50	0	0

Reporting group values	Age 2 to <6 years,	Total	

	8.5 mg/kg		
Number of subjects	14	117	
Age Categorical Units: Participants			
<=18 years	14	117	
Between 18 and 65 years	0	0	
>=65 years	0	0	
Age Continuous Units: Years			
arithmetic mean	4.81		
standard deviation	± 0.868	-	
Sex: Female, Male Units: Participants			
Female	5	56	
Male	9	61	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	4	7	
Asian	0	10	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	8	66	
White	2	30	
More than one race	0	4	
Unknown or Not Reported	0	0	
Age, Customized Units: Subjects			
0 - <28 d	0	0	
28 d - <2 y	0	0	
2 y - <12 y	14	67	
12 y - <18 y	0	50	

End points

End points reporting groups

Reporting group title	Age 12 to <18 years, 5 mg/kg
Reporting group description: Age 12 to <18 years, 5 mg/kg	
Reporting group title	Age 6 to <12 years, 5 mg/kg
Reporting group description: Age 6 to <12 years, 5 mg/kg	
Reporting group title	Age 6 to <12 years, 8.5 mg/kg
Reporting group description: Age 6 to <12 years, 8.5 mg/kg	
Reporting group title	Age 2 to <6 years, 8.5 mg/kg
Reporting group description: Age 2 to <6 years, 8.5 mg/kg	

Primary: Pharmacokinetics (PK): AUCd15 of crizanlizumab after first dose - Part A

End point title	Pharmacokinetics (PK): AUCd15 of crizanlizumab after first dose - Part A[1]

End point description:

The area under the curve (AUC) from time zero to the last measurable concentration sampling time (tlast)
(mass x time x volume-1) following the first dose. AUCd15 was calculated based on serum concentrations of crizanlizumab.

End point type	Primary

End point timeframe:

Week 1

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: single arm study - statistical analyses is not applicable.

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	13	10
Units: hr*ug/mL				
arithmetic mean (standard deviation)	10500 (± 2290)	8180 (± 1620)	20600 (± 4530)	14400 (± 3990)

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics (PK) - AUCtau for serum crizanlizumab after multiple doses - Part A - steady state

End point title	Pharmacokinetics (PK) - AUCtau for serum crizanlizumab after multiple doses - Part A - steady state[2]

End point description:

The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1).

End point type	Primary

End point timeframe:

Week 15 - Steady state

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: single arm study - statistical analyses is not applicable.

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	11	12
Units: hr*ug/mL				
arithmetic mean (standard deviation)	15800 (± 2080)	14800 (± 3770)	35700 (± 8100)	22100 (± 6200)

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics (PK) - Cmax for Crizanlizumab after first dose and multiple doses - Part A - steady state

End point title	Pharmacokinetics (PK) - Cmax for Crizanlizumab after first dose and multiple doses - Part A - steady state[3]

End point description:

The maximum (peak) observed, serum, drug concentration after single or multiple dose administration (mass x volume-1)

End point type	Primary

End point timeframe:

Week 1 (after first dose) and Week 15 (steady state)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: single arm study - statistical analyses is not applicable.

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	13	12
Units: ug/mL				
arithmetic mean (standard deviation)				
PK Single Dose (Week 1) (n=11,11,13,10)	80.5 (± 17.7)	65.9 (± 11.3)	175 (± 36.0)	110 (± 37.3)
PK Multiple Dose - Week 15 (n=7,8,12,12)	95.6 (± 26.6)	77.5 (± 19.0)	171 (± 35.3)	111 (± 27.4)

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacodynamics (PD) - P-selectin inhibition parameters for crizanlizumab after first dose - Part A - AUCd15

End point title	Pharmacodynamics (PD) - P-selectin inhibition parameters for crizanlizumab after first dose - Part A - AUCd15[4]

End point description:

The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1) following the first dose. AUCd15 was calculated based on P-selectin inhibition curves.

End point type	Primary

End point timeframe:

Week 1

Notes:

[4] - 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: single arm study - statistical analyses is not applicable.

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	12	13	0[5]
Units: hr*{Percent} inhibition P-selectin				
arithmetic mean (standard deviation)	33700 (± 2440)	34400 (± 3660)	33200 (± 3410)	()

Notes:

[5] - insufficient samples

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacodynamics (PD) - P-selectin inhibition parameters for crizanlizumab - Part A - AUCtau after multiple dose - steady state

End point title	Pharmacodynamics (PD) - P-selectin inhibition parameters for crizanlizumab - Part A - AUCtau after multiple dose - steady state[6]

End point description:

The AUC of %inhibition calculated to the end of a dosing interval (tau) after multiple dose. AUCtau was calculated based on P-selectin inhibition curves.

End point type	Primary

End point timeframe:

Week 15 - Steady state

Notes:

[6] - 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: single arm study - statistical analyses is not applicable.

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	7	11	10
Units: hr*{Percent} inhibition P-selectin				
arithmetic mean (standard deviation)	66700 (± 9560)	64800 (± 3550)	68600 (± 9210)	66300 (± 5710)

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of any adverse events (AEs) as a measure of safety and tolerability

End point title	Frequency of any adverse events (AEs) as a measure of safety and tolerability[7]

End point description:

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject

End point type	Primary

End point timeframe:

Adverse events are reported from the first dose of study treatment until end of study treatment Week 103 plus 105 days post-treatment follow-up, up to a maximum timeframe of approximately 2 years and 3.25 months.

Notes:

[7] - 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: single arm study - statistical analyses is not applicable.

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	13	40	14
Units: Participants				
Adverse events (AEs)	47	13	38	14
AEs -Treatment-related	16	5	14	4
Serious Adverse events (SAEs)	18	9	20	12
SAEs -Treatment-related	1	1	2	1
Fatal SAEs	1	0	0	0
Fatal SAEs-Treatment-related	0	0	0	0
AEs leading to dose interruption/reduction	17	6	10	7
AEs requiring additional therapy	45	13	37	14

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate Vaso Occlusive Crisis (VOC) events leading to healthcare visit in clinic / Emergency Room (ER) / hospital

End point title	Annualized rate Vaso Occlusive Crisis (VOC) events leading to healthcare visit in clinic / Emergency Room (ER) / hospital

End point description:

VOC is defined as pain crises as well as other complicated crises, such as acute chest syndrome (ACS), priapism, and hepatic or splenic sequestration.
The baseline annualized rate of VOC was defined as the number of VOCs leading to healthcare visit occurring within the last 12 months prior to screening until first dose.

This annualized rate of VOC was calculated by multiplying the number of VOCs by 365 and dividing by the number of days in the observation period. (Parts A and B)

End point type	Secondary

End point timeframe:

Baseline, Year 1 and Year 2

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	13	40	14
Units: VOC events per year				
median (full range (min-max))				
Baseline annualized (annual.) rate of VOC	3.00 (1.0 to 26.0)	1.00 (0.0 to 6.0)	2.00 (1.0 to 13.0)	1.00 (1.0 to 5.0)
Annualized rate of VOC on treatment (up to Year 2)	1.80 (0.0 to 14.5)	0.79 (0.0 to 10.4)	1.48 (0.0 to 8.7)	1.22 (0.0 to 5.3)
Annual. rate of VOC on trt. Year 1 (n=42,11,35,12)	2.00 (0.0 to 14.0)	0.00 (0.0 to 4.0)	1.00 (0.0 to 6.0)	0.00 (0.0 to 3.0)
Annual. rate of VOC on trt. Year 2 (n=32,10,27,10)	2.00 (0.0 to 8.0)	0.00 (0.0 to 5.0)	1.00 (0.0 to 9.0)	2.00 (0.0 to 4.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate Vaso Occlusive Crisis (VOC) events treated at home (based on documentation by health care provider following phone contact with the patient)

End point title	Annualized rate Vaso Occlusive Crisis (VOC) events treated at home (based on documentation by health care provider following phone contact with the patient)

End point description:

VOC is defined as pain crises as well as other complicated crises, such as acute chest syndrome (ACS), priapism, and hepatic or splenic sequestration.

This annualized rate of VOC was calculated by multiplying the number of VOCs by 365 and dividing by the number of days in the observation period. (Parts A and B)

End point type	Secondary

End point timeframe:

Up to Year 2

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	2	10	2
Units: rate				
median (full range (min-max))	0.94 (0.5 to 3.9)	2.71 (0.5 to 4.9)	0.49 (0.49 to 3.0)	0.73 (0.5 to 1.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate Vaso Occlusive Crisis (VOC) events leading to healthcare visit - uncomplicated pain crisis

End point title	Annualized rate Vaso Occlusive Crisis (VOC) events leading to healthcare visit - uncomplicated pain crisis

End point description:

VOC is defined as pain crises as well as other complicated crises, such as acute chest syndrome (ACS), priapism, and hepatic or splenic sequestration.

This annualized rate of VOC was calculated by multiplying the number of VOCs by 365 and dividing by the number of days in the observation period. (Parts A and B)

Uncomplicated pain crisis is defined as an acute episode of pain with no known cause for pain other than a vaso-occlusive event; and requiring treatment with a parenteral or oral opioids or other parenteral analgesic; but is NOT classified as an acute chest syndrome, hepatic sequestration, splenic sequestration or priapism. The end of an uncomplicated pain crisis will be considered the resolution of acute pain, such that residual pain (or absence of any pain) is considered to be chronic, and the current pain medication regimen is considered to be for this chronic pain.

End point type	Secondary

End point timeframe:

Up to Year 2

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	12	38	14
Units: rate				
median (full range (min-max))	1.79 (0.0 to 14.5)	0.98 (0.0 to 10.4)	1.47 (0.0 to 8.7)	0.97 (0.0 to 5.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate Vaso Occlusive Crisis (VOC) events leading to healthcare visit - acute chest syndrome

End point title	Annualized rate Vaso Occlusive Crisis (VOC) events leading to healthcare visit - acute chest syndrome

End point description:

VOC is defined as pain crises as well as other complicated crises, such as acute chest syndrome (ACS), priapism, and hepatic or splenic sequestration.

This annualized rate of VOC was calculated by multiplying the number of VOCs by 365 and dividing by the number of days in the observation period. (Parts A and B)

Acute Chest Syndrome (ACS) is defined on the basis of the finding of a new pulmonary infiltrate involving at least one complete lung segment that was consistent with alveolar consolidation, but excluding atelectasis (as indicated by chest X-ray). At least one of the following additional signs or symptoms needs to be present as well: chest pain, a temperature of more than 38.5°C, tachypnea, wheezing or cough. ACS will be considered resolved when the patient is no longer hospitalized (unless for reason other than the ACS episode) and none of the additional signs or symptoms above are present (unless for reason other than the ACS).

End point type	Secondary

End point timeframe:

Up to Year 2

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	4	15	6
Units: rate				
median (full range (min-max))	0.49 (0.0 to 3.7)	0.64 (0.0 to 1.5)	0.49 (0.0 to 1.0)	0.49 (0.0 to 1.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate Vaso Occlusive Crisis (VOC) events treated at home (based on documentation by health care provider following phone contact with the patient) - hepatic sequestration

End point title	Annualized rate Vaso Occlusive Crisis (VOC) events treated at home (based on documentation by health care provider following phone contact with the patient) - hepatic sequestration

End point description:

VOC is defined as pain crises as well as other complicated crises, such as acute chest syndrome (ACS), priapism, and hepatic or splenic sequestration.

This annualized rate of VOC was calculated by multiplying the number of VOCs by 365 and dividing by the number of days in the observation period. (Parts A and B)

Hepatic sequestration is defined on the basis of findings of right upper quadrant pain, an enlarged liver,

and an acute decrease in hemoglobin concentration (e.g. a decrease in hemoglobin of ~ 2 g/dL). Acute hepatic sequestration will be considered resolved when right upper quadrant pain has returned to baseline (pre-event) levels and hemoglobin has been stable for 24 hrs.

There were no patients with VOC events of hepatic sequestration treated at home. Therefore, there were no observations which met the report criteria.

End point type	Secondary

End point timeframe:

Up to Year 2

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	13	40	14
Units: VOC events per year	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate Vaso Occlusive Crisis (VOC) events leading to healthcare visit - splenic sequestration

End point title	Annualized rate Vaso Occlusive Crisis (VOC) events leading to healthcare visit - splenic sequestration

End point description:

VOC is defined as pain crises as well as other complicated crises, such as acute chest syndrome (ACS), priapism, and hepatic or splenic sequestration.

This annualized rate of VOC was calculated by multiplying the number of VOCs by 365 and dividing by the number of days in the observation period. (Parts A and B)

Splenic sequestration if defined on the basis of findings of left upper quadrant pain, an enlarged spleen, and an acute decrease in hemoglobin concentration (e.g., a decrease in hemoglobin of ~ 2 g/dL). Acute splenic sequestration will be considered resolved when left upper quadrant pain has returned to baseline (pre-event) levels and hemoglobin has been stable for 24 hrs.

End point type	Secondary

End point timeframe:

Up to Year 2

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	1	1	0[8]
Units: rate				
median (full range (min-max))	0.00 (0.0 to 0.5)	0.00 (0.0 to 0.0)	0.00 (0.0 to 0.0)	(to)

Notes:

[8] - There were no participants with VOC)events leading to healthcare visit - splenic sequestration

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate Vaso Occlusive Crisis (VOC) events leading to healthcare visit - priapism

End point title	Annualized rate Vaso Occlusive Crisis (VOC) events leading to healthcare visit - priapism

End point description:

VOC is defined as pain crises as well as other complicated crises, such as acute chest syndrome (ACS), priapism, and hepatic or splenic sequestration.

This annualized rate of VOC was calculated by multiplying the number of VOCs by 365 and dividing by the number of days in the observation period. (Parts A and B)

Priapism is defined as an unwanted or painful penile erection lasting at least 30 minutes. The end of an acute priapism event will be when the unwanted erection has resolved for at least 2 hours.

End point type	Secondary

End point timeframe:

Up to Year 2

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[9]	1	1	0[10]
Units: rate				
median (full range (min-max))	(to)	0.49 (0.49 to 0.49)	0.00 (0.0 to 0.0)	(to)

Notes:

[9] - There were no participants with VOC events leading to healthcare visit - priapism

[10] - There were no participants with VOC events leading to healthcare visit - priapism

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate of hospitalizations and Emergency Room (ER) visits (VOC-related)

End point title	Annualized rate of hospitalizations and Emergency Room (ER) visits (VOC-related)

End point description:

VOC is defined as pain crises as well as other complicated crises, such as acute chest syndrome (ACS), priapism, and hepatic or splenic sequestration.

This rate was calculated by multiplying the number of hospitalizations and ER visits (VOC-related) by 365 and dividing by the number of days in the observation period.
Units would be something like: hospitalizations and ER visits per year. (Parts A and B)

End point type	Secondary

End point timeframe:

Up to Year 2

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	13	40	14
Units: rate				
median (full range (min-max))				
Up to Year 2	1.78 (0.0 to 13.5)	0.50 (0.0 to 10.4)	1.01 (0.0 to 9.6)	0.74 (0.0 to 5.3)
Year 1 (n=42,11,35,12)	2.00 (0.0 to 14.0)	0.00 (0.0 to 5.0)	1.00 (0.0 to 6.0)	0.00 (0.0 to 3.0)
Year 2 (n=32,10,27,10)	2.00 (0.0 to 9.0)	0.00 (0.0 to 5.0)	1.00 (0.0 to 10.0)	1.00 (0.0 to 3.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate of hospitalizations and Emergency Room (ER) visits (total)

End point title	Annualized rate of hospitalizations and Emergency Room (ER) visits (total)

End point description:

VOC is defined as pain crises as well as other complicated crises, such as acute chest syndrome (ACS), priapism, and hepatic or splenic sequestration.
The baseline annualized rate of VOC was defined as the number of VOCs leading to healthcare visit occurring within the last 12 months prior to screening until first dose.

This rate was calculated by multiplying the number of hospitalizations and ER visits (VOC-related) by 365 and dividing by the number of days in the observation period.
Units would be something like: hospitalizations and ER visits per year. (Parts A and B)

End point type	Secondary

End point timeframe:

Up to Year 2

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	13	40	14
Units: rate				
median (full range (min-max))				
Up to Year 2	2.68 (0.0 to 15.5)	1.46 (0.0 to 11.4)	1.59 (0.0 to 11.7)	1.74 (0.0 to 7.7)

Year 1 (n=42,11,35,12)	2.00 (0.0 to 16.0)	1.00 (0.0 to 5.0)	2.00 (0.0 to 7.0)	2.00 (0.0 to 8.0)
Year 2 (n=32,10,27,10)	2.50 (0.0 to 10.0)	1.00 (0.0 to 8.0)	1.00 (0.0 to 10.0)	2.00 (0.0 to 4.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized days of Emergency Room (ER) / hospitalization (both overall and VOC-related)

End point title	Annualized days of Emergency Room (ER) / hospitalization (both overall and VOC-related)

End point description:

VOC is defined as pain crises as well as other complicated crises, such as acute chest syndrome (ACS), priapism, and hepatic or splenic sequestration.
The baseline annualized rate of VOC was defined as the number of VOCs leading to healthcare visit occurring within the last 12 months prior to screening until first dose.

This rate was calculated by multiplying the number of days of ER/hospitalizations (both overall and VOC-related) by 365 and dividing by the number of days in the observation period. (Parts A and B)

End point type	Secondary

End point timeframe:

Years 1 and 2

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	13	40	14
Units: Days per year				
median (full range (min-max))				
On treatment - VOC related (up to Year 2)	6.74 (0.0 to 87.0)	0.98 (0.0 to 59.2)	5.36 (0.0 to 40.0)	2.20 (0.0 to 42.7)
On treatment - Total (up to Year 2)	12.37 (0.0 to 87.0)	5.41 (0.0 to 59.2)	9.03 (0.0 to 57.5)	10.48 (0.0 to 42.7)
Year 1 - VOC related (n=42,11,12, 12)	7.00 (0.0 to 60.3)	0.00 (0.0 to 23.0)	5.00 (0.0 to 37.0)	0.00 (0.0 to 29.0)
Year 1 - Total (n=42,11,12, 12)	7.00 (0.0 to 60.3)	2.00 (0.0 to 24.0)	11.00 (0.0 to 37.0)	6.50 (0.0 to 34.0)
Year 2 - VOC related (n=32,10,11, 10)	10.50 (0.0 to 71.0)	0.00 (0.0 to 48.0)	2.00 (0.0 to 40.0)	3.00 (0.0 to 19.0)
Year 2 - Total (n=32,10,11, 10)	13.00 (0.0 to 71.0)	2.00 (0.0 to 64.0)	3.00 (0.0 to 40.0)	10.50 (0.0 to 37.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate of dactylitis events

End point title	Annualized rate of dactylitis events

End point description:

Dactylitis, also known as 'hand-foot syndrome', is a complication of acute vaso-occlusive disease characterized by pain and edema of the digits as well as the dorsum of the hands or feet, or both simultaneously, often accompanied by increased local temperature and erythema.

There were no patients with dactylitis events. Therefore, there were no observations which met the report criteria.

End point type	Secondary

End point timeframe:

On Treatment, up to Year 2

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	13	40	14
Units: dactylitis events per year	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in hemoglobin

End point title	Absolute change from baseline in hemoglobin

End point description:

Hemoglobin is a protein that carries oxygen through the body. It attaches to red blood cells, delivers oxygen throughout the body, and transports carbon dioxide back to the lungs. In sickle cell disease, red blood cells are crescent or sickle-shaped due to a genetic mutation, and those sickled red blood cells can clog blood flow, causing debilitating pain and even organ damage.

End point type	Secondary

End point timeframe:

Baseline, Week 27, Year 2

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	9	36	11
Units: g/L				
arithmetic mean (standard deviation)				
Week 27	-1.26 (± 11.472)	2.33 (± 6.856)	-0.33 (± 7.015)	1.55 (± 9.905)
End Of Treatment / Year 2 (n=24,6,11,2)	-5.38 (± 11.088)	2.33 (± 7.941)	-1.18 (± 11.677)	15.00 (± 1.414)

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: measurement of anti-drug antibodies (ADA) to crizanlizumab

End point title	Immunogenicity: measurement of anti-drug antibodies (ADA) to crizanlizumab

End point description:

Anti-drug antibodies (ADA) are antibodies elicited from therapeutics and they are used to measure immunogenicity.

End point type	Secondary

End point timeframe:

up to Year 2

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	13	39	14
Units: Participants				
Baseline - Negative	50	13	39	14
Baseline - Positive	0	0	0	0
Baseline - Missing	0	0	1	0
Post-baseline - Any positive	0	1	1	0
Post-baseline - only last sample positive	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Notable on-treatment findings from the Electrocardiogram (ECG) assessments

End point title	Notable on-treatment findings from the Electrocardiogram (ECG) assessments

End point description:

QTcF = QT interval corrected by Fridericia’s formula
QTcB = Corrected QT interval Bazett's Formula
QT = QT interval
PR = PR interval
QRS = QRS interval
RR = RR interval
HR = heart rate
In = increase

De = decrease

End point type	Secondary
End point timeframe: Baseline, up to Year 2	

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	13	40	13
Units: Participants				
QTcF (ms)-In >30 to <=60 ms (n=49,13,37,12)	1	1	2	1
QTcF (ms)- In >60 ms (n=49,13,37,12)	0	0	0	0
QTcF (ms)- New >450 to <=480 ms (n=49,13,40,13)	3	0	0	0
QTcF (ms)- New >480 to <=500 ms (n=49,13,40,13)	0	0	1	0
QTcF (ms)-New >500 ms (n=49,13,40,13)	0	0	0	0
QTcB (ms)-In >30 to <=60 ms (n=49,13,37,12)	12	3	7	1
QTcB (ms)-In >60 ms (n=49,13,37,12)	0	0	0	0
QTcB (ms)-New >450 to <=480 ms (n=40,12,35,13)	10	2	14	6
QTcB (ms)-New >480 to <=500 ms (n=49,13,40,13)	3	0	1	0
QTcB (ms)-New >500 ms (n=49,13,40,13)	0	0	0	0
QT (ms)-In >30 to <=60 ms (n=49,13,37,12)	13	5	17	3
QT (ms)-In >60 ms (n=49,13,37,12)	2	0	2	0
QT (ms)-New >450 to <=480 ms (n=49,13,40,13)	0	0	0	0
QT (ms)-New >480 to <=500 ms (n=49,13,40,13)	0	0	0	0
QT (ms)-New >500 ms (n=49,13,40,13)	0	0	0	0
PR (ms)-In >25% and PR >200 ms (n=48,13,37,12)	0	0	0	0
PR (ms)-New PR >200 ms (n=48,13,40,13)	2	0	0	0
QRS (ms)- In >25% and QRS >120 ms (n=49,13,37,12)	0	0	0	0
QRS (ms)-New QRS >120 ms (n=49,13,40,13)	0	0	0	0
RR (ms)-In >25% and RR >1200 ms (n=49,13,37,12)	1	0	0	0
RR (ms)-De >25% and RR <600 ms (n=49,12,34,7)	0	1	2	0
HR (bpm)-In >25% and HR >100 bpm (n=49,12,34,7)	1	1	3	0
HR (bpm)-De >25% and HR <50 bpm (n=49,13,37,12)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Growth and sexual maturation assessments (Tanner stage) - abnormalities - for female participants at risk of delayed puberty at start date of study treatment

End point title	Growth and sexual maturation assessments (Tanner stage) - abnormalities - for female participants at risk of delayed puberty at start date of study treatment

End point description:

As assessed per Tanner criteria.

The number of Participants Analyzed row refer to participants who have not started puberty and have not had delayed puberty prior to
start date of study treatment.

Delayed puberty in females is defined as failure to attain Tanner Stage 2 (for both breast development and pubic
hair) by age 13, or absence of menarche by age 15 or within 5 years of attainment of Tanner Stage 2.

End point type	Secondary

End point timeframe:

Week 51

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[11]	3	12	5
Units: Participants				
Delayed puberty = yes		0	0	0
Delayed puberty = no		0	0	0
unknown / NA - pt not yet in puberty age range		3	12	5

Notes:

[11] - Participants had already started puberty prior to study enrolment.

Statistical analyses

No statistical analyses for this end point

Secondary: Growth and sexual maturation assessments (Tanner stage) - abnormalities - for male participants at risk of delayed puberty at start date of study treatment

End point title	Growth and sexual maturation assessments (Tanner stage) - abnormalities - for male participants at risk of delayed puberty

	at start date of study treatment

End point description:

As assessed per Tanner criteria.

The number of Participants Analyzed row refer to participants who have not started puberty and have not had delayed puberty prior to
start date of study treatment.

Delayed puberty in males is defined as failure to attain Tanner Stage 2 (for both genitalia and pubic hair)
by age 14.

End point type	Secondary

End point timeframe:

Week 51

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	7	18	9
Units: Participants				
Delayed puberty = yes	0	0	0	0
Delayed puberty = no	4	0	0	0
unknown / NA - pt not yet in puberty age range	0	7	18	9

Statistical analyses

No statistical analyses for this end point

Secondary: PK pre-dose concentrations of crizanlizumab prior to each study drug dose - Part A

End point title	PK pre-dose concentrations of crizanlizumab prior to each study drug dose - Part A

End point description:

End point type	Secondary

End point timeframe:

Week 3, Week 7, Week 11, Week 15, Week 19, Week 23, Week 27, Week 31, Week 35, Week 39, Week 43, Week 47 and Week 51 (Day 1, 0 hr (pre-dose))

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	12	13	12
Units: µg/mL				
arithmetic mean (standard deviation)				

Week 3 Day 1, 0 hr (pre-dose) (n=11,12,13,10)	16.8 (± 4.40)	14.1 (± 5.61)	30.1 (± 6.17)	19.8 (± 5.62)
Week 7 Day 1, 0 hr (pre-dose) (n=9,12,12,12)	10.7 (± 3.30)	8.70 (± 5.32)	22.1 (± 8.09)	13.4 (± 3.21)
Week 11 Day 1, 0 hr (pre-dose) (n=9,11,12,11)	10.2 (± 4.92)	6.02 (± 4.43)	20.1 (± 9.36)	11.0 (± 3.80)
Week 15 Day 1, 0 hr (pre-dose) (n=7,9,11,12)	9.42 (± 6.47)	8.45 (± 2.93)	20.4 (± 7.22)	10.3 (± 5.84)
Week 19 Day 1, 0 hr (pre-dose) (n=6,9,12,11)	6.77 (± 4.53)	7.75 (± 4.92)	18.8 (± 5.28)	10.2 (± 5.93)
Week 23 Day 1, 0 hr (pre-dose) (n=9,12,12,10)	6.17 (± 3.92)	7.15 (± 5.23)	20.0 (± 6.74)	10.6 (± 5.24)
Week 27 Day 1, 0 hr (pre-dose) (n=9,10,12,10)	8.05 (± 5.32)	7.70 (± 5.93)	22.4 (± 8.71)	11.8 (± 9.30)
Week 31 Day 1, 0 hr (pre-dose) (n=6,10,11,10)	9.46 (± 4.34)	8.57 (± 6.17)	19.3 (± 6.36)	9.68 (± 8.29)
Week 35 Day 1, 0 hr (pre-dose) (n=5,11,10,9)	12.0 (± 6.04)	6.88 (± 3.04)	17.9 (± 8.03)	8.43 (± 6.78)
Week 39 Day 1, 0 hr (pre-dose) (n=7,11,10,11)	4.93 (± 3.00)	7.04 (± 5.75)	19.9 (± 5.21)	12.8 (± 7.98)
Week 43 Day 1, 0 hr (pre-dose) (n=8,10,11,8)	9.23 (± 4.73)	7.45 (± 5.66)	18.0 (± 8.07)	12.8 (± 4.95)
Week 47 Day 1, 0 hr (pre-dose) (n=8,8,10,10)	7.32 (± 3.84)	10.4 (± 7.29)	14.6 (± 8.22)	10.5 (± 9.26)
Week 51 Day 1, 0 hr (pre-dose) (n=5,9,10,8)	9.78 (± 6.61)	9.44 (± 8.22)	12.8 (± 10.6)	10.3 (± 3.21)

Statistical analyses

No statistical analyses for this end point

Secondary: PK pre-dose concentrations of crizanlizumab prior to each study drug dose - Parts A and B

End point title	PK pre-dose concentrations of crizanlizumab prior to each study drug dose - Parts A and B

End point description:

End point type	Secondary

End point timeframe:

Week 3, Week 7, Week 11, Week 15, Week 19, Week 23, Week 27, Week 31, Week 35, Week 39, Week 43, Week 47 and Week 51 (0 hr (pre-dose))

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	12	36	13
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 3 Day 1, 0 hr (pre-dose) (n=45,12,36,11)	16.6 (± 4.40)	14.1 (± 5.61)	23.6 (± 7.54)	20.0 (± 5.37)
Week 7 Day 1, 0 hr (pre-dose) (n=44,12,35,13)	10.3 (± 5.49)	8.70 (± 5.32)	16.3 (± 7.50)	14.4 (± 4.57)

Week 11 Day 1, 0 hr (pre-dose)(n=45,11,33,11)	9.18 (± 5.57)	6.02 (± 4.43)	15.3 (± 7.78)	11.0 (± 3.80)
Week 15 Day 1, 0 hr (pre-dose) (n=39,9,33,12)	8.65 (± 5.73)	8.45 (± 2.93)	16.7 (± 7.34)	10.3 (± 5.84)
Week 19 Day 1, 0 hr (pre-dose) (n=38,9,35,11)	8.13 (± 5.65)	7.75 (± 4.92)	17.5 (± 5.93)	10.2 (± 5.93)
Week 23 Day 1, 0 hr (pre-dose) (n=43,12,35,10)	7.09 (± 4.45)	7.15 (± 5.23)	16.6 (± 6.90)	10.6 (± 5.24)
Week 27 Day 1, 0 hr (pre-dose) (n=40,10,34,10)	7.07 (± 4.26)	7.70 (± 5.93)	16.5 (± 8.45)	11.8 (± 9.30)
Week 31 Day 1, 0 hr (pre-dose) (n=39,10,35,10)	7.30 (± 4.80)	8.57 (± 6.17)	16.1 (± 7.57)	9.68 (± 8.29)
Week 35 Day 1, 0 hr (pre-dose) (n=35,11,32,10)	8.96 (± 4.94)	6.88 (± 3.04)	13.6 (± 7.75)	10.0 (± 8.11)
Week 39 Day 1, 0 hr (pre-dose) (n=38,11,35,12)	7.69 (± 5.46)	7.04 (± 5.75)	14.2 (± 7.79)	13.4 (± 7.89)
Week 43 Day 1, 0 hr (pre-dose) (n=35,10,34,9)	8.68 (± 4.50)	7.45 (± 5.66)	14.8 (± 6.94)	13.6 (± 5.15)
Week 47 Day 1, 0 hr (pre-dose)	8.99 (± 5.76)	10.4 (± 7.29)	13.8 (± 6.80)	10.5 (± 9.26)
Week 51 Day 1, 0 hr (pre-dose)	8.48 (± 5.48)	9.44 (± 8.22)	13.4 (± 7.90)	11.6 (± 4.90)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent P-selectin inhibition of crizanlizumab prior to dosing - Part A

End point title	Percent P-selectin inhibition of crizanlizumab prior to dosing - Part A

End point description:

A PD marker of crizanlizumab is the ex vivo P-selectin inhibition measured by a surface plasmon resonance assay using human serum samples. Crizanlizumab in serum samples binds to spiked Psel-Ig (P-selectin coupled to Ig) and inhibits its binding to a PSGL1 peptide.

End point type	Secondary

End point timeframe:

Weeks 3, 7, 11,15, 19, 23, 27, 31, 35, 39, 43,47,51 (Day 1, 0 hr (pre-dose))

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	12	13	10
Units: % inhibition P-selectin				
arithmetic mean (standard deviation)				
Week 3 Day 1, 0 hr (pre-dose) (n=11,12,13,9)	100 (± 0.0924)	97.9 (± 2.97)	99.1 (± 1.41)	98.6 (± 2.54)
Week 7 Day 1, 0 hr (pre-dose) (n=9,11,12,10)	99.0 (± 1.61)	94.2 (± 12.2)	98.5 (± 3.48)	98.9 (± 1.91)
Week 11 Day 1, 0 hr (pre-dose) (n=9,9,12,9)	97.7 (± 4.56)	80.8 (± 32.4)	98.5 (± 2.93)	98.4 (± 2.50)
Week 15 Day 1, 0 hr (pre-dose) (n=6,8,11,10)	96.6 (± 8.04)	99.8 (± 0.422)	99.2 (± 1.86)	91.7 (± 19.8)

Week 19 Day 1, 0 hr (pre-dose) (n=6,9,12,10)	88.6 (± 20.6)	83.5 (± 34.8)	99.2 (± 1.54)	96.7 (± 5.51)
Week 23 Day 1, 0 hr (pre-dose) (n=9,10,11,9)	83.8 (± 28.9)	91.2 (± 14.0)	99.5 (± 1.24)	92.2 (± 15.7)
Week 27 Day 1, 0 hr (pre-dose) (n=9,9,11,8)	88.0 (± 25.0)	90.8 (± 20.4)	99.4 (± 1.36)	85.4 (± 19.1)
Week 31 Day 1, 0 hr (pre-dose) (n=6,9,9,9)	97.8 (± 2.83)	88.9 (± 21.0)	99.6 (± 1.30)	75.5 (± 37.9)
Week 35 Day 1, 0 hr (pre-dose) (n=5,10,8,9)	97.2 (± 6.04)	92.3 (± 10.6)	97.9 (± 3.81)	67.4 (± 42.1)
Week 39 Day 1, 0 hr (pre-dose) (n=7,7,8,9)	80.8 (± 28.0)	88.6 (± 25.3)	99.1 (± 2.01)	87.6 (± 19.2)
Week 43 Day 1, 0 hr (pre-dose) (n=8,3,9,6)	96.7 (± 4.19)	99.0 (± 1.67)	98.8 (± 2.14)	98.8 (± 2.37)
Week 47 Day 1, 0 hr (pre-dose) (n=8,2,8,8)	87.1 (± 30.5)	98.8 (± 1.77)	98.1 (± 3.73)	69.8 (± 44.0)
Week 51 Day 1, 0 hr (pre-dose) (n=5,3,8,7)	80.9 (± 34.0)	95.4 (± 4.24)	98.9 (± 1.86)	92.1 (± 13.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent P-selectin inhibition of crizanlizumab prior to dosing - Part A and B

End point title	Percent P-selectin inhibition of crizanlizumab prior to dosing - Part A and B

End point description:

A PD marker of crizanlizumab is the ex vivo P-selectin inhibition measured by a surface plasmon resonance assay using human serum samples. Crizanlizumab in serum samples binds to spiked Psel-Ig (P-selectin coupled to Ig) and inhibits its binding to a PSGL1 peptide.

End point type	Secondary

End point timeframe:

Weeks 3, 7, 11,15, 19, 23, 27, 31, 35, 39, 43,47,51 (Day 1, 0 hr (pre-dose))

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	12	36	12
Units: % inhibition P-selectin				
arithmetic mean (standard deviation)				
Week 3 Day 1, 0 hr (pre-dose) (n=42,12,36,11)	99.3 (± 2.14)	97.9 (± 2.97)	98.3 (± 3.74)	97.6 (± 3.71)
Week 7 Day 1, 0 hr (pre-dose) (n=41,12,35,12)	93.7 (± 17.0)	94.6 (± 11.7)	97.1 (± 7.36)	97.3 (± 5.92)
Week 11 Day 1, 0 hr (pre-dose) (n=41,10,33,10)	92.7 (± 17.8)	82.3 (± 30.9)	97.5 (± 6.08)	98.3 (± 2.39)
Week 15 Day 1, 0 hr (pre-dose) (n=39,9,33,11)	92.6 (± 18.9)	98.9 (± 2.90)	96.8 (± 8.46)	92.5 (± 19.0)
Week 19 Day 1, 0 hr (pre-dose) (n=36,9,35,10)	92.4 (± 12.3)	83.5 (± 34.8)	96.8 (± 7.36)	96.7 (± 5.51)

Week 23 Day 1, 0 hr (pre-dose) (n=42,11,34,9)	86.5 (± 26.3)	92.0 (± 13.5)	94.2 (± 17.6)	92.2 (± 15.7)
Week 27 Day 1, 0 hr (pre-dose) (n=37,10,33,9)	87.6 (± 26.1)	91.6 (± 19.4)	95.4 (± 10.4)	87.0 (± 18.5)
Week 31 Day 1, 0 hr (pre-dose) (n=36,10,32,9)	90.9 (± 18.7)	89.1 (± 19.8)	97.3 (± 7.02)	75.5 (± 37.9)
Week 35 Day 1, 0 hr (pre-dose) (n=32,11,29,10)	93.1 (± 18.0)	92.8 (± 10.3)	92.7 (± 16.4)	70.6 (± 41.0)
Week 39 Day 1, 0 hr (pre-dose) (n=33,8,33,11)	85.4 (± 23.6)	89.7 (± 23.6)	92.7 (± 18.7)	89.8 (± 17.9)
Week 43 Day 1, 0 hr (pre-dose) (n=31,3,32,8)	93.1 (± 15.4)	99.0 (± 1.67)	95.3 (± 11.0)	99.1 (± 2.08)
Week 47 Day 1, 0 hr (pre-dose) (n=28,2,32,9)	91.7 (± 17.7)	98.8 (± 1.77)	95.8 (± 7.45)	73.1 (± 42.4)
Week 51 Day 1, 0 hr (pre-dose) (n=27,3,26,9)	86.4 (± 25.8)	95.4 (± 4.24)	92.5 (± 19.3)	93.8 (± 11.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events by preferred term related to study treatment

End point title	Adverse events by preferred term related to study treatment

End point description:

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject

End point type	Secondary

End point timeframe:

Adverse events are reported from the first dose of study treatment until end of study treatment Week 103 plus 105 days post-treatment follow-up, up to a maximum timeframe of approximately 2 years and 3.25 months.

End point values	Age 12 to <18 years, 5 mg/kg	Age 6 to <12 years, 5 mg/kg	Age 6 to <12 years, 8.5 mg/kg	Age 2 to <6 years, 8.5 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	13	40	14
Units: Participants				
Number of participants with at least one event	16	5	14	4
Infusion related reaction	5	2	3	1
Back pain	3	0	4	2
Nausea	3	0	1	0
Pain in extremity	2	0	2	0
Sickle cell anaemia with crisis	0	0	2	1
Arthralgia	0	1	1	0
Conjunctivitis	1	1	0	0
Dizziness	2	0	0	0
Headache	1	0	1	0
Infusion site pain	1	0	1	0

Myalgia	1	1	0	0
Neutropenia	0	0	1	1
Pain	1	1	0	0
Vomiting	2	0	0	0
Abdominal pain	0	1	0	0
Agitation	1	0	0	0
Alopecia	0	0	1	0
Anaemia	0	0	1	0
Asthenia	0	0	1	0
Blood bilirubin increased	1	0	0	0
Blood creatine phosphokinase increased	1	0	0	0
Dyspnoea	0	1	0	0
Fatigue	1	0	0	0
Hot flush	1	0	0	0
Hypersensitivity	0	0	1	0
Malaise	0	1	0	0
Muscle fatigue	1	0	0	0
Neck pain	1	0	0	0
Paraesthesia	0	0	1	0
Pruritus	0	1	0	0
Pyrexia	0	1	0	0
Sacral pain	0	0	1	0
Spinal pain	0	0	1	0
Vascular access complication	0	1	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported from the first dose of study treatment until end of study treatment Week 103 plus 105 days post-treatment follow-up, up to a maximum timeframe of approximately 2 years and 3.25 months.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events fi eld "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Age 12 to < 18 years,@5 mg/kg
Reporting group description:	
Age 12 to < 18 years,@5 mg/kg	
Reporting group title	Age 6 to < 12 years,@5 mg/kg
Reporting group description:	
Age 6 to < 12 years,@5 mg/kg	
Reporting group title	All@Participants
Reporting group description:	
All@Participants	
Reporting group title	Age 2 to < 6 years,@8.5 mg/kg
Reporting group description:	
Age 2 to < 6 years,@8.5 mg/kg	
Reporting group title	Age 6 to < 12 years,@8.5 mg/kg
Reporting group description:	
Age 6 to < 12 years,@8.5 mg/kg	

Serious adverse events	Age 12 to < 18 years,@5 mg/kg	Age 6 to < 12 years,@5 mg/kg	All@Participants
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 50 (36.00%)	9 / 13 (69.23%)	59 / 117 (50.43%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Superficial vein thrombosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Hyperthermia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	6 / 117 (5.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 50 (4.00%)	2 / 13 (15.38%)	9 / 117 (7.69%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute chest syndrome			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory distress			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Human rhinovirus test positive			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
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			
Brain herniation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Infusion related reaction			
subjects affected / exposed	1 / 50 (2.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Syncope			

subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status migrainosus			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 50 (4.00%)	1 / 13 (7.69%)	9 / 117 (7.69%)
occurrences causally related to treatment / all	0 / 3	0 / 1	1 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric lymphadenitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 50 (0.00%)	2 / 13 (15.38%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	4 / 117 (3.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Costochondritis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fasciitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 50 (2.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			

subjects affected / exposed	4 / 50 (8.00%)	0 / 13 (0.00%)	7 / 117 (5.98%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Escherichia urinary tract infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis bacterial			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Metapneumovirus infection			

subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 50 (2.00%)	1 / 13 (7.69%)	9 / 117 (7.69%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parvovirus B19 infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
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 viral			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
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 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
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	1 / 50 (2.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Thrombophlebitis septic			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
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 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			

subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Age 2 to < 6 years,@8.5 mg/kg	Age 6 to < 12 years,@8.5 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)	20 / 40 (50.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Superficial vein thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	3 / 14 (21.43%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 14 (28.57%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			

subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute chest syndrome			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (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	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Human rhinovirus test positive			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Brain herniation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status migrainosus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 14 (7.14%)	5 / 40 (12.50%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric lymphadenitis			

subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	0 / 14 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 14 (21.43%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fasciitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			

subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 14 (0.00%)	3 / 40 (7.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	2 / 14 (14.29%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			

subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 14 (21.43%)	4 / 40 (10.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			

subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parvovirus B19 infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (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 / 14 (7.14%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (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	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis septic			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 14 (7.14%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Age 12 to < 18 years,@5 mg/kg	Age 6 to < 12 years,@5 mg/kg	All@Participants
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 50 (92.00%)	13 / 13 (100.00%)	108 / 117 (92.31%)
Vascular disorders			
Pallor			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	2 / 50 (4.00%)	0 / 13 (0.00%)	4 / 117 (3.42%)
occurrences (all)	3	0	6
Phlebitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	2 / 50 (4.00%)	0 / 13 (0.00%)	5 / 117 (4.27%)
occurrences (all)	3	0	6
Hyperthermia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	3 / 50 (6.00%)	0 / 13 (0.00%)	4 / 117 (3.42%)
occurrences (all)	5	0	6
Device related thrombosis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Chest pain			
subjects affected / exposed	3 / 50 (6.00%)	2 / 13 (15.38%)	10 / 117 (8.55%)
occurrences (all)	3	2	12
Malaise			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	12 / 50 (24.00%)	5 / 13 (38.46%)	38 / 117 (32.48%)
occurrences (all)	18	9	62
Pain			

subjects affected / exposed	2 / 50 (4.00%)	3 / 13 (23.08%)	11 / 117 (9.40%)
occurrences (all)	4	4	16
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	2	2
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	2 / 117 (1.71%)
occurrences (all)	0	0	2
Asthma exercise induced			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Adenoidal hypertrophy			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	5 / 50 (10.00%)	2 / 13 (15.38%)	21 / 117 (17.95%)
occurrences (all)	7	2	35
Pleural effusion			
subjects affected / exposed	1 / 50 (2.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences (all)	1	1	2
Oropharyngeal pain			
subjects affected / exposed	4 / 50 (8.00%)	1 / 13 (7.69%)	6 / 117 (5.13%)
occurrences (all)	5	2	10
Nasal congestion			
subjects affected / exposed	3 / 50 (6.00%)	1 / 13 (7.69%)	6 / 117 (5.13%)
occurrences (all)	4	1	9
Hypoxia			
subjects affected / exposed	2 / 50 (4.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences (all)	6	0	7
Epistaxis			
subjects affected / exposed	3 / 50 (6.00%)	3 / 13 (23.08%)	8 / 117 (6.84%)
occurrences (all)	4	3	9
Dyspnoea			

subjects affected / exposed	1 / 50 (2.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences (all)	2	1	3
Rhinitis allergic			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences (all)	1	0	3
Rhinorrhoea			
subjects affected / exposed	5 / 50 (10.00%)	1 / 13 (7.69%)	10 / 117 (8.55%)
occurrences (all)	8	1	13
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 50 (8.00%)	0 / 13 (0.00%)	5 / 117 (4.27%)
occurrences (all)	4	0	5
Insomnia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences (all)	5	0	5
Suicidal ideation			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	2 / 117 (1.71%)
occurrences (all)	0	0	8
Blood bilirubin increased			
subjects affected / exposed	3 / 50 (6.00%)	1 / 13 (7.69%)	5 / 117 (4.27%)
occurrences (all)	11	3	15
Cardiac murmur			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences (all)	0	1	2
C-reactive protein increased			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences (all)	0	0	4
Alanine aminotransferase increased			
subjects affected / exposed	2 / 50 (4.00%)	1 / 13 (7.69%)	5 / 117 (4.27%)
occurrences (all)	4	1	7
Amylase increased			

subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Anti factor Xa activity decreased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Arterial flow velocity increased			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 50 (6.00%)	2 / 13 (15.38%)	6 / 117 (5.13%)
occurrences (all)	5	5	11
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 50 (2.00%)	1 / 13 (7.69%)	3 / 117 (2.56%)
occurrences (all)	3	1	5
SARS-CoV-2 test positive			
subjects affected / exposed	3 / 50 (6.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
SARS-CoV-2 test negative			
subjects affected / exposed	12 / 50 (24.00%)	3 / 13 (23.08%)	15 / 117 (12.82%)
occurrences (all)	19	10	29
Polymerase chain reaction negative			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Lymphocyte count decreased			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Influenza virus test negative			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Influenza A virus test negative			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Epstein-Barr virus test positive			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
International normalised ratio increased			
subjects affected / exposed	1 / 50 (2.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences (all)	1	1	2
Injury, poisoning and procedural complications			
Eye contusion			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Eye injury			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Femur fracture			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Infusion related reaction			
subjects affected / exposed	4 / 50 (8.00%)	2 / 13 (15.38%)	10 / 117 (8.55%)
occurrences (all)	5	3	13
Joint injury			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences (all)	0	1	2
Limb injury			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences (all)	0	0	3
Nasal injury			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Penis injury			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Skeletal injury			

subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Vascular access complication			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Right ventricular enlargement			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 50 (10.00%)	1 / 13 (7.69%)	7 / 117 (5.98%)
occurrences (all)	7	1	9
Headache			
subjects affected / exposed	19 / 50 (38.00%)	4 / 13 (30.77%)	36 / 117 (30.77%)
occurrences (all)	30	4	52
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	6 / 117 (5.13%)
occurrences (all)	1	0	7
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	2 / 117 (1.71%)
occurrences (all)	0	0	2
Lymphocytosis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Leukocytosis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	2 / 117 (1.71%)
occurrences (all)	0	0	5
Anaemia			
subjects affected / exposed	8 / 50 (16.00%)	1 / 13 (7.69%)	16 / 117 (13.68%)
occurrences (all)	8	1	24
Thrombocytopenia			

subjects affected / exposed	0 / 50 (0.00%)	2 / 13 (15.38%)	4 / 117 (3.42%)
occurrences (all)	0	2	4
Thrombocytosis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	6 / 117 (5.13%)
occurrences (all)	0	0	6
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Ear pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences (all)	0	1	3
Eye disorders			
Xerophthalmia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 50 (20.00%)	5 / 13 (38.46%)	28 / 117 (23.93%)
occurrences (all)	14	5	34
Abdominal pain upper			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	4 / 117 (3.42%)
occurrences (all)	1	0	6
Constipation			
subjects affected / exposed	9 / 50 (18.00%)	3 / 13 (23.08%)	20 / 117 (17.09%)
occurrences (all)	11	4	24
Diarrhoea			
subjects affected / exposed	5 / 50 (10.00%)	1 / 13 (7.69%)	13 / 117 (11.11%)
occurrences (all)	6	1	16
Vomiting			
subjects affected / exposed	14 / 50 (28.00%)	2 / 13 (15.38%)	21 / 117 (17.95%)
occurrences (all)	21	3	31
Gastrointestinal disorder			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Nausea			

subjects affected / exposed	9 / 50 (18.00%)	0 / 13 (0.00%)	14 / 117 (11.97%)
occurrences (all)	17	0	23
Odynophagia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	2 / 50 (4.00%)	1 / 13 (7.69%)	3 / 117 (2.56%)
occurrences (all)	2	1	3
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 50 (2.00%)	1 / 13 (7.69%)	5 / 117 (4.27%)
occurrences (all)	1	1	5
Cholecystitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Biliary colic			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Hypertransaminasaemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Jaundice			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 50 (2.00%)	1 / 13 (7.69%)	4 / 117 (3.42%)
occurrences (all)	1	1	4
Pruritus			
subjects affected / exposed	4 / 50 (8.00%)	1 / 13 (7.69%)	5 / 117 (4.27%)
occurrences (all)	5	1	6
Nail dystrophy			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Urticaria			

subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 50 (6.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences (all)	5	0	5
Dysuria			
subjects affected / exposed	3 / 50 (6.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 50 (2.00%)	2 / 13 (15.38%)	5 / 117 (4.27%)
occurrences (all)	1	2	6
Mobility decreased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Bone pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences (all)	1	0	3
Bone infarction			
subjects affected / exposed	1 / 50 (2.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences (all)	1	1	2
Back pain			
subjects affected / exposed	11 / 50 (22.00%)	2 / 13 (15.38%)	26 / 117 (22.22%)
occurrences (all)	31	15	80
Arthralgia			
subjects affected / exposed	11 / 50 (22.00%)	1 / 13 (7.69%)	20 / 117 (17.09%)
occurrences (all)	17	7	38
Myalgia			
subjects affected / exposed	3 / 50 (6.00%)	1 / 13 (7.69%)	6 / 117 (5.13%)
occurrences (all)	4	2	8
Neck pain			
subjects affected / exposed	2 / 50 (4.00%)	0 / 13 (0.00%)	4 / 117 (3.42%)
occurrences (all)	2	0	4
Spinal pain			

subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences (all)	0	1	2
Pain in extremity			
subjects affected / exposed	11 / 50 (22.00%)	3 / 13 (23.08%)	27 / 117 (23.08%)
occurrences (all)	21	4	53
Osteonecrosis			
subjects affected / exposed	4 / 50 (8.00%)	0 / 13 (0.00%)	7 / 117 (5.98%)
occurrences (all)	4	0	7
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences (all)	0	1	2
Nasopharyngitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	5 / 117 (4.27%)
occurrences (all)	0	0	6
Influenza			
subjects affected / exposed	2 / 50 (4.00%)	2 / 13 (15.38%)	12 / 117 (10.26%)
occurrences (all)	2	2	14
Gastroenteritis			
subjects affected / exposed	3 / 50 (6.00%)	0 / 13 (0.00%)	6 / 117 (5.13%)
occurrences (all)	3	0	6
Conjunctivitis			
subjects affected / exposed	1 / 50 (2.00%)	1 / 13 (7.69%)	3 / 117 (2.56%)
occurrences (all)	1	1	3
COVID-19			
subjects affected / exposed	11 / 50 (22.00%)	1 / 13 (7.69%)	18 / 117 (15.38%)
occurrences (all)	14	1	21
Bronchitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences (all)	0	1	2
Eye infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	1 / 50 (2.00%)	2 / 13 (15.38%)	5 / 117 (4.27%)
occurrences (all)	1	2	6

Suspected COVID-19			
subjects affected / exposed	3 / 50 (6.00%)	1 / 13 (7.69%)	4 / 117 (3.42%)
occurrences (all)	3	1	4
Tonsillitis			
subjects affected / exposed	1 / 50 (2.00%)	2 / 13 (15.38%)	6 / 117 (5.13%)
occurrences (all)	1	2	6
Upper respiratory tract infection			
subjects affected / exposed	9 / 50 (18.00%)	1 / 13 (7.69%)	16 / 117 (13.68%)
occurrences (all)	11	2	25
Urinary tract infection			
subjects affected / exposed	6 / 50 (12.00%)	1 / 13 (7.69%)	11 / 117 (9.40%)
occurrences (all)	9	1	14
Rhinitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	3	3
Respiratory tract infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	4 / 117 (3.42%)
occurrences (all)	1	0	4
Pneumonia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 13 (0.00%)	9 / 117 (7.69%)
occurrences (all)	3	0	10
Pharyngitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	2 / 117 (1.71%)
occurrences (all)	0	3	4
Otitis media			
subjects affected / exposed	1 / 50 (2.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences (all)	1	0	3
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences (all)	0	0	4
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	2 / 50 (4.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences (all)	2	0	3
Vitamin D deficiency			
subjects affected / exposed	0 / 50 (0.00%)	0 / 13 (0.00%)	2 / 117 (1.71%)
occurrences (all)	0	0	2
Iron deficiency			
subjects affected / exposed	0 / 50 (0.00%)	1 / 13 (7.69%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Hypokalaemia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 13 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3

Non-serious adverse events	Age 2 to < 6 years,@8.5 mg/kg	Age 6 to < 12 years,@8.5 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 14 (92.86%)	36 / 40 (90.00%)	
Vascular disorders			
Pallor			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Hypertension			
subjects affected / exposed	2 / 14 (14.29%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Phlebitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 14 (7.14%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Hyperthermia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Device related thrombosis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Chest pain			
subjects affected / exposed	1 / 14 (7.14%)	4 / 40 (10.00%)	
occurrences (all)	1	6	
Malaise			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	5 / 14 (35.71%)	16 / 40 (40.00%)	
occurrences (all)	7	28	
Pain			
subjects affected / exposed	2 / 14 (14.29%)	4 / 40 (10.00%)	
occurrences (all)	2	6	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	2 / 14 (14.29%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Asthma exercise induced			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Adenoidal hypertrophy			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	5 / 14 (35.71%)	9 / 40 (22.50%)	
occurrences (all)	13	13	
Pleural effusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			

subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	3	
Nasal congestion			
subjects affected / exposed	0 / 14 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	4	
Hypoxia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Rhinitis allergic			
subjects affected / exposed	1 / 14 (7.14%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Rhinorrhoea			
subjects affected / exposed	2 / 14 (14.29%)	2 / 40 (5.00%)	
occurrences (all)	2	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Suicidal ideation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 40 (2.50%)	
occurrences (all)	7	1	
Blood bilirubin increased			

subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)		
occurrences (all)	0	1		
Cardiac murmur				
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)		
occurrences (all)	0	1		
C-reactive protein increased				
subjects affected / exposed	2 / 14 (14.29%)	1 / 40 (2.50%)		
occurrences (all)	3	1		
Alanine aminotransferase increased				
subjects affected / exposed	0 / 14 (0.00%)	2 / 40 (5.00%)		
occurrences (all)	0	2		
Amylase increased				
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)		
occurrences (all)	0	0		
Anti factor Xa activity decreased				
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)		
occurrences (all)	0	0		
Arterial flow velocity increased				
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)		
occurrences (all)	1	0		
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)		
occurrences (all)	0	1		
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)		
occurrences (all)	1	0		
SARS-CoV-2 test positive				
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)		
occurrences (all)	0	0		
SARS-CoV-2 test negative				
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)		
occurrences (all)	0	0		
Polymerase chain reaction negative				
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)		
occurrences (all)	0	0		

Lymphocyte count decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Influenza virus test negative			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Influenza A virus test negative			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Epstein-Barr virus test positive			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
International normalised ratio increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Eye contusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Eye injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Femur fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Infusion related reaction			
subjects affected / exposed	1 / 14 (7.14%)	3 / 40 (7.50%)	
occurrences (all)	1	4	
Joint injury			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Limb injury			

subjects affected / exposed	1 / 14 (7.14%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Nasal injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Penis injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Skeletal injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Vascular access complication			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Right ventricular enlargement			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	3 / 14 (21.43%)	10 / 40 (25.00%)	
occurrences (all)	4	14	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 14 (14.29%)	3 / 40 (7.50%)	
occurrences (all)	2	4	
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Lymphocytosis			

subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Leukocytosis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 40 (2.50%)	
occurrences (all)	4	1	
Anaemia			
subjects affected / exposed	3 / 14 (21.43%)	4 / 40 (10.00%)	
occurrences (all)	8	7	
Thrombocytopenia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Thrombocytosis			
subjects affected / exposed	2 / 14 (14.29%)	4 / 40 (10.00%)	
occurrences (all)	2	4	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Ear pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	2	
Eye disorders			
Xerophthalmia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)	12 / 40 (30.00%)	
occurrences (all)	1	14	
Abdominal pain upper			
subjects affected / exposed	0 / 14 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	5	
Constipation			
subjects affected / exposed	2 / 14 (14.29%)	6 / 40 (15.00%)	
occurrences (all)	2	7	
Diarrhoea			

subjects affected / exposed	2 / 14 (14.29%)	5 / 40 (12.50%)	
occurrences (all)	4	5	
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)	4 / 40 (10.00%)	
occurrences (all)	2	5	
Gastrointestinal disorder			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 14 (0.00%)	5 / 40 (12.50%)	
occurrences (all)	0	6	
Odynophagia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 14 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Cholecystitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Biliary colic			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Jaundice			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	0 / 14 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Nail dystrophy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Urticaria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Dysuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 40 (2.50%)	
occurrences (all)	1	2	
Mobility decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Bone pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Bone infarction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	4 / 14 (28.57%)	9 / 40 (22.50%)	
occurrences (all)	7	27	
Arthralgia			

subjects affected / exposed	1 / 14 (7.14%)	7 / 40 (17.50%)	
occurrences (all)	1	13	
Myalgia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Neck pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Spinal pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	3 / 14 (21.43%)	10 / 40 (25.00%)	
occurrences (all)	3	25	
Osteonecrosis			
subjects affected / exposed	0 / 14 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	3 / 14 (21.43%)	2 / 40 (5.00%)	
occurrences (all)	4	2	
Influenza			
subjects affected / exposed	0 / 14 (0.00%)	8 / 40 (20.00%)	
occurrences (all)	0	10	
Gastroenteritis			
subjects affected / exposed	0 / 14 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Conjunctivitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
COVID-19			
subjects affected / exposed	2 / 14 (14.29%)	4 / 40 (10.00%)	
occurrences (all)	2	4	

Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Eye infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Suspected COVID-19			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Tonsillitis			
subjects affected / exposed	1 / 14 (7.14%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Upper respiratory tract infection			
subjects affected / exposed	4 / 14 (28.57%)	2 / 40 (5.00%)	
occurrences (all)	9	3	
Urinary tract infection			
subjects affected / exposed	3 / 14 (21.43%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Rhinitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection			
subjects affected / exposed	2 / 14 (14.29%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)	5 / 40 (12.50%)	
occurrences (all)	1	6	
Pharyngitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	

Otitis media			
subjects affected / exposed	1 / 14 (7.14%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	2 / 40 (5.00%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 14 (7.14%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	2 / 14 (14.29%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Iron deficiency			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Hypokalaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2018	1. To update inclusion criteria: for participants receiving HU/HC: dose alterations of HU/HC performed during part A were not allowed to avoid any potential influence with the study treatment and PK results. Participants with active HIV were excluded as immunological effects of crizanlizumab were not sufficiently explored so far. 2. Addition of a DMC to be in charge of the review of the key safety and PK data review at each dosing confirmation in Part A including the recommendation to open the next age group and to open enrolment in Part B to ensure pediatric participant safety was monitored. 3. Pregnancy test was extended to all females of childbearing potential. 4. To update the declaration of Helsinki directive to fit to the last directive version (Art. 3 Par. 2 of the Directive 2005/28/EC).
29 January 2020	1. To update study objectives in order to - Modify the wording of the PK/PD endpoint for Part A to account for potential participants who had study treatment interruptions prior to Week 15, where multiple dose was defined as 3 consecutives doses (not including the loading dose at Week 3 Day 1) in the primary objective. - Change the wording "number of" to "annualized rate of" in the secondary objectives to account for participants who had not completed the full treatment period and standardize the outputs to one-year time-frame. This applied to all the secondary objectives to assess the long-term efficacy of crizanlizumab in 6 months to < 18-year-old participants at the time of study entry and to the RBC transfusions exploratory objective. - Include assessment of PK/PD at the time of transfusions as part of the exploratory objectives. 2. Risk benefit section has been updated to include information on immunogenicity and interference with automated platelets counts in line with the current version of the IB. 3. QTcF prolongation section had been removed, based on the current safety profile of crizanlizumab showing no QT liability as supported by absence of clinically relevant effect on QTc in SCD participants treated with crizanlizumab based on PK-QT analysis and assessment of safety as listed in the current IB.
30 March 2021	The primary purpose of this amendment was to update the requirement for a 105-days post-treatment follow-up visit for all participants. The intention of the 105-day post-treatment follow-up period was to capture any potential AEs including development of ADAs following discontinuation from study treatment, taking into account the half-life of the drug. This amendment clarified that participants continuing crizanlizumab after the EOT visit, via commercial supply or post-trial access (e.g. enrollment in a Novartis roll-over protocol to provide continued drug treatment) would not have to perform the 105-days post-treatment follow-up visit in this study.

21 July 2021	1. To update and clarify the criteria used for dose confirmation following single-dose analysis in Part A of each group. The decision was based on first dose PK results, key safety data, and Novartis's assessment in conjunction with DMC recommendations. This amendment allowed evaluation of the newly defined dose in a new cohort of participants enrolled into Group 2 Part A (see study status above). 2. To include some language to address COVID-19-related changes to study conduct and allow some flexibility when needed. Recommendations for handling of study treatment in case of active or suspected COVID-19 infection were added. 3. To consider uptake of voxelotor within 30 days of screening or plan to start voxelotor during the course of the study as an exclusion criterion. A wash-out period of 30 days was required prior to screening to prevent impact on the results. 4. To modify guidance given to manage infusion-related reactions and corresponding dose interruption and re-initiation. Pre-medication prophylaxis against IRRs had been revised and was now allowed.
31 March 2022	The primary purpose of this amendment was to: • update the options of post-trial access for participants in this trial who continue to derive clinical benefit from the treatment based on the Investigator's evaluation. The post-trial access language was revised to reflect the options available to participants to continue treatment after completion of the study. This may include access to Novartis investigational product in a rollover protocol or provision of the Novartis investigational product in a non-trial setting (known as post-study drug supply [PSDS]) when no further safety or efficacy data are required, or any other mechanism appropriate as per the country regulations. • update the risks and benefits of treatment with crizanlizumab to reflect the most recent available clinical data. • align with the requirements of EU Clinical Trial Regulation (EU CTR) to accommodate the transfer of the study under this regulation.
14 March 2024	The primary purpose of this protocol amendment was to amend the study plan by not extending it to the cohort of Group 3 Part B as Novartis no longer intended to enroll participants in Group 3 Part B (6 months to 6 years) of the trial. The rationale for cancelling the Group 3 Part B was to focus on age groups where the manifestation of Sickle Cell Disease (SCD) and the feasibility of intervention assessment were more suitable. The original study plan required at least 8 participants aged 2-<6 years to evaluate and determine the age-appropriate dose. Fourteen participants had already been enrolled in Group 3 Part A (participants 2 to <6 years), that were expected to provide sufficient data to study the PK parameters for this age group. Study of the youngest age group (6 months to < 24 months) had been withdrawn in its entirety due to the revocation of the conditional marketing authorization of crizanlizumab in the EU and UK. Therefore, Novartis decided not to study crizanlizumab for the reduction of VOCs in additional participants with SCD below the age of 6 years, as very young children with SCD are less likely to experience frequent vaso-occlusive crises (VOC) episodes compared to older children, adolescents, and adults.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported