Clinical trial results:
A Phase II, multicenter, randomized, open label two arm study evaluating the effect
of crizanlizumab + standard of care and standard of care alone on renal function in sickle cell
disease patients 16 years with chronic kidney disease due to sickle cell nephropathy
(STEADFAST)

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

Summary

EudraCT number	2018-003608-38
Trial protocol	GB GR ES FR IT NL IE
Global end of trial date	20 March 2023

Results information

Result version number	v1 (current)
This version publication date	05 April 2024
First version publication date	05 April 2024

Trial information

Trial identification

Sponsor protocol code	CSEG101A2203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04053764
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, 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	20 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on albuminuria (albumin to creatinine ratio, ACR) decrease at 12 months, as assessed by the proportion of patients with ≥ 30% decrease in ACR at 12 months from baseline.

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	10 December 2019
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	Brazil: 8
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Lebanon: 1
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Panama: 1
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Türkiye: 17

Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	58
EEA total number of subjects	18

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	58
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled in 24 centers in 11 countries.

Pre-assignment

Screening details:

Patients were stratified at randomization based on CKD risk category (moderate risk or high/very high risk) and HU/HC use (Yes/No).
At visit "Week 1 Day 1" all eligible patients were randomized via IRT to one of the treatment arms.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Crizanlizumab + Standard of Care

Arm description:

5 mg/kg by intravenous (i.v.) infusion at Week 1 Day 1, Week 3 Day 1 and Day 1 of every 4-week cycle until Week 51 in addition to their usual standard of care treatment.

Arm type	Experimental
Investigational medicinal product name	HU/HC, ACE inhibitors, and/or ARBs
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

IV as the drug insert for use

Investigational medicinal product name	Crizanlizumab
Investigational medicinal product code	SEG101
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg IV

Arm title	Standard of Care (SOC)

Arm description:

Patients in the standard of care alone arm will continue to receive their usual standard of care treatment.

Arm type	Active comparator
Investigational medicinal product name	HU/HC, ACE inhibitors, and/or ARBs
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

IV as the drug insert for use

Number of subjects in period 1	Crizanlizumab + Standard of Care	Standard of Care (SOC)
Started	30	28
Entered post-treatment f/u, discontinued	7 [1]	1 [2]
Did not enter post-treatment follow-up	3 [3]	2 [4]
Not Treated	1 [5]	0 [6]
Completed	20	25
Not completed	10	3
Consent withdrawn by subject	6	2
Physician decision	2	1
Adverse event, non-fatal	1	-
Pregnancy	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Numbers reported for these milestones are for informational purposes only.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Numbers reported for these milestones are for informational purposes only.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Numbers reported for these milestones are for informational purposes only.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Numbers reported for these milestones are for informational purposes only.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Numbers reported for these milestones are just for informational purposes

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Numbers reported for these milestones are for informational purposes only.

Baseline characteristics

Reporting groups

Reporting group title	Crizanlizumab + Standard of Care
Reporting group description:	
5 mg/kg by intravenous (i.v.) infusion at Week 1 Day 1, Week 3 Day 1 and Day 1 of every 4-week cycle until Week 51 in addition to their usual standard of care treatment.	
Reporting group title	Standard of Care (SOC)
Reporting group description:	
Patients in the standard of care alone arm will continue to receive their usual standard of care treatment.	

Reporting group values	Crizanlizumab + Standard of Care	Standard of Care (SOC)	Total
Number of subjects	30	28	58
Age categorical			
Units: Subjects			
Adults (18-64 years)	30	28	58
Age Continuous			
Units: Years			
arithmetic mean	41.8	41.1	
standard deviation	± 9.52	± 8.71	-
Sex: Female, Male			
Units: Participants			
Female	20	17	37
Male	10	11	21
Race/Ethnicity, Customized			
Units: Subjects			
Black or African American	15	15	30
White	15	12	27
Multiple	0	1	1

End points

End points reporting groups

Reporting group title	Crizanlizumab + Standard of Care
Reporting group description:	
5 mg/kg by intravenous (i.v.) infusion at Week 1 Day 1, Week 3 Day 1 and Day 1 of every 4-week cycle until Week 51 in addition to their usual standard of care treatment.	
Reporting group title	Standard of Care (SOC)
Reporting group description:	
Patients in the standard of care alone arm will continue to receive their usual standard of care treatment.	
Subject analysis set title	All Patients
Subject analysis set type	Full analysis
Subject analysis set description:	
All the participants enrolled in the trial.	
Subject analysis set title	crizanlizumab + standard of care
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
5 mg/kg by intravenous (i.v.) infusion at Week 1 Day 1, Week 3 Day 1 and Day 1 of every 4-week cycle until Week 51 in addition to their usual standard of care treatment.	

Primary: Percentage of participants with ≥ 30% decrease in albuminuria (ACR) at 12 months

End point title	Percentage of participants with ≥ 30% decrease in albuminuria (ACR) at 12 months
End point description:	
The effect of SEG101 on clinical disease activity was measured by at least 30% decrease in Albumin to Creatinine Ratio (ACR) from baseline to month 12. A reduction from baseline indicates improvement in patients.	
End point type	Primary
End point timeframe:	
Baseline to 12 months	

End point values	Crizanlizumab + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	28		
Units: participants	10	6		

Statistical analyses

Statistical analysis title	Decrease in albuminuria at 12 months
Comparison groups	Crizanlizumab + Standard of Care v Standard of Care (SOC)

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	7.14

Secondary: Change from baseline in albuminuria (ACR) at 3, 6, 9 and 12 months

End point title	Change from baseline in albuminuria (ACR) at 3, 6, 9 and 12 months

End point description:

The effect of SEG101 on clinical disease activity was measured was measured by the change in albuminuria (ACR) between baseline and month 3, baseline and month 6, baseline and month 9, baseline and month 12. A reduction from baseline indicates improvement in patients.

End point type	Secondary

End point timeframe:

Baseline to 3, 6, 9, and 12 months

End point values	Crizanlizumab + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	28		
Units: mg/g				
arithmetic mean (standard deviation)				
Baseline (BL)	597.0 (± 534.3)	499.0 (± 486.7)		
Month 3 change from BL (n = 26, 27)	-56.9 (± 362.8)	159.0 (± 809.9)		
Month 6 change from BL (n = 23, 25)	-98.5 (± 382.2)	-35.4 (± 384.4)		
Month 9 change from BL (n = 23, 24)	-12.3 (± 586.6)	95.2 (± 376.2)		
Month 12 change from BL (n = 21, 24	17.7 (± 620.7)	14.7 (± 307.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with ≥ 30% decrease in albuminuria (ACR) at 6 months

End point title	Percentage of participants with ≥ 30% decrease in albuminuria (ACR) at 6 months

End point description:

The effect of SEG101 on clinical disease activity was measured by at least 30% decrease in Albumin to Creatinine Ratio (ACR) from baseline to month 6. A reduction from baseline indicates improvement in patients.

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Crizanlizumab + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	28		
Units: Percentage of participants				
number (not applicable)	30.0	35.7		

Statistical analyses

Statistical analysis title	Decrease in albuminuria at 6 months
Comparison groups	Crizanlizumab + Standard of Care v Standard of Care (SOC)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	2.31

Secondary: Percentage of participants with Protein/creatinine ratio (PCR) improvement and stable PCR at 12 months

End point title	Percentage of participants with Protein/creatinine ratio (PCR) improvement and stable PCR at 12 months

End point description:

The effect of SEG101 on clinical disease activity was measured by counting patients who had Stable PCR: within ± 20% change from baseline to month 12. PCR improvement: ≥ 20% decrease in PCR from baseline indicates improvement in patients.

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Crizanlizumab + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	28		
Units: Percentage of participants				
number (not applicable)				
% of subjects with PCR improvement at 12 months	33.3	35.7		
% of subjects with stable PCR at 12 months	16.7	25.0		

Statistical analyses

Statistical analysis title	PCR Improvement 2
Statistical analysis description:	
Stable PCR	
Comparison groups	Crizanlizumab + Standard of Care v Standard of Care (SOC)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	3.2

Statistical analysis title	PCR Improvement
Comparison groups	Crizanlizumab + Standard of Care v Standard of Care (SOC)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	3.02

Secondary: Percentage change in estimated glomerular filtration rate (eGFR)

End point title	Percentage change in estimated glomerular filtration rate (eGFR)

End point description:

The effect of SEG101 on clinical disease activity was measured by at least 30% decrease in Albumin to Creatinine Ratio (ACR) from baseline to month 6. The percentage change in eGFR was calculated as the post-baseline eGFR value minus the baseline eGFR divided by the eGFR at baseline. A reduction from baseline indicates improvement in participants.

End point type	Secondary

End point timeframe:

Baseline to 3, 6, 9, and 12 months

End point values	Crizanlizumab + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	28		
Units: Percentage change in eGFR				
arithmetic mean (standard deviation)				
Baseline (BL) (n = 28, 28)	107.9 (± 28.0)	102.5 (± 23.2)		
Month 3 change from BL (n = 24, 26)	-2.5 (± 8.9)	-0.5 (± 10.0)		
Month 6 change from BL (n = 21, 25)	-2.7 (± 5.5)	-7.3 (± 12.7)		
Month 9 change from BL (n = 23,23)	-0.2 (± 12.8)	-2.7 (± 8.7)		
Month 12 change from BL (n =16, 24)	-4.9 (± 14.1)	-6.3 (± 13.2)		

Statistical analyses

Statistical analysis title	eGFR

Statistical analysis description:

From baseline to 3 months

Comparison groups	Crizanlizumab + Standard of Care v Standard of Care (SOC)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.53
upper limit	4.65
Variability estimate	Standard error of the mean
Dispersion value	2.53

Statistical analysis title	eGFR 2

Statistical analysis description:

From baseline to 6 months

Comparison groups	Crizanlizumab + Standard of Care v Standard of Care (SOC)

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	4.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.02
upper limit	11.4
Variability estimate	Standard error of the mean
Dispersion value	3.32

Statistical analysis title	eGFR 3
Statistical analysis description:	
From baseline to 9 months	
Comparison groups	Crizanlizumab + Standard of Care v Standard of Care (SOC)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	4.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.58
upper limit	11.68
Variability estimate	Standard error of the mean
Dispersion value	3.77

Statistical analysis title	eGFR 4
Statistical analysis description:	
From baseline to 12 months	
Comparison groups	Crizanlizumab + Standard of Care v Standard of Care (SOC)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	5.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.28
upper limit	13.67
Variability estimate	Standard error of the mean
Dispersion value	4.17

Secondary: Slope of albumin to creatinine ratio (ACR) decline

End point title	Slope of albumin to creatinine ratio (ACR) decline
End point description:	
The effect of SEG101 on clinical disease activity was measured by the slope of ACR between baseline and Month 12. A reduction from baseline indicates improvement in patients.	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Crizanlizumab + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: ACR decline rate				
least squares mean (standard error)	1.70 (± 8.655)	4.49 (± 8.159)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with progression of chronic kidney disease (CKD) at 12 months

End point title	Percentage of participants with progression of chronic kidney disease (CKD) at 12 months
End point description:	

The effect of SEG101 on clinical disease activity was measured by percentage of participants with CKD progression between baseline and Month 12. A reduction from baseline indicates improvement in participants.
CKD progression is defined as an increase in CKD progression category, a 25% or greater drop in eGFR from baseline or at least 50% increase in ACR for patients with severe (A3) albuminuria and a doubling of albumin levels in patients with moderate (A2) albuminuria.

End point type	Secondary
End point timeframe:	
Baseline to 12 months	

End point values	Crizanlizumab + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	28		
Units: Percentage of participants				
number (not applicable)	13.3	32.1		

Statistical analyses

Statistical analysis title	Progression of CKD
Comparison groups	Crizanlizumab + Standard of Care v Standard of Care (SOC)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	1.21

Secondary: Slope of estimated glomerular filtration rate (eGFR) decline

End point title	Slope of estimated glomerular filtration rate (eGFR) decline

End point description:

The effect of SEG101 on clinical disease activity was measured by the slope of eGFR between baseline and Month 12. The calculation of eGFR is based on the chronic kidney disease epidemiology collaboration (CKD-EPI) (for patients ≥ 18) and Creatinine-based "Bedside Schwartz" (for patients < 18) equations. A reduction in drop rate from baseline indicates improvement in patients.

End point type	Secondary

End point timeframe:

Baseline to 12 months

End point values	Crizanlizumab + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: eGFR decline rate				
least squares mean (standard error)	-0.1 (± 0.18)	-0.4 (± 0.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Shift table for Chronic kidney disease (CKD) progression

End point title	Shift table for Chronic kidney disease (CKD) progression

End point description:

The effect of SEG101 on clinical disease activity was measured by percentage of participants with CKD progression between baseline and Month 12. A reduction from baseline indicates improvement in patients.

End point type	Secondary

End point timeframe:

Baseline and month 12

End point values	Crizanlizumab + Standard of Care	Standard of Care (SOC)	All Patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	30	28	58	
Units: Percentage of participants				
number (not applicable)				
Cat 0 at baseline (BL)	3.3	14.3	8.6	
Cat 0 at baseline to Cat 2 at Worst post-BL	100.0	75.0	80.0	
Cat 0 at baseline to Cat 3 at Worst post-BL	0	25.0	20.0	
Cat 0 at baseline to Cat 4 at Worst post-BL	0	0	0	
Cat 0 at baseline to Missing at Worst post-BL	0	0	0	
Cat 1 at baseline	36.7	53.6	44.8	
Cat 1 at baseline to Cat 2 at Worst post-BL	36.4	40.0	38.5	
Cat 1 at baseline to Cat 3 at Worst post-BL	45.5	53.3	50.0	
Cat 1 at baseline to Cat 4 at Worst post-BL	0	6.7	3.8	
Cat 1 at baseline to Missing at Worst post-BL	18.2	0	7.7	
Cat 2 at baseline	43.3	28.6	36.2	
Cat 2 at baseline to Cat 2 at Worst post-BL	15.4	12.5	14.3	
Cat 2 at baseline to Cat 3 at Worst post-BL	69.2	75.5	71.4	
Cat 2 at baseline to Cat 4 at Worst post-BL	7.7	12.5	9.5	
Cat 2 at baseline to Missing at Worst post-BL	7.7	0	4.8	
Cat 3 at baseline	6.7	3.6	5.2	
Cat 3 at baseline to Cat 2 at Worst post-BL	0	0	0	
Cat 3 at baseline to Cat 3 at Worst post-BL	50.0	0	33.3	
Cat 3 at baseline to Cat 4 at Worst post-BL	50.0	100.0	66.7	
Cat 3 at BL to Missing at Worst post-BL	0	0	0	
Cat 4 at baseline	0	0	0	
Cat 4 at baseline to Cat 2 at Worst post-BL	0	0	0	
Cat 4 at baseline to Cat 3 at Worst post-BL	0	0	0	

Cat 4 at baseline to Cat 4 at Worst post-BL	0	0	0	
Cat 4 at baseline to Missing at Worst post-BL	0	0	0	
Cat Missing at baseline	10.0	0	5.2	
Cat Missing baseline to Cat 2 at Worst post-BL	0	0	0	
Cat Missing baseline to Cat 3 at Worst post-BL	0	0	0	
Cat Missing baseline to Cat 4 at Worst post-BL	0	0	0	
Cat Missing baseline to Missing at Worst post-BL	100.0	0	100.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of participants with anti-drug antibodies (ADA) to crizanlizumab

End point title	Immunogenicity: Number of participants with anti-drug antibodies (ADA) to crizanlizumab[1]

End point description:

The effect of SEG101 on clinical disease activity was measured by percentage of participants shifted to different worst post-baseline categories between baseline and Month 12. An increase in percentage shifting from higher category to lower category indicates improvement in patients.
Baseline is defined as the last non-missing value prior to the first dose.

End point type	Secondary

End point timeframe:

Baseline to follow-up period (at select time points), assessed up to approximately 1 year and 4 months

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK was assessed for only arm with experimental drug, not comparison drug.

End point values	Crizanlizumab + Standard of Care			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Percentage of participants				
number (not applicable)				
Negative at baseline to Only last sample positive	0			
Negative at baseline to Any positive	3.4			
Negative at baseline to All positive	0			
Negative at baseline to All Negative	89.7			
Negative at baseline to All Missing	6.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate of visits to emergency room (ER) and hospitalizations

End point title	Annualized rate of visits to emergency room (ER) and hospitalizations

End point description:

The effect of SEG101 on clinical disease activity was measured by summarizing the annualized rate of visits to ER and hospitalizations between baseline and 1 year 4 months. Annualized rate of hospitalizations and ER visits due to VOC =(Number of ER/hospitalizations reported until End date x 365.25)/(End date-date of first dose of study treatment+1). A reduction from baseline indicates improvement in patients.

End point type	Secondary

End point timeframe:

Baseline to follow-up period (at select time points), assessed up to approximately 1 year and 4 months

End point values	Crizanlizumab + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	28		
Units: rate/year				
arithmetic mean (standard deviation)	0.6 (± 2.1)	1.1 (± 3.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean serum concentration (Ctrough) of crizanlizumab

End point title	Mean serum concentration (Ctrough) of crizanlizumab

End point description:

The effect of SEG101 on clinical disease activity was measured by checking the concentration of the Drug in serum at different time points.
Crizanlizumab pre-dose/trough pharmacokinetic samples were taken at select time points.

End point type	Secondary

End point timeframe:

Pre-dose and 336 hours post-dose on Week 3 Day 1; pre-dose and 672 hours post dose on Week 11 Day 1, Week 23 Day 1 and Week 39 Day 1; and 672 hours post dose on Week 53 Day 1

End point values	crizanlizumab + standard of care			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 3 Day1: 0 hours pre-dose (n = 25)	11.6 (± 2.66)			

Week 3 Day1: 336 hours post-dose (n = 24)	12.1 (± 2.38)
Week 11 Day1: 0 hours pre-dose (n = 24)	4.78 (± 3.49)
Week 11 Day1: 672 hours post-dose (n = 23)	5.67 (± 3.11)
Week 23 Day1: 0 hours pre-dose (n = 23)	4.77 (± 2.82)
Week 23 Day1: 672 hours post-dose (n = 21)	5.54 (± 2.21)
Week 39 Day1: 0 hours pre-dose (n = 20)	5.55 (± 2.34)
Week 39 Day1: 672 hours post-dose (n = 17)	5.16 (± 2.10)
Week 53 Day1: 672 hours post-dose (n = 16)	15.2 (± 5.18)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment to 105 days after the last dose of study treatment with a median duration of exposure to crizanlizumab of 50.1 weeks.

Adverse event reporting additional description:

An Adverse Event is any sign or symptom that occurs during the conduct of the trial and safety follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Crizanlizumab + Standard of Care

Reporting group description:

mg/kg by intravenous (i.v.) infusion at Week 1 Day 1, Week 3 Day 1 and Day 1 of every 4-week cycle until Week 51 in addition to their usual standard of care treatment

Reporting group title	Staandard of Care (SOC)

Reporting group description:

Patients in the standard of care alone arm will continue to receive their usual standard of care treatment.

Reporting group title	All Participants

Reporting group description:

All Participants enrolled in the trial from whom safety was collected.

Serious adverse events	Crizanlizumab + Standard of Care	Staandard of Care (SOC)	All Participants
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 29 (6.90%)	2 / 28 (7.14%)	4 / 57 (7.02%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Hyperthyroidism			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	1 / 57 (1.75%)
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			
Influenza			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Crizanlizumab + Standard of Care	Staandard of Care (SOC)	All Participants
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 29 (72.41%)	19 / 28 (67.86%)	40 / 57 (70.18%)
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	2 / 57 (3.51%)
occurrences (all)	0	2	2
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 29 (20.69%)	4 / 28 (14.29%)	10 / 57 (17.54%)
occurrences (all)	8	5	13
Migraine			
subjects affected / exposed	2 / 29 (6.90%)	1 / 28 (3.57%)	3 / 57 (5.26%)
occurrences (all)	2	2	4
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 29 (10.34%)	2 / 28 (7.14%)	5 / 57 (8.77%)
occurrences (all)	6	2	8
Fatigue			
subjects affected / exposed	2 / 29 (6.90%)	3 / 28 (10.71%)	5 / 57 (8.77%)
occurrences (all)	2	4	6
Oedema peripheral			
subjects affected / exposed	0 / 29 (0.00%)	3 / 28 (10.71%)	3 / 57 (5.26%)
occurrences (all)	0	3	3

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	2 / 57 (3.51%)
occurrences (all)	0	2	2
Constipation			
subjects affected / exposed	3 / 29 (10.34%)	0 / 28 (0.00%)	3 / 57 (5.26%)
occurrences (all)	3	0	3
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	2 / 57 (3.51%)
occurrences (all)	3	0	3
Vomiting			
subjects affected / exposed	1 / 29 (3.45%)	7 / 28 (25.00%)	8 / 57 (14.04%)
occurrences (all)	2	8	10
Nausea			
subjects affected / exposed	4 / 29 (13.79%)	5 / 28 (17.86%)	9 / 57 (15.79%)
occurrences (all)	5	6	11
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	2 / 57 (3.51%)
occurrences (all)	0	2	2
Cough			
subjects affected / exposed	2 / 29 (6.90%)	4 / 28 (14.29%)	6 / 57 (10.53%)
occurrences (all)	2	5	7
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 29 (10.34%)	1 / 28 (3.57%)	4 / 57 (7.02%)
occurrences (all)	7	1	8
Dry skin			
subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	2 / 57 (3.51%)
occurrences (all)	3	0	3
Rash			
subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	2 / 57 (3.51%)
occurrences (all)	3	0	3
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	5 / 29 (17.24%)	3 / 28 (10.71%)	8 / 57 (14.04%)
occurrences (all)	7	4	11
Back pain			
subjects affected / exposed	3 / 29 (10.34%)	3 / 28 (10.71%)	6 / 57 (10.53%)
occurrences (all)	5	3	8
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	2 / 57 (3.51%)
occurrences (all)	3	0	3
Influenza			
subjects affected / exposed	4 / 29 (13.79%)	4 / 28 (14.29%)	8 / 57 (14.04%)
occurrences (all)	4	4	8
COVID-19			
subjects affected / exposed	7 / 29 (24.14%)	4 / 28 (14.29%)	11 / 57 (19.30%)
occurrences (all)	11	4	15
Pharyngitis			
subjects affected / exposed	2 / 29 (6.90%)	1 / 28 (3.57%)	3 / 57 (5.26%)
occurrences (all)	3	1	4
Urinary tract infection			
subjects affected / exposed	3 / 29 (10.34%)	0 / 28 (0.00%)	3 / 57 (5.26%)
occurrences (all)	4	0	4
Tooth infection			
subjects affected / exposed	4 / 29 (13.79%)	0 / 28 (0.00%)	4 / 57 (7.02%)
occurrences (all)	4	0	4
Subcutaneous abscess			
subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	2 / 57 (3.51%)
occurrences (all)	2	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2020	At the time of this amendment, 1 patient was enrolled in the study. The reasons why this amendment was undertaken was to refine the data collection for the assessment of the primary and secondary efficacy endpoints, reduce confounding factors, strengthen the primary estimand framework by providing additional clarity regarding the handling of intercurrent events and clarifying the summary measure and providing additional clarity on the management of infusion related reactions.
09 March 2021	At the time of this amendment, 23 patients had been enrolled. The primary purpose of this amendment was to broaden the inclusion/exclusion criteria to allow for greater patient eligibility, modify study assessments, update sample collection requirements to reduce patient burden based on current clinical practice in the management of SCD-related CKD and amend the statistical power and sample size calculation.
02 December 2021	At the time of this amendment, only 47 out of planned 148 patients were randomized after almost two years. A decision was made to stop recruitment (screening) by 17-Nov-2021, and all eligible patients were expected to be enrolled by 15-Dec-2021. This decision was not triggered by any new and/or unexpected safety concerns. The ongoing patients continued in the study until discontinuation or completion. The primary purpose of this amendment was to adjust the sample size and planned statistical analyses. As a result of the reduced sample size and low statistical power, no formal hypothesis testing was conducted, and descriptive statistics with the 95% confidence intervals were provided instead.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: