# 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<br>Units: Subjects | | | |
| Adults (18-64 years) | 30 | 28 | 58 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 41.8 | 41.1 | |
| standard deviation | ± 9.52 | ± 8.71 | - |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 20 | 17 | 37 |
| Male | 10 | 11 | 21 |
| Race/Ethnicity, Customized<br>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:<br>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:<br>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: 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 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:<br>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: Slope of estimated glomerular filtration rate (eGFR) decline

| End point title | Slope of estimated glomerular filtration rate (eGFR) decline |
|---|---|
| End point description:<br>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:<br>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:<br>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,<br>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.<br>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,<br>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<br>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: