## Clinical trial results:

# A 28-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center, study in recombinant human erythropoietin (rhEPO) naïve non-dialysis participants with anemia associated with chronic kidney disease to evaluate the efficacy, safety and effects on quality of life of daprodustat compared to placebo

### Summary

| | |
|---|---|
| EudraCT number | 2017-002270-39 |
| Trial protocol | GB ES PL IT RO |
| Global end of trial date | 07 October 2020 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 21 October 2021 |
| First version publication date | 21 October 2021 |

### Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 205270 |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, TW8 9GS |
| Public contact | GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com |
| Scientific contact | GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.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 | 22 February 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 07 October 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To compare the efficacy of daprodustat to placebo on mean change in hemoglobin (Hgb) levels
Secondary objectives of the trial:
To compare the proportion of participants achieving increases in Hgb when treated with daprodustat versus placebo;
To compare daprodustat to placebo for health related quality-of-life;
To compare daprodustat to placebo on additional Hgb endpoints;
To compare daprodustat to placebo on the time to rescue;
To compare daprodustat to placebo for improving symptoms of anemia of chronic kidney disease (CKD);
To compare daprodustat to placebo on the severity and change in symptoms;
To compare daprodustat to placebo for improving health related quality-of-life;
To compare daprodustat to placebo on improving work productivity and regular daily activity impairment;
To compare daprodustat to placebo on improving health status;
To compare daprodustat to placebo on blood pressure (BP)

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 05 March 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 21 |
| Country: Number of subjects enrolled | Brazil: 39 |
| Country: Number of subjects enrolled | Canada: 39 |
| Country: Number of subjects enrolled | Argentina: 26 |
| Country: Number of subjects enrolled | Korea, Republic of: 39 |
| Country: Number of subjects enrolled | Mexico: 105 |
| Country: Number of subjects enrolled | Russian Federation: 40 |
| Country: Number of subjects enrolled | United States: 172 |
| Country: Number of subjects enrolled | France: 15 |
| Country: Number of subjects enrolled | Italy: 21 |
| Country: Number of subjects enrolled | Poland: 31 |
| Country: Number of subjects enrolled | Romania: 47 |
| Country: Number of subjects enrolled | Spain: 1 |

| Country: Number of subjects enrolled | United Kingdom: 18 |
|---|---|
| Worldwide total number of subjects | 614 |
| EEA total number of subjects | 115 |

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) | 256 |
| From 65 to 84 years | 321 |
| 85 years and over | 37 |

# Subject disposition

## Recruitment

Recruitment details:

This was a multicenter study conducted at 142 centers in 14 countries. Participants were randomized to receive either Daprodustat or Placebo.

## Pre-assignment

Screening details:

A total of 1336 participants were screened, of which 722 were screen failures. A total of 614 participants were enrolled in the study.

## Period 1

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

### Arms

| Are arms mutually exclusive? | Yes |
|---|---|
| **Arm title** | Placebo |

Arm description:

Participants received matching placebo once daily orally for up to 28 weeks followed by 4 weeks of follow-up.

| Arm type | Placebo |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received matching placebo orally once daily.

| **Arm title** | Daprodustat |
|---|---|

Arm description:

Participants received daprodustat film-coated tablets with titrated dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 milligrams (mg) once daily orally for up to 28 weeks, followed by 4 weeks of follow-up. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (11 to 12 grams per deciliter [g/dL])

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Daprodustat |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received daprodustat film-coated tablets with titrated dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 milligrams (mg)
once daily orally.

| Number of subjects in period 1 | Placebo | Daprodustat |
|---|---|---|
| Started | 307 | 307 |
| Completed | 290 | 300 |
| Not completed | 17 | 7 |
| Consent withdrawn by subject | 4 | 2 |
| Physician decision | 1 | - |
| Adverse event, non-fatal | 5 | 3 |
| Lost to follow-up | 7 | 2 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Placebo |
|---|---|
| Reporting group description: | |
| Participants received matching placebo once daily orally for up to 28 weeks followed by 4 weeks of follow-up. | |
| Reporting group title | Daprodustat |
| Reporting group description: | |
| Participants received daprodustat film-coated tablets with titrated dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 milligrams (mg) once daily orally for up to 28 weeks, followed by 4 weeks of follow-up. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (11 to 12 grams per deciliter [g/dL]) | |

| Reporting group values | Placebo | Daprodustat | Total |
|---|---|---|---|
| Number of subjects | 307 | 307 | 614 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 121 | 135 | 256 |
| From 65-84 years | 165 | 156 | 321 |
| 85 years and over | 21 | 16 | 37 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 66.6 | 65.3 | |
| standard deviation | ± 12.93 | ± 13.43 | - |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 178 | 176 | 354 |
| Male | 129 | 131 | 260 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| AMERICAN INDIAN OR ALASKA NATIVE | 34 | 34 | 68 |
| ASIAN: CENTRAL/SOUTH ASIAN HERITAGE | 3 | 6 | 9 |
| ASIAN:JAPANESE/EAST(E). ASIAN/SOUTH E.ASIA HERITAGE | 24 | 24 | 48 |
| ASIAN: MIXED ASIAN RACE | 1 | 0 | 1 |
| BLACK OR AFRICAN AMERICAN | 47 | 44 | 91 |
| NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER | 1 | 0 | 1 |
| WHITE | 195 | 197 | 392 |
| BLACK OR AFRICAN AMERICAN AND WHITE | 2 | 2 | 4 |

## End points

### End points reporting groups

| Reporting group title | Placebo |
|---|---|
| Reporting group description: | |
| Participants received matching placebo once daily orally for up to 28 weeks followed by 4 weeks of follow-up. | |
| Reporting group title | Daprodustat |
| Reporting group description: | |
| Participants received daprodustat film-coated tablets with titrated dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 milligrams (mg) once daily orally for up to 28 weeks, followed by 4 weeks of follow-up. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (11 to 12 grams per deciliter [g/dL]) | |

### Primary: Mean change in hemoglobin from Baseline and over the evaluation period (mean over Week 24 and 28)

| End point title | Mean change in hemoglobin from Baseline and over the evaluation period (mean over Week 24 and 28) |
|---|---|
| End point description: | |

Blood samples were collected at given time points from participants for hemoglobin measurements. Evaluation period hemoglobin value was defined as the mean of all available post-randomization hemoglobin values (on and off-treatment) during the evaluation period (Week 24 to Week 28 inclusive). For the primary analysis, the missing post-Baseline hemoglobin values were imputed using pre-specified multiple imputations. Change from Baseline was defined as the average of post-randomization values during the evaluation period minus Baseline value. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Analysis was performed using the Analysis of Covariance (ANCOVA) model with terms for treatment, Baseline hemoglobin, and region. Intent-to-Treat (ITT) Population comprised all randomized participants regardless of whether they took study drug.

| End point type | Primary |
|---|---|
| End point timeframe: | |
| Baseline (Day 1) and Week 24 to Week 28 | |

| End point values | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 307[1] | 307[2] | | |
| Units: Grams per deciliter | | | | |
| least squares mean (standard error) | 0.19 (± 0.062) | 1.58 (± 0.061) | | |

Notes:

[1] - ITT Population

[2] - ITT Population

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Statistical analysis description: | |
| Treatment group comparisons were based on a ANCOVA model with terms for treatment, Baseline hemoglobin, and region. | |
| Comparison groups | Placebo v Daprodustat |

| Number of subjects included in analysis | 614 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [3] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | 1.4 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 1.23 |
|     upper limit | 1.56 |

Notes:

[3] - One-sided p-value based on test of null hypothesis: (Daprodustat - Placebo) <= 0 versus alternative: difference > 0.

## Secondary: Percentage of participants with hemoglobin increase of >=1.0 grams per deciliter from Baseline to evaluation period

| End point title | Percentage of participants with hemoglobin increase of >=1.0 grams per deciliter from Baseline to evaluation period |
|---|---|

End point description:

Blood samples were collected at given time points for hemoglobin measurements. Evaluation period hemoglobin value was defined as the mean of all available post-randomization hemoglobin values (on and off-treatment) during the evaluation period (Week 24 to Week 28 inclusive). For the primary analysis, the missing post-Baseline hemoglobin values were imputed using pre-specified multiple imputations. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Percentage of participants with hemoglobin increase of >=1.0 grams per deciliter from Baseline to evaluation period was analyzed using Cochran-Mantel-Haenszel (CMH) chi-squared test. The percentage values presented has been rounded off.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1) and Week 24 to Week 28

| **End point values** | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 307[4] | 307[5] | | |
| Units: Percentage of participants | 18 | 77 | | |

Notes:

[4] - ITT Population

[5] - ITT Population

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Treatment group comparisons were based on a Cochran-Mantel-Haenszel test adjusted for treatment group and region.

| Comparison groups | Placebo v Daprodustat |
|---|---|

| Number of subjects included in analysis | 614 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [6] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Response rate |
| Point estimate | 0.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 0.63 |

Notes:

[6] - One-sided p-value was based on test of null hypothesis: (Daprodustat - Placebo) <=0 versus alternative: difference > 0

## Secondary: Change from Baseline in short form-36 (SF-36) questionnaire vitality domain score by traditional scoring at Week 28

| End point title | Change from Baseline in short form-36 (SF-36) questionnaire vitality domain score by traditional scoring at Week 28 |
|---|---|

End point description:

The SF-36 acute version 2 is a 36-item generic quality of life instrument designed to measure a participant's level of performance in the 8 health domains: Physical Functioning, Role-Physical (role limitations caused by physical problems), Social Functioning, Bodily Pain, Mental Health, Role-Emotional (role limitations caused by emotional problems), Vitality, and General Perception of Health.Each domain is scored from 0 (poorer health) to 100 (better health). Vitality domain score ranges from 0-100; higher score indicates a better health state & better functioning. Change from Baseline was calculated as Post-Dose Visit Value at Week 28 minus Baseline. For primary analysis, the missing on-treatment Week 28 SF-36 Vitality domain scores were imputed using pre-specified multiple imputations. Baseline value was latest non-missing pre-dose assessment on or before randomization date. Analysis was performed using ANCOVA model with terms for treatment, Baseline score, and region.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1) and Week 28

| **End point values** | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 307[7] | 307[8] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | 1.93 (± 1.161) | 7.29 (± 1.121) | | |

Notes:

[7] - ITT Population

[8] - ITT Population

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis |
|---|---|

Statistical analysis description:

Treatment group comparisons were based on ANCOVA model with terms for treatment, Baseline score, and region.

| Comparison groups | Placebo v Daprodustat |
|---|---|

| Number of subjects included in analysis | 614 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0005 [9] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 5.36 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 2.17 |
|     upper limit | 8.56 |

Notes:

[9] - One-sided p-value based on test of null hypothesis:(Daprodustat-Placebo) <= 0 vs alternative: difference >0.

## Secondary: Percentage of participants with Hgb response (Hgb in the 11-12 grams/deciliter range) During Evaluation Period (Week 24 to Week 28 inclusive)

| End point title | Percentage of participants with Hgb response (Hgb in the 11-12 grams/deciliter range) During Evaluation Period (Week 24 to Week 28 inclusive) |
|---|---|

End point description:

Mean hemoglobin during the evaluation period was defined as the mean of all evaluable hemoglobin values during the evaluation period (Week 24 to Week 28 inclusive) including any evaluable unscheduled hemoglobin values that were taken during this period. Percentage of participants with Hgb response was defined as participants with mean Hgb within range (11-12 grams per deciliter during the evaluation period (Week 24 to Week 28 inclusive) and it was analyzed using Cochran-Mantel-Haenszel (CMH) chi-squared test. The percentage values presented has been rounded off.

| End point type | Secondary |
|---|---|

End point timeframe:

Week 24 to Week 28

| End point values | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 307[10] | 307[11] | | |
| Units: Percentage of participants | 8 | 52 | | |

Notes:

[10] - ITT Population

[11] - ITT Population

## Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|

Statistical analysis description:

Treatment group comparisons are based on a Cochran-Mantel-Haenszel test adjusted for treatment group, and region

| Comparison groups | Placebo v Daprodustat |
|---|---|

| Number of subjects included in analysis | 614 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [12] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Response rate |
| Point estimate | 0.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.37 |
| upper limit | 0.52 |

Notes:

[12] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative:
difference >0.

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**Secondary: Percentage of time with Hgb within the target range (11-12 grams per deciliter) During Evaluation Period (Week 24 to Week 28 inclusive) (Hodges-Lehmann Estimate)**

| End point title | Percentage of time with Hgb within the target range (11-12 grams per deciliter) During Evaluation Period (Week 24 to Week 28 inclusive) (Hodges-Lehmann Estimate) |
|---|---|

End point description:

Percentage of days for which participant's Hgb was within the target range of 11-12 grams per deciliter during the evaluation period (Week 24 to Week 28 inclusive), including any unscheduled evaluable Hgb values that were taken during this time period. Percentage of time for which Hgb was within the target range (11-12 grams per deciliter) for a participant was calculated by dividing 'the total number of days that Hgb was within range during Week 24 to 28' by 'the total number of days the participant remained on treatment during Week 24 to 28'. Only those participants with data available at the indicated time points were analyzed.

| End point type | Secondary |
|---|---|

End point timeframe:

Week 24 to Week 28

| **End point values** | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216[13] | 252[14] | | |
| Units: Percentage of days | | | | |
| median (full range (min-max)) | 0.00 (0.0 to 100.0) | 53.59 (0.0 to 100.0) | | |

Notes:

[13] - ITT Population

[14] - ITT Population

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis |
|---|---|
| Statistical analysis description: | |
| Hodges-Lehmann Estimate of treatment difference has been reported. | |
| Comparison groups | Placebo v Daprodustat |

| | |
|---|---|
| Number of subjects included in analysis | 468 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Hodges-Lehmann Estimate |
| Parameter estimate | Difference in treatment effect |
| Point estimate | 38.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 25 |
| upper limit | 54.55 |

## Secondary: Percentage of participants with Hgb response (Hgb in the 11-12 grams/deciliter range) During Evaluation Period (Week 24 to Week 28 inclusive) (Mann-Whitney Estimate)

| | |
|---|---|
| End point title | Percentage of participants with Hgb response (Hgb in the 11-12 grams/deciliter range) During Evaluation Period (Week 24 to Week 28 inclusive) (Mann-Whitney Estimate) |

End point description:

Percentage of days for which participant's Hgb was within the target range of 11-12 grams per deciliter during the evaluation period (Week 24 to Week 28 inclusive), including any unscheduled evaluable Hgb values that were taken during this time period. Percentage of time for which Hgb was within the target range (11-12 grams per deciliter) for a participant was calculated by dividing 'the total number of days that Hgb was within range during Week 24 to 28' by 'the total number of days the participant remained on treatment during Week 24 to 28'. Only those participants with data available at the indicated time points were analyzed.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Week 24 to Week 28

| End point values | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 216[15] | 252[16] | | |
| Units: Percentage of days | | | | |
| median (full range (min-max)) | 0.00 (0.0 to 100.0) | 53.59 (0.0 to 100.0) | | |

Notes:

[15] - ITT Population

[16] - ITT Population

## Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|

Statistical analysis description:

Mann-Whitney estimate of the treatment difference stratified by region has been presented.

| Comparison groups | Placebo v Daprodustat |
|---|---|

| Number of subjects included in analysis | 468 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [17] |
| Method | van Elteren test |
| Parameter estimate | Difference in treatment effect |
| Point estimate | 0.768 |
| Confidence interval | |
|    level | 95 % |
|    sides | 2-sided |
|    lower limit | 0.729 |
|    upper limit | 0.806 |

Notes:

[17] - One-sided superiority p-value from the van Elteren test

## Secondary: Change from Baseline in Post-randomization Hgb at Week 28

| End point title | Change from Baseline in Post-randomization Hgb at Week 28 |
|---|---|

End point description:

Blood samples were collected at given time points for hemoglobin measurements. Change from Baseline in Hgb was analyzed using a mixed model repeated measures (MMRM) approach. Change from Baseline was calculated as Post-dose visit value minus Baseline. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1) and Week 28

| **End point values** | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 301[18] | 299[19] | | |
| Units: Grams per deciliter | | | | |
| least squares mean (standard error) | 0.20 (± 0.070) | 1.56 (± 0.069) | | |

Notes:

[18] - ITT Population

[19] - ITT Population

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis |
|---|---|

Statistical analysis description:

Treatment group comparisons were based on MMRM fitted from baseline up to Week 28, with factors for treatment, time, region, Baseline Hb and Baseline Hb by time and treatment by time interactions.

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 600 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [20] |
| Method | MMRM |
| Parameter estimate | LS Mean difference |
| Point estimate | 1.36 |

| | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.16 |
| upper limit | 1.55 |

Notes:

[20] - One-sided superiority p-value from the MMRM model

## Secondary: Rate of participants permanently stopping randomized treatment due to meeting rescue criteria

| End point title | Rate of participants permanently stopping randomized treatment due to meeting rescue criteria |
|---|---|

End point description:

The incidence rate of participants permanently stopping randomized treatment due to meeting rescue criteria is presented.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to Week 28

| **End point values** | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 307[21] | 307[22] | | |
| Units: Events per 100 person year | | | | |
| number (confidence interval 95%) | 18.88 (12.33 to 27.66) | 1.33 (0.16 to 4.82) | | |

Notes:

[21] - ITT Population

[22] - ITT Population

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis |
|---|---|

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model adjusted for treatment group and region.

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 614 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 [23] |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.02 |
| upper limit | 0.3 |

Notes:

[23] - One-sided p-value was based on Wald test of null hypothesis: (Daprodustat/Placebo) >=1 versus alternative: ratio<1.

## Secondary: Change from Baseline by domain and single item scores on the Chronic Kidney Disease -Anemia Questionnaire (CKD-AQ) symptom questionnaire

| End point title | Change from Baseline by domain and single item scores on the Chronic Kidney Disease -Anemia Questionnaire (CKD-AQ) symptom questionnaire |
|---|---|

End point description:

CKD-AQ is 21-item patient reported outcomes measure assessing symptoms & symptom impact in participants with anemia associated with CKD.CKD-AQ identified 3 domains:1.Tired/Low Energy/Weak scale consisting of 10items;2.Chest Pain/Shortness of Breath scale consisting of 4items;3.Cognitive scale consisting of 3items;&single items;4.Difficulty Sleeping;5.Difficulty Standing for long periods of time;6.Severity of Shortness of breath while sitting/resting;7.Time with Shortness of breath while not doing activity.Single-item measures were recorded based on 0-100 scoring:0 is worst possible&100 is best possible score.Total domain score is calculated as average of items in each domain &ranged from 0-100:0 is worst possible &100 is best possible score.Change from Baseline was calculated as post-dose visit value minus Baseline.Baseline value was latest non-missing pre-dose assessment on/before randomization date.Only those participants with data available at indicated time points were analyzed.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1) and Week 28

| **End point values** | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 193[24] | 212[25] | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Tired/Low Energy/Weak Domain | 2.81 (± 1.132) | 8.72 (± 1.086) | | |
| Chest Pain/Shortness of Breath Domain | 0.62 (± 0.971) | 3.55 (± 0.932) | | |
| Cognitive Domain | 0.48 (± 1.042) | 4.27 (± 0.999) | | |
| Difficulty in Sleeping | 2.61 (± 1.643) | 5.22 (± 1.577) | | |
| Difficulty Standing for Long Periods of Time | 1.55 (± 1.630) | 6.19 (± 1.563) | | |
| Severity of Shortness of Breath While Sitting/Rest | 0.43 (± 0.995) | 3.11 (± 0.954) | | |
| Time with Shortness of BreathnotDoingActivity | 0.29 (± 1.083) | 2.30 (± 1.037) | | |

Notes:

[24] - ITT Population

[25] - ITT Population

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Tired/Low Energy/Weak domain.

| Comparison groups | Placebo v Daprodustat |
|---|---|

| Number of subjects included in analysis | 405 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [26] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 5.91 |
| Confidence interval | |
|    level | 95 % |
|    sides | 2-sided |
|    lower limit | 2.83 |
|    upper limit | 9 |

Notes:

[26] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

| Statistical analysis title | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Chest Pain/Shortness of Breath Domain.

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0152 [27] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 2.93 |
| Confidence interval | |
|    level | 95 % |
|    sides | 2-sided |
|    lower limit | 0.28 |
|    upper limit | 5.57 |

Notes:

[27] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

| Statistical analysis title | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Cognitive Domain.

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0045 [28] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 3.79 |

| Confidence interval | |
| --- | --- |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 6.63 |

Notes:

[28] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

| **Statistical analysis title** | Statistical Analysis 4 |
| --- | --- |

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Difficulty Sleeping

| Comparison groups | Placebo v Daprodustat |
| --- | --- |
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1267 [29] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 2.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.87 |
| upper limit | 7.09 |

Notes:

[29] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

| **Statistical analysis title** | Statistical Analysis 5 |
| --- | --- |

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Difficulty Standing for Long Periods of Time

| Comparison groups | Placebo v Daprodustat |
| --- | --- |
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0203 [30] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 4.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 9.09 |

Notes:

[30] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

| **Statistical analysis title** | Statistical Analysis 6 |
| --- | --- |

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Severity of Shortness of Breath While Sitting or Resting

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0266 [31] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 2.68 |
| Confidence interval | |
|    level | 95 % |
|    sides | 2-sided |
|    lower limit | -0.04 |
|    upper limit | 5.39 |

Notes:

[31] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

| **Statistical analysis title** | Statistical Analysis 7 |
|---|---|

Statistical analysis description:

Analysis was performed by MMRM with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Time with Shortness of Breath While not Doing an Activity

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0907 [32] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 2.01 |
| Confidence interval | |
|    level | 95 % |
|    sides | 2-sided |
|    lower limit | -0.94 |
|    upper limit | 4.96 |

Notes:

[32] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

## Secondary: Change from Baseline in Patient Global Impression of Severity (PGI-S)

| End point title | Change from Baseline in Patient Global Impression of Severity (PGI-S) |
|---|---|

End point description:

The PGI-S is a 1-item questionnaire designed to assess participant's impression of disease severity on a 5-point disease severity scale (0=absent, 1=mild, 2=moderate, 3=severe, or 4=very severe). A higher score indicated worse outcome. Change from Baseline was calculated as Post-Dose visit value minus Baseline. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Adjusted mean and standard error is presented. Only those participants with data available at the indicated time points were analyzed.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1) and Week 28

| End point values | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 193[33] | 212[34] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | -0.04 (± 0.055) | -0.18 (± 0.052) | | |

Notes:

[33] - ITT Population

[34] - ITT Population

## Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|
| Statistical analysis description: | |
| MMRM fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions. | |
| Comparison groups | Placebo v Daprodustat |
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0391 [35] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.13 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -0.28 |
|     upper limit | 0.02 |

Notes:

[35] - One-sided p-value was based on test of null hypothesis: (Daprodustat-rhEPO) >=0 versus alternative: difference <0

## Secondary: Change from Baseline in the SF-36 physical functioning Domain

| End point title | Change from Baseline in the SF-36 physical functioning Domain |
|---|---|

End point description:

The SF-36 acute version 2 is a 36-item generic quality of life instrument designed to measure a participant's level of performance in the following eight health domains: physical functioning, role-physical (role limitations caused by physical problems), social functioning, bodily pain, mental health, role-emotional (role limitations caused by emotional problems), vitality, and general perception of health. Each domain is scored from 0 (poorer health) to 100 (better health). Physical functioning domain score ranges from 0-100; higher score indicates a better health state and better functioning. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1) and Week 28

| End point values | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190[36] | 210[37] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | 1.23 (± 1.354) | 3.80 (± 1.298) | | |

Notes:

[36] - ITT Population

[37] - ITT Population

## Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|

Statistical analysis description:

MMRM fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions.

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0858 [38] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 2.57 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -1.12 |
|     upper limit | 6.26 |

Notes:

[38] - One sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 vs. alternative: difference >0.

## Secondary: Change from Baseline of the SF-36 individual items in the vitality Domain

| End point title | Change from Baseline of the SF-36 individual items in the vitality Domain |
|---|---|

End point description:

The SF-36 acute version 2 is a 36-item generic quality of life instrument designed to measure a participant's level of performance in the following eight health domains: physical functioning, role-physical (role limitations caused by physical problems), social functioning, bodily pain, mental health, role-emotional (role limitations caused by emotional problems), vitality, and general perception of health. Individual vitality item includes: 1. Did you feel full of life?, 2. Did you have a lot of energy?, 3. Did you feel worn out?, 4. Did you feel tired?. Score of each item in the vitality domain ranges from 0-100; higher score indicates better health state and better functioning. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1) and Week 28

| End point values | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190[39] | 210[40] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Did you feel full of life? | -0.02 (± 0.070) | 0.16 (± 0.067) | | |
| Did you have a lot of energy? | 0.09 (± 0.066) | 0.26 (± 0.063) | | |
| Did you feel worn out? | 0.16 (± 0.067) | 0.34 (± 0.064) | | |
| Did you feel tired? | 0.08 (± 0.060) | 0.34 (± 0.057) | | |

Notes:

[39] - ITT Population

[40] - ITT Population


## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

MMRM fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Did you feel full of life?

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0357 [41] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.36 |

Notes:

[41] - One sided p-value based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

| Statistical analysis title | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

MMRM fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and
treatment by time interactions for Did you have a lot of energy?

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0328 [42] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.17 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.01 |
| upper limit | 0.35 |

Notes:

[42] - One-sided p-value based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

MMRM fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and
treatment by time interactions for Did you feel worn out?

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0252 [43] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0.37 |

Notes:

[43] - One-sided p-value based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

| **Statistical analysis title** | Statistical Analysis 4 |
|---|---|

Statistical analysis description:

MMRM fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions for Did you feel tired?

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 [44] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 0.42 |

Notes:

[44] - One-sided p-value based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus alternative: difference >0.

**Secondary: Number of participants currently employed as per work productivity and activity impairment questionnaire: Anemic symptoms clinical practice version**

## (WPAI-ANS-CPV)

| End point title | Number of participants currently employed as per work productivity and activity impairment questionnaire: Anemic symptoms clinical practice version (WPAI-ANS-CPV) |
|---|---|

End point description:

WPAI-ANS-CPV is anemia specific questionnaire designed as self-reported quantitative assessment of social functioning related to work and regular daily activities. It contains 2 concepts-work productivity impairment measured via absenteeism (time missed from work), presenteeism (impairment at work) and regular daily activity impairment. WPAI questions (Q) were:1) currently employed, 2) work time missed due to problem, 3) impairment while working due to problem, 4) overall work impairment due to problem, 5) activity impairment due to problem. WPAI generates 4 domain scores:percent (%) of work time missed(absenteeism),% of impairment while working (presenteeism), % of overall work impairment (absenteeism and presenteeism combined), % of activity impairment. Number of participants currently employed as per WPAI-ANS-CPV is presented. Only those participants with data available at the indicated time points were analyzed (represented by n=X in category titles).

| End point type | Secondary |
|---|---|

End point timeframe:

Week 8, Week 12 and Week 28

| **End point values** | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 249[45] | 251[46] | | |
| Units: Participants | | | | |
| Week 8, No, n=249, 250 | 195 | 204 | | |
| Week 8, Yes, n=249, 250 | 54 | 46 | | |
| Week 12, No, n=234, 251 | 183 | 212 | | |
| Week 12, Yes, n=234, 251 | 51 | 39 | | |
| Week 28, No, n=193, 213 | 158 | 178 | | |
| Week 28, Yes, n=193, 213 | 35 | 35 | | |

Notes:

[45] - ITT Population

[46] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in WPAI-ANS-CPV: Percent time missed from Work

| End point title | Change from Baseline in WPAI-ANS-CPV: Percent time missed from Work |
|---|---|

End point description:

WPAI-ANS-CPV is anemia specific questionnaire designed as self-reported quantitative assessment of social functioning related to work&regular daily activities.It contain concepts-work productivity impairment measured via absenteeism(time missed from work),presenteeism(impairment at work)&regular daily activity impairment.WPAI Qs were:1)currently employed,2)work time missed due to problem,3)impairment while working due to problem,4)overall work impairment due to problem,5)activity impairment due to problem.Percent work time missed due to problem was subscale&calculated as: $Q2/(Q2+Q4)$ for those who were currently employed.Subscale score was expressed as impairment percentage (range:0-100%) where higher numbers indicate greater impairment&less productivity.Change from Baseline was calculated as post-dose visit minus Baseline.Baseline was latest non-missing predose assessment on/before randomization date.Only those participants with data available at indicated time points are presented.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1), Week 8, Week 12 and Week 28

| End point values | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 50[47] | 39[48] | | |
| Units: Percentage of time | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 8, n=50, 39 | -2.4 (± 28.40) | -6.1 (± 24.92) | | |
| Week 12, n=46, 31 | 0.9 (± 28.79) | 4.2 (± 27.96) | | |
| Week 28, n=28, 25 | 0.0 (± 33.59) | 0.3 (± 31.01) | | |

Notes:

[47] - ITT Population

[48] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in WPAI-ANS-CPV: mean hours missed from work in the past 7 days

| End point title | Change from Baseline in WPAI-ANS-CPV: mean hours missed from work in the past 7 days |
|---|---|

End point description:

WPAI-ANS-CPV is anemia specific questionnaire designed as self-reported quantitative assessment of social functioning related to work and regular daily activities. It contains 2 concepts-work productivity impairment measured via absenteeism (time missed from work), presenteeism (impairment at work) and regular daily activity impairment. WPAI questions (Q) were: 1) currently employed, 2) work time missed due to problem, 3) impairment while working due to problem, 4) overall work impairment due to problem, 5) activity impairment due to problem. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at indicated time points are presented (presented by n=X in category titles).

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1), Week 8, Week 12 and Week 28

| End point values | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 50[49] | 39[50] | | |
| Units: Percentage of hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 8, n=50, 39 | 0.1 (± 18.46) | -1.8 (± 11.88) | | |
| Week 12, n=46, 31 | 1.4 (± 14.07) | 2.4 (± 16.83) | | |
| Week 28, n=28, 25 | 0.3 (± 19.90) | 1.0 (± 14.24) | | |

Notes:

[49] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in WPAI: Percent Impairment at Work

| End point title | Change from Baseline in WPAI: Percent Impairment at Work |
|---|---|

End point description:

WPAI-ANS-CPV is anemia specific questionnaire designed as self-reported quantitative assessment of social functioning related to work&regular daily activities.It contains2concepts-work productivity impairment measured via absenteeism(time missed from work),presenteeism(impairment at work)&regular daily activity impairment.WPAI Qs:1)currently employed,2)work time missed due to problem,3)impairment while working due to problem,4)overall work impairment due to problem,5)activity impairment due to problem.% Impairment while Working due to Problem was subscale&calculated asQ5/10 for those who were currently employed,actually worked in past7day.Subscale score was expressed as impairment percentage(range:0-100%),higher number indicate greater impairment,less productivity.Change fromBaseline=post-dose visit value-Baseline.Baseline was latest non-missing pre-dose assessment on/before randomization date.Only participants with data available at indicated time point are presented(n=X)

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1), Week 8, Week 12 and Week 28

| **End point values** | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45[51] | 32[52] | | |
| Units: Percentage of impairment | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 8, n=45, 32 | -5.1 (± 18.42) | -11.3 (± 24.06) | | |
| Week 12, n=41, 26 | -4.6 (± 18.99) | -8.8 (± 23.38) | | |
| Week 28, n=24, 20 | -9.6 (± 25.62) | -9.0 (± 22.92) | | |

Notes:

[51] - ITT Population

[52] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in WPAI: Percent overall work impairment

| End point title | Change from Baseline in WPAI: Percent overall work impairment |
|---|---|

End point description:

WPAI-ANS-CPV is anemia specific questionnaire designed as self-reported quantitative assessment of social functioning related to work & regular daily activities. WPAI Questions(Q)were:1)currently employed,2)work time missed due to problem,3)impairment while working due to problem,4)overall

work impairment due to problem,5)activity impairment due to problem.Percent overall work impairment due to problem was subscale & calculated as: $Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))\times(Q5/10)]$ for those who were currently employed.Subscale score was expressed as impairment percentage (range:0-100%) where higher numbers indicate greater impairment. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline was latest non-missing pre-dose assessment on/before randomization date. Only those participants with data available at indicated time points were analyzed (n=X).

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1), Week 8, Week 12 and Week 28

| **End point values** | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45[53] | 32[54] | | |
| Units: Percentage of impairment | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 8, n=45, 32 | -4.3 (± 24.04) | -12.0 (± 25.90) | | |
| Week 12, n=41, 26 | 0.5 (± 25.81) | -3.2 (± 33.35) | | |
| Week 28, n=24, 20 | -9.3 (± 37.45) | -8.4 (± 19.12) | | |

Notes:

[53] - ITT Population

[54] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in WPAI: Percent regular daily activity impairment

| End point title | Change from Baseline in WPAI: Percent regular daily activity impairment |
|---|---|

End point description:

WPAI-ANS-CPV is anemia specific questionnaire designed as self-reported quantitative assessment of social functioning related to work and regular daily activities.WPAI Questions (Q) were: 1) currently employed, 2) work time missed due to problem, 3) impairment while working due to problem, 4) overall work impairment due to problem, 5) activity impairment due to problem. Percent activity impairment due to problem was a subscale and calculated as: Q5/10 for all respondents. Subscale score was expressed as an impairment percentage (range: 0-100%) where higher numbers indicate greater impairment. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was the latest non-missing pre-dose assessment on or before randomization date.Only those participants with data available at the indicated time points were analyzed (represented by n=X in category titles).

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1), Week 8, Week 12 and Week 28

| End point values | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 246[55] | 248[56] | | |
| Units: Percentage of impairment | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 8, n=243, 248 | -4.6 (± 23.67) | -7.7 (± 24.53) | | |
| Week 12, n=228, 246 | -5.2 (± 25.40) | -8.6 (± 24.58) | | |
| Week 28, n=187, 210 | -6.7 (± 28.93) | -12.2 (± 27.50) | | |

Notes:

[55] - ITT Population

[56] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in EuroQol 5 Dimension 5 Level Health Utility Index (EQ-5D-5L) utility score

| End point title | Change from Baseline in EuroQol 5 Dimension 5 Level Health Utility Index (EQ-5D-5L) utility score |
|---|---|

End point description:

The EQ-5D-5L is a self-assessment questionnaire, consisting of 5 items covering 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a 5-point Likert scale (1: no problems, 2: slight problems, 3: moderate problems, 4: severe problems, and 5: extreme problems). The responses for the five dimension together form a five-figure description of health state. Each of these five-figure health states has attached valuation (utility score), expressed as single index on a scale from 0-1, where 1 is full health and 0 is worst health. The higher the score the better the health status. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at indicated time points are presented.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1) and Week 28

| End point values | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106[57] | 116[58] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | 0.01 (± 0.015) | 0.03 (± 0.014) | | |

Notes:

[57] - ITT Population

[58] - ITT Population

## Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|

Statistical analysis description:

Based on MMRM model fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions.

| Comparison groups | Placebo v Daprodustat |
|---|---|

| Number of subjects included in analysis | 222 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1098 [59] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.07 |

Notes:

[59] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 versus. alternative: difference >0.

## Secondary: Change from Baseline in EuroQol visual analogue scale (EQ-VAS) score

| End point title | Change from Baseline in EuroQol visual analogue scale (EQ-VAS) score |
|---|---|

End point description:

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'the best health you can imagine' and 'the worst health you can imagine' at the time of completion. It is a self-assessment visual analogue scale, ranging from 0=worst imaginable to 100=best. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Adjusted mean and standard error is presented. Only those participants with data available at indicated time points are presented.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1) and Week 28

| **End point values** | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106[60] | 116[61] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | 0.80 (± 1.427) | 5.30 (± 1.373) | | |

Notes:

[60] - ITT Population

[61] - ITT Population

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis |
|---|---|

Statistical analysis description:

Mixed model repeated measures model fitted from Baseline up to Week 28 with factors for treatment, time, region, Baseline value and Baseline value by time and treatment by time interactions.

| Comparison groups | Placebo v Daprodustat |
|---|---|

| Number of subjects included in analysis | 222 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.012 [62] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 4.5 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 0.6 |
|     upper limit | 8.4 |

Notes:

[62] - One-sided p-value was based on test of null hypothesis: (Daprodustat-Placebo) <=0 vs. alternative: difference >0.

## Secondary: Change from Baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) at Week 28

| End point title | Change from Baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) at Week 28 |
|---|---|

End point description:

SBP, DBP and MAP were measured with participants in a seated position after at least a 5-minute of rest. MAP is the average BP in an individual's arteries during a single cardiac cycle. Change from Baseline was calculated as post-dose visit value minus Baseline. Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. Only those participants with data available at the indicated time points were analyzed.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1) and Week 28

| **End point values** | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 202[63] | 230[64] | | |
| Units: Millimeters of mercury (mmHg) | | | | |
| least squares mean (standard error) | | | | |
|     SBP | -0.63 (± 1.045) | -0.23 (± 0.981) | | |
|     DBP | -0.96 (± 0.625) | 0.84 (± 0.587) | | |
|     MAP | -0.82 (± 0.674) | 0.49 (± 0.632) | | |

Notes:

[63] - ITT Population

[64] - ITT Population

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

MMRM model fitted from Baseline up to Week 28, with factors for treatment, time, region, Baseline SBP and Baseline SBP by time and treatment by time interactions.

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 432 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6106 [65] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.42 |
| upper limit | 3.22 |

Notes:

[65] - One-sided p-value was based on test of null hypothesis: (Daprodustat - Placebo) >= 0 versus alternative:
difference <0

| Statistical analysis title | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

MMRM model fitted from Baseline up to Week 28, with factors for treatment, time, region, Baseline DBP and Baseline DBP by time and treatment by time interactions.

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 432 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9819 [66] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 1.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.12 |
| upper limit | 3.49 |

Notes:

[66] - One-sided p-value was based on test of null hypothesis: (Daprodustat - Placebo) >= 0 versus alternative:
difference < 0

| Statistical analysis title | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

MMRM model fitted from Baseline up to Week 28, with factors for treatment, time, region, Baseline MAP and Baseline MAP by time and treatment by time interactions.

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 432 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9215 [67] |
| Method | MMRM |
| Parameter estimate | Mean difference (net) |
| Point estimate | 1.31 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.51 |
| upper limit | 3.13 |

Notes:

[67] - One-sided p-value was based on test of null hypothesis: (Daprodustat - Placebo) >= 0 versus alternative:
difference <0

## Secondary: Percentage of participants with at least one BP) exacerbation event

| End point title | Percentage of participants with at least one BP) exacerbation event |
|---|---|

End point description:

Percentage of participants with at least one BP exacerbation event is presented. BP exacerbation is defined as: SBP exacerbation: SBP >= 25 mmHg increase from Baseline or SBP >= 180 mmHg; DBP exacerbation: DBP >= 15 mmHg increase from Baseline or DBP >= 110 mmHg. Percentage of participants with at least one BP exacerbation event is presented. The percentage values presented has been rounded off.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to Week 28

| **End point values** | Placebo | Daprodustat | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 307 | 307 | | |
| Units: Percentage of participants | 26 | 32 | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis |
|---|---|

Statistical analysis description:

Cochran-Mantel-Haenszel test was performed for treatment group comparison.

| Comparison groups | Placebo v Daprodustat |
|---|---|
| Number of subjects included in analysis | 614 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.068 [68] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Response rate |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.13 |

Notes:

[68] - One-sided p-value based on test of null hypothesis: (Daprodustat - Placebo) <= 0 versus alternative: difference > 0.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All cause mortality, serious adverse events (SAEs) and non-serious AEs were collected up to follow-up (Week 32).

Adverse event reporting additional description:

Safety Population comprised of all randomized participants who received at least 1 dose of study treatment.Treatment emergent non-serious adverse events & serious adverse events are reported.One participant who was randomized to placebo accidently received daprodustat during study & was evaluated in daprodustat treatment group for safety outcome.

| Assessment type | Systematic |
|---|---|

### Dictionary used

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 23.1 |

### Reporting groups

| Reporting group title | Placebo |
|---|---|

Reporting group description:

Participants received matching placebo once daily orally for up to 28 weeks followed by 4 weeks of follow-up.

| Reporting group title | Daprodustat |
|---|---|

Reporting group description:

Participants received daprodustat film-coated tablets with titrated dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 milligrams (mg) once daily orally for up to 28 weeks, followed by 4 weeks of follow-up. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (11 to 12 grams per deciliter [g/dL])

| Serious adverse events | Placebo | Daprodustat | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 68 / 306 (22.22%) | 62 / 308 (20.13%) | |
| number of deaths (all causes) | 16 | 10 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pituitary tumour benign | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Plasma cell myeloma | | | |

| | | |
|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

**Vascular disorders**

Hypertension

| | | |
|---|---|---|
| subjects affected / exposed | 2 / 306 (0.65%) | 2 / 308 (0.65%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Hypotension

| | | |
|---|---|---|
| subjects affected / exposed | 3 / 306 (0.98%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Hypertensive crisis

| | | |
|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Hypertensive emergency

| | | |
|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Hypovolaemic shock

| | | |
|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 |

Peripheral arterial occlusive disease

| | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Thrombophlebitis superficial

| | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

**General disorders and administration site conditions**

| | | | | | |
|---|---|---|---|---|---|
| Death | | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | | | |
| General physical health deterioration | | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | | |
| Respiratory, thoracic and mediastinal disorders | | | | | |
| Acute pulmonary oedema | | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 3 / 308 (0.97%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | | |
| Pulmonary oedema | | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 1 / 308 (0.32%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | | |
| Acute interstitial pneumonitis | | | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | | |
| Bronchial hyperreactivity | | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | | |
| Chronic obstructive pulmonary disease | | | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | | |
| Interstitial lung disease | | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | | |

| | | | | |
|---|---|---|---|---|
| Pleural effusion | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Pulmonary hypertension | | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Psychiatric disorders | | | | |
| Bipolar disorder | | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Investigations | | | | |
| Blood pressure increased | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Hepatic enzyme increased | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Liver function test abnormal | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (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 | | | | |
| Femur fracture | | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 2 / 308 (0.65%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Cervical vertebral fracture | | | | |

| | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Craniocerebral injury

| | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Humerus fracture

| | | |
|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Kidney rupture

| | | |
|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Ligament sprain

| | | |
|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Subdural haematoma

| | | |
|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Transplant dysfunction

| | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Upper limb fracture

| | | |
|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Vascular pseudoaneurysm

| | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

**Cardiac disorders**

Cardiac failure congestive

| | | |
|---|---|---|
| subjects affected / exposed | 2 / 306 (0.65%) | 3 / 308 (0.97%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Cardiac failure acute

| | | |
|---|---|---|
| subjects affected / exposed | 4 / 306 (1.31%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Acute coronary syndrome

| | | |
|---|---|---|
| subjects affected / exposed | 2 / 306 (0.65%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 |

Atrial fibrillation

| | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 3 / 308 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 |

Bradycardia

| | | |
|---|---|---|
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Left ventricular failure

| | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 2 / 308 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Acute myocardial infarction

| | | |
|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Angina pectoris

| | subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
|---|---|---|---|---|---|
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Angina unstable | | | | | |
| | subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Arrhythmia | | | | | |
| | subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| Atrial flutter | | | | | |
| | subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Atrial thrombosis | | | | | |
| | subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Cardiac failure chronic | | | | | |
| | subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Coronary artery disease | | | | | |
| | subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Mitral valve incompetence | | | | | |
| | subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Myocardial infarction | | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| **Myocardial ischaemia** | | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| **Right ventricular failure** | | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| **Cardiac failure** | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 4 / 308 (1.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| **Tricuspid valve incompetence** | | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| **Nervous system disorders** | | | | |
| **Syncope** | | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 3 / 308 (0.97%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| **Autonomic nervous system imbalance** | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| **Encephalopathy** | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| **Ischaemic stroke** | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Sciatica** | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Blood and lymphatic system disorders** | | | |
| **Anaemia** | | | |
| subjects affected / exposed | 8 / 306 (2.61%) | 2 / 308 (0.65%) | |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Ear and labyrinth disorders** | | | |
| **Hypoacusis** | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Tympanic membrane perforation** | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Vertigo positional** | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Eye disorders** | | | |
| **Ulcerative keratitis** | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Vitreous haemorrhage** | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| Gastrointestinal disorders | | | | |
|---|---|---|---|---|
| Gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 1 / 308 (0.32%) | | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| Vomiting | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 2 / 308 (0.65%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Constipation | | | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 308 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 1 / 308 (0.32%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Abdominal pain upper | | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Ascites | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Colitis | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Diabetic gastropathy | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| Diarrhoea | | | | |

| | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

**Large intestine polyp**

| | | |
|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

**Nausea**

| | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

**Hepatobiliary disorders**

**Autoimmune hepatitis**

| | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

**Cholangitis**

| | | |
|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

**Cholelithiasis**

| | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

**Skin and subcutaneous tissue disorders**

**Skin ulcer**

| | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

**Renal and urinary disorders**

**Acute kidney injury**

| | | |
|---|---|---|
| subjects affected / exposed | 5 / 306 (1.63%) | 5 / 308 (1.62%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

| | | | | |
|---|---|---|---|---|
| **Renal failure** | | | | |
| subjects affected / exposed | 6 / 306 (1.96%) | 2 / 308 (0.65%) | | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| **End stage renal disease** | | | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 2 / 308 (0.65%) | | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| **Renal impairment** | | | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 1 / 308 (0.32%) | | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| **Azotaemia** | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 1 / 308 (0.32%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| **Urinary retention** | | | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 308 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| **Chronic kidney disease** | | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| **IgA nephropathy** | | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| **Nephrolithiasis** | | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| **Nephropathy toxic** | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Nephrotic syndrome** | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Renal haematoma** | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Musculoskeletal and connective tissue disorders** | | | |
| **Arthralgia** | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Atlantoaxial instability** | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Osteoarthritis** | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Infections and infestations** | | | |
| **Sepsis** | | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 2 / 308 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Cellulitis** | | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 1 / 308 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | |
|---|---|---|
| **Urinary tract infection** | | |
| subjects affected / exposed | 4 / 306 (1.31%) | 2 / 308 (0.65%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| **Septic shock** | | |
| subjects affected / exposed | 2 / 306 (0.65%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 |
| **Pneumonia** | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 2 / 308 (0.65%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| **Urosepsis** | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 2 / 308 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 |
| **COVID-19** | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| **Diabetic foot infection** | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| **Ear infection** | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| **Endophthalmitis** | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| **Escherichia urinary tract infection** | | |

|  | | |
|---|---|---|
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| **Gastroenteritis** | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| **Lower respiratory tract infection** | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| **Otitis externa** | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| **Perirectal abscess** | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| 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 | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| **Pyelonephritis** | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| **Upper respiratory tract infection** | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| **Metabolism and nutrition disorders** | | |
| Hypoglycaemia | | |

|  |  |  |  |  |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 306 (0.33%) | 2 / 308 (0.65%) |  |  |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 |  |  |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |  |  |
| **Fluid overload** |  |  |  |  |
| subjects affected / exposed | 1 / 306 (0.33%) | 1 / 308 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 |  |  |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |  |  |
| **Dehydration** |  |  |  |  |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |  |  |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |  |  |
| **Diabetic ketoacidosis** |  |  |  |  |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |  |  |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |  |  |
| **Hyperglycaemia** |  |  |  |  |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |  |  |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |  |  |
| **Hyperkalaemia** |  |  |  |  |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |  |  |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |  |  |
| **Hyponatraemia** |  |  |  |  |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (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 | Placebo | Daprodustat | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events<br>    subjects affected / exposed | 44 / 306 (14.38%) | 49 / 308 (15.91%) | |
| Vascular disorders<br>    Hypertension<br>        subjects affected / exposed<br><br>        occurrences (all) | <br><br>14 / 306 (4.58%)<br><br>14 | <br><br>21 / 308 (6.82%)<br><br>27 | |
| General disorders and administration site conditions<br>    Oedema peripheral<br>        subjects affected / exposed<br><br>        occurrences (all) | <br><br><br>21 / 306 (6.86%)<br><br>23 | <br><br><br>12 / 308 (3.90%)<br><br>14 | |
| Gastrointestinal disorders<br>    Diarrhoea<br>        subjects affected / exposed<br><br>        occurrences (all) | <br><br>17 / 306 (5.56%)<br><br>22 | <br><br>24 / 308 (7.79%)<br><br>26 | |

# More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?  Yes

| Date | Amendment |
|---|---|
| 02 April 2018 | Country Specific Protocol ITA-1: Edited footnote 11 to include evaluation of all iron parameters at Week 4 in Section 2: Schedule of Activities; Exclude participants with a lower electrocardiogram (ECG) criteria based on Frederica's QT Interval Corrected for Heart Rate (QTcF) and not Bazett's QT Interval Corrected for Heart Rate (QTcB); exclude participants with second or third degree atrioventricular (AV) block in Exclusion Criteria (Crit) Exclusion 18; replaced QTcB with QTcF in Electrocardiograms section. |
| 23 August 2019 | Amendment 1:Added footnote17 to state when study treatment should be dispensed;Revised footnote9 to permit HemoCue Hgb retest with new blood sample; Revised footnote12 to clarify the purpose of participant reminder card;Edited footnote15 to add ultrasound assessments for ADPKD participants at end of treatment.Added row to conduct assessment regarding HCRU  by participants at each visit starting with Day1 & after study treatment discontinuation;Added renal ultrasound for ADPKD participants upon discontinuation of study treatment ;Updated risk assessment table with language related to IB update;Added secondary & exploratory endpoints objectives related to BP exacerbations & concomitant medications;Revised secondary endpoints for work productivity& regular daily activity impairment captured on WPAI-ANS-CPV;Amended exploratory objectives for Hgb change to evaluate participants achieving Hgb increase of >=1.0 g/dL instead of >=1.2g/dL;Updated exploratory objective to capture time to first rhEPO Transfusion use;Edited inclusion Crit5 to provide clarity for requirements of compliance with oral iron dosing prior to Day1 & removed need for stable iron dose prior to screening;Edited ex crit 13 edited to include use of investigational device;Added ex crit22 for uncontrolled hypertension;Instructions to repeat & average HemoCue Hgb assessment for Hgb <8.5 g/dL;Added information regarding discontinuation of study treatment in participants with ADPKD;Added language related to alternative methods of follow-up;Added language regarding alternative methods of follow-up for participants potentially lost to follow-up;Added language regarding retests with new blood sample entering HemoCue Hgb values into IRT  system;Added worsening of hypertension as additional AESI; Added guidance on conducting ultrasound for participants with ADPKD based on different clinical scenarios in study;Changes made to provide guidance regarding the conduct of study at French site only. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial?  No

## Limitations and caveats

 None reported