# Clinical trial results:
# A 52-week open-label (sponsor-blind), randomized, active controlled, parallel-group, multi-center study to evaluate the efficacy and safety of daprodustat compared to recombinant human erythropoietin in subjects with anemia associated with chronic kidney disease who are initiating dialysis

## Summary

| | |
|---|---|
| EudraCT number | 2016-000507-86 |
| Trial protocol | ES DE PL GB IT |
| Global end of trial date | 24 September 2020 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 08 October 2021 |
| First version publication date | 08 October 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 201410 |

**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 | 12 March 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 24 September 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To compare daprodustat to recombinant human erythropoietin (rhEPO) for hemoglobin (Hgb) efficacy (non-inferiority)

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 11 May 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 54 |
| Country: Number of subjects enrolled | Germany: 5 |
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | Poland: 22 |
| Country: Number of subjects enrolled | Russian Federation: 72 |
| Country: Number of subjects enrolled | Spain: 7 |
| Country: Number of subjects enrolled | United Kingdom: 14 |
| Country: Number of subjects enrolled | Argentina: 56 |
| Country: Number of subjects enrolled | Australia: 7 |
| Country: Number of subjects enrolled | Canada: 2 |
| Country: Number of subjects enrolled | India: 14 |
| Country: Number of subjects enrolled | Korea, Republic of: 22 |
| Country: Number of subjects enrolled | Malaysia: 14 |
| Country: Number of subjects enrolled | Mexico: 20 |
| Worldwide total number of subjects | 312 |
| EEA total number of subjects | 37 |

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) | 229 |
| From 65 to 84 years | 81 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details:

This was a multicenter study conducted across 14 countries. Participants were randomized to receive either Daprodustat or Darbepoetin alfa.

### Pre-assignment

Screening details:

A total of 312 participants were randomized in the study.

### Period 1

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

### Arms

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

Arm description:

Participants received daprodustat film-coated tablets with titrated dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16, and 24 milligrams (mg) orally once daily for up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin (Hgb) in the target range (10 to 11 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 dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 or 24 mg orally once daily for 52 weeks.

| | |
|---|---|
| **Arm title** | Darbepoetin alfa |

Arm description:

Participants received darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection with 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 120, 160, 200, 300 and 400 microgram (mcg) for 52 weeks. Study treatment was dose-titrated to achieve and maintain Hgb in the target range (10 to 11 g/dL).

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Darbepoetin alfa |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use, Intravenous use |

Dosage and administration details:

Participants received darbepoetin alfa as PFS for subcutaneous or IV injection with 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 120, 160, 200, 300 and 400 mcg for 52 weeks.

| **Number of subjects in period 1** | Daprodustat | Darbepoetin alfa |
|---|---|---|
| Started | 157 | 155 |
| Completed | 155 | 151 |
| Not completed | 2 | 4 |
| Consent withdrawn by subject | 2 | 3 |
| Lost to follow-up | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| 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, and 24 milligrams (mg) orally once daily for up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin (Hgb) in the target range (10 to 11 grams per deciliter [g/dL]). | |
| Reporting group title | Darbepoetin alfa |
| Reporting group description: | |
| Participants received darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection with 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 120, 160, 200, 300 and 400 microgram (mcg) for 52 weeks. Study treatment was dose-titrated to achieve and maintain Hgb in the target range (10 to 11 g/dL). | |

| Reporting group values | Daprodustat | Darbepoetin alfa | Total |
|---|---|---|---|
| Number of subjects | 157 | 155 | 312 |
| Age categorical<br>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) | 119 | 110 | 229 |
| From 65-84 years | 38 | 43 | 81 |
| 85 years and over | 0 | 2 | 2 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 53.7 | 55.8 | |
| standard deviation | ± 14.31 | ± 15.70 | - |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 61 | 57 | 118 |
| Male | 96 | 98 | 194 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| American Indian (AI) or Alaskan Native (AN) | 5 | 2 | 7 |
| Asian: Central/South Asian Heritage | 7 | 6 | 13 |
| Asian: East Asian Heritage | 8 | 16 | 24 |
| Asian: South East Asian Heritage | 11 | 9 | 20 |
| Black or African American | 16 | 13 | 29 |
| White: Arabic/North African Heritage | 1 | 0 | 1 |
| White: White/Caucasian/European Heritage | 109 | 107 | 216 |
| Mixed race: AI or AN and White | 0 | 2 | 2 |

## End points

### End points reporting groups

| 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, and 24 milligrams (mg) orally once daily for up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin (Hgb) in the target range (10 to 11 grams per deciliter [g/dL]). | |
| Reporting group title | Darbepoetin alfa |
| Reporting group description: | |
| Participants received darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection with 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 120, 160, 200, 300 and 400 microgram (mcg) for 52 weeks. Study treatment was dose-titrated to achieve and maintain Hgb in the target range (10 to 11 g/dL). | |
| Subject analysis set title | Daprodustat 1 mg |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants received film-coated tablets of daprodustat 1 mg orally once daily for 52 weeks. | |
| Subject analysis set title | Daprodustat 2 mg |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants received film-coated tablets of daprodustat 2 mg orally once daily for 52 weeks. | |
| Subject analysis set title | Daprodustat 4 mg |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants received film-coated tablets of daprodustat 4 mg orally once daily for 52 weeks. | |
| Subject analysis set title | Daprodustat 6 mg |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants received film-coated tablets of daprodustat 6 mg orally once daily for 52 weeks. | |
| Subject analysis set title | Daprodustat 8 mg |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants received film-coated tablets of daprodustat 8 mg orally once daily for 52 weeks. | |
| Subject analysis set title | Daprodustat 10 mg |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants received film-coated tablets of daprodustat 10 mg orally once daily for 52 weeks. | |

### Primary: Mean Change from Baseline in Hemoglobin (Hgb) During Evaluation Period (Week 28 to Week 52)

| End point title | Mean Change from Baseline in Hemoglobin (Hgb) During Evaluation Period (Week 28 to Week 52) |
|---|---|
| End point description: | |
| Blood samples were collected from participants for Hgb measurement. Hgb during the evaluation period was defined as the mean of all available post-randomization Hgb values (on and off-treatment) during the evaluation period (Week 28 to Week 52). For the primary analysis missing post-Baseline Hgb 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 was defined as the latest non-missing pre-dose assessment on or before the randomization date. An analysis of covariance (ANCOVA) model including randomization stratification factors Baseline Hgb and treatment was performed to obtain a point estimate and two-sided 95 percent (%) confidence interval (CI) for the treatment difference (daprodustat-darbepoetin alfa). Intent-to-Treat (ITT) Population comprised all randomized participants (who received a treatment randomization number). | |

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (Pre-dose on Day 1) and evaluation period (Week 28 to Week 52)

| **End point values** | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 157[1] | 155[2] | | |
| Units: Grams per deciliter | | | | |
| least squares mean (standard error) | 1.02 (± 0.086) | 1.12 (± 0.085) | | |

Notes:

[1] - ITT Population.

[2] - ITT Population.

### Statistical analyses

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

Statistical analysis description:

An ANCOVA model including randomization stratification factors Baseline Hgb and treatment was performed to obtain a point estimate and two-sided 95% CI for the treatment difference (daprodustat-darbepoetin alfa).

| Comparison groups | Daprodustat v Darbepoetin alfa |
|---|---|
| Number of subjects included in analysis | 312 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[3] |
| Parameter estimate | Least square (LS) mean difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.34 |
| upper limit | 0.14 |

Notes:

[3] - Non-inferiority was to be established if the lower limit of the two-sided 95% CI for the treatment difference was greater than the pre-specified non-inferiority margin of -0.75 g/dL.

## Secondary: Average Monthly Intravenous Iron Dose (milligrams) from Baseline to Week 52

| End point title | Average Monthly Intravenous Iron Dose (milligrams) from Baseline to Week 52 |
|---|---|

End point description:

Total IV iron dose per participant was calculated from Day 1 to the earliest of (Week 52 visit date, first blood [red blood cells or whole blood] transfusion date and treatment stop date plus [+] 1 day) which corresponds to the time while the participant was on randomized treatment and before receiving a blood transfusion. Average monthly IV iron dose was calculated by Total IV iron dose divided by (/) (the number of days from Day 1 to the earliest of [Week 52 visit date, first blood transfusion date and treatment stop date +1] /30.4375 days). Data for participants until they underwent a red blood cells or whole blood transfusion was included in the analysis. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

Baseline (Day 1) to Week 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156[4] | 154[5] | | |
| Units: Milligram | | | | |
| least squares mean (standard error) | 144.7 (± 10.90) | 125.3 (± 10.97) | | |

Notes:

[4] - ITT Population.

[5] - ITT Population.

### Statistical analyses

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

Statistical analysis description:

An ANCOVA model was used to compare the difference in this average monthly IV iron dose between arms, including factors for Baseline dose, treatment and the randomization stratification factors.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 310 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8949 |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | 19.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11 |
| upper limit | 49.9 |

## Secondary: Change from Baseline in Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Blood Pressure (MAP) at Week 52

| End point title | Change from Baseline in Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Blood Pressure (MAP) at Week 52 |
|---|---|

End point description:

SBP, DBP and MAP were measured in a semi-supine or seated position in the dialysis chair after at least a 5-minutes of rest. MAP is an average BP in an individual's arteries during a single cardiac cycle. Change from Baseline was calculated as post-dose visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. This analysis was carried out by using mixed model repeated measures (MMRM) model. 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 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 153[6] | 149[7] | | |
| Units: Millimeter of mercury | | | | |
| least squares mean (standard error) | | | | |
| SBP | -3.57 (± 2.063) | -6.80 (± 2.931) | | |
| DBP | 0.21 (± 1.216) | -4.01 (± 1.650) | | |
| MAP | -0.95 (± 1.364) | -5.05 (± 1.894) | | |

Notes:

[6] - ITT Population.

[7] - ITT Population.

## Statistical analyses

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

Statistical analysis description:

The difference in change from Baseline in SBP at Week 52 was analyzed with a MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8168 |
| Method | Mixed model repeated measures (MMRM) |
| Parameter estimate | LS mean difference |
| Point estimate | 3.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.82 |
| upper limit | 10.27 |

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

Statistical analysis description:

The difference in change from Baseline in DBP at Week 52 was analyzed with a MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9793 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 4.21 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.17 |
| upper limit | 8.26 |

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

Statistical analysis description:

The difference in change from Baseline in MAP at Week 52 was analyzed with a MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 302 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9597 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 4.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.51 |
| upper limit | 8.7 |

## Secondary: Change from Baseline in SBP, DBP, MAP at End of Treatment

| End point title | Change from Baseline in SBP, DBP, MAP at End of Treatment |
|---|---|

End point description:

SBP, DBP and MAP were measured in a semi-supine or seated position in the dialysis chair after at least a 5-minutes of rest. MAP is an average BP in an individual's arteries during a single cardiac cycle. End of treatment value for the blood pressure parameters were defined as the latest value on or before the last non-zero dose date plus (+) 1 day. Change from Baseline was calculated as post-dose visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. This analysis was carried out by using ANCOVA model. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

Baseline (Day 1) and end of treatment (last on-treatment value until Week 52)

| **End point values** | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 154[8] | 153[9] | | |
| Units: Millimeter of mercury | | | | |
| least squares mean (standard error) | | | | |
| SBP | -3.23 (± 1.659) | -3.14 (± 1.664) | | |

| | | | | |
|---|---|---|---|---|
| DBP | 0.60 (± 1.016) | -1.39 (± 1.020) | | |
| MAP | -0.68 (± 1.092) | -1.97 (± 1.096) | | |

Notes:

[8] - ITT Population.

[9] - ITT Population.

## Statistical analyses

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

Statistical analysis description:

The difference in change from Baseline in SBP at the derived end of treatment was analyzed with an ANCOVA model including terms for treatment, prognostic randomization stratification factors.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 307 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.484 |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -0.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.72 |
| upper limit | 4.53 |

| **Statistical analysis title** | Statistical analysis 2 |
|---|---|

Statistical analysis description:

The difference in change from Baseline in DBP at the derived end of treatment was analyzed with an ANCOVA model including terms for treatment, prognostic randomization stratification factors.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 307 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9156 |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | 1.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.85 |
| upper limit | 4.82 |

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

Statistical analysis description:

The difference in change from Baseline in MAP at the derived end of treatment was analyzed with an ANCOVA model including terms for treatment, prognostic randomization stratification factors.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 307 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7966 |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | 1.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.76 |
| upper limit | 4.33 |

## Secondary: Blood Pressure (BP) Exacerbation Events Rate per 100 Participant Years

| | |
|---|---|
| End point title | Blood Pressure (BP) Exacerbation Events Rate per 100 Participant Years |

End point description:

BP exacerbation event is defined (based on post-dialysis BP) as SBP >=25 millimeter of mercury (mmHg) increased from Baseline or SBP >=180 mmHg; or DBP >=15 mmHg increased from Baseline or DBP >=110 mmHg. The BP exacerbation events per 100 participant years was estimated using the Negative Binomial Model.

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

End point timeframe:

Up to Week 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 155[10] | 154[11] | | |
| Units: Events per 100 participant year | | | | |
| number (confidence interval 95%) | 352.50 (268.89 to 462.09) | 350.00 (267.72 to 457.56) | | |

Notes:

[10] - ITT Population.

[11] - ITT Population.

### Statistical analyses

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

Statistical analysis description:

Model estimated exacerbation rates, ratio of model estimated exacerbation rates and CIs were estimated using a negative binomial model for the treatment group comparison.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |

| | |
|---|---|
| Number of subjects included in analysis | 309 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5174 |
| Method | Negative binomial model |
| Parameter estimate | Ratio of exacerbation rate |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.39 |

## Secondary: Number of Participants with at Least one Blood Pressure Exacerbation Event During Study

| | |
|---|---|
| End point title | Number of Participants with at Least one Blood Pressure Exacerbation Event During Study |

End point description:

BP exacerbation was defined (based on post-dialysis BP) as: SBP >=25 mmHg increased from Baseline or SBP >=180 mmHg; DBP >=15 mmHg increased from Baseline or DBP >=110 mmHg. Number of participants with at least one blood pressure exacerbation event is presented. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

Up to Week 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 155[12] | 154[13] | | |
| Units: Participants | 91 | 100 | | |

Notes:

[12] - ITT Population.

[13] - ITT Population.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Post-randomization Hgb at Week 52

| | |
|---|---|
| End point title | Change From Baseline in Post-randomization Hgb at Week 52 |

End point description:

Blood samples were collected from participants for Hgb measurements. Change from Baseline was calculated as post-dose visit value minus Baseline value. Baseline was defined as 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 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 139[14] | 141[15] | | |
| Units: Grams per deciliter | | | | |
| least squares mean (standard error) | 1.17 (± 0.117) | 1.13 (± 0.115) | | |

Notes:

[14] - ITT Population.

[15] - ITT Population.

### Statistical analyses

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

Statistical analysis description:

The difference in change from Baseline in post-randomization Hgb at Week 52 was analyzed with a MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 280 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[16] |
| Parameter estimate | LS mean difference |
| Point estimate | 0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.29 |
| upper limit | 0.36 |

Notes:

[16] - Non-inferiority was to be established if the lower limit of the two-sided 95% CI for the treatment difference was greater than the pre-specified non-inferiority margin of -0.75 g/dL.

## Secondary: Number of Hgb Responders (Hgb in the Analysis Range of 10 to 11.5 grams/deciliter) During Evaluation Period (Week 28 to Week 52)

| End point title | Number of Hgb Responders (Hgb in the Analysis Range of 10 to 11.5 grams/deciliter) During Evaluation Period (Week 28 to Week 52) |
|---|---|

End point description:

Mean Hgb during the evaluation period was defined as the mean of all evaluable Hgb values during the evaluation period (Week 28 to Week 52) including any evaluable unscheduled Hgb values that were taken during this time period. Hgb responders were defined as number of participants with a mean Hgb during the evaluation period that falls within the Hgb analysis range of 10-11.5 g/dL. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

Weeks 28 to 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 133[17] | 133[18] | | |
| Units: Participants | 86 | 87 | | |

Notes:

[17] - ITT Population.

[18] - ITT Population.

### Statistical analyses

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

Statistical analysis description:

A Cochran-Mantel-Haenszel (CMH) test adjusted for treatment and randomization stratification factors were used to compare the number of responders between the treatment groups.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5411 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in response rate |
| Point estimate | -0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.2 |
| upper limit | 10.7 |

## Secondary: Percentage of Time for which Hgb was within the Analysis Range (10 to 11.5 g/dL) During Evaluation Period (Week 28 to Week 52): Non-inferiority analysis

| End point title | Percentage of Time for which Hgb was within the Analysis Range (10 to 11.5 g/dL) During Evaluation Period (Week 28 to Week 52): Non-inferiority analysis |
|---|---|

End point description:

Percentage of days for which a participant's Hgb was within the analysis range of 10-11.5 g/dL (both inclusive) during the evaluation period (Week 28 to Week 52), including any unscheduled evaluable Hgb values that were taken during this time period was calculated. Percentage of time for which Hgb was within range for a participant was calculated by dividing 'the total number of days that Hgb was within range during Weeks 28 to 52' by 'the total number of days the participant remained on treatment during Weeks 28 to 52'. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

Weeks 28 to 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128[19] | 129[20] | | |
| Units: Percentage of days | | | | |
| median (full range (min-max)) | 57.0 (0.0 to 100.0) | 54.7 (0.0 to 100.0) | | |

Notes:

[19] - ITT Population.

[20] - ITT Population.

### Statistical analyses

| Statistical analysis title | Statistical analysis |
|---|---|
| Statistical analysis description: | |
| Hodges-Lehmann Estimate of Treatment Difference has been reported. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 257 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[21] |
| Parameter estimate | Median difference (final values) |
| Point estimate | 2.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.45 |
| upper limit | 11.27 |

Notes:

[21] - Non-inferiority was to be established if the lower limit of the two-sided 95% confidence interval for the treatment difference was greater than non-inferiority margin of -15%.

### Secondary: Percentage of Time for which Hgb was within the Analysis Range (10 to 11.5 g/dL) During Evaluation Period (Week 28 to Week 52): Superiority analysis

| End point title | Percentage of Time for which Hgb was within the Analysis Range (10 to 11.5 g/dL) During Evaluation Period (Week 28 to Week 52): Superiority analysis |
|---|---|

End point description:

Percentage of days for which a participant's Hgb was within the analysis range of 10-11.5 g/dL (both inclusive) during the evaluation period (Week 28 to Week 52), including any unscheduled evaluable Hgb values that were taken during this time period was calculated. Percentage of time for which Hgb was within range for a participant was calculated by dividing 'the total number of days that Hgb was within range during Weeks 28 to 52' by 'the total number of days the participant remained on treatment during Weeks 28 to 52'. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

Weeks 28 to 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128[22] | 129[23] | | |
| Units: Percentage of days | | | | |
| median (full range (min-max)) | 57.0 (0.0 to 100.0) | 54.7 (0.0 to 100.0) | | |

Notes:

[22] - ITT Population.

[23] - ITT Population.

### Statistical analyses

| Statistical analysis title | Statistical analysis |
|---|---|
| Statistical analysis description: | |
| Mann-Whitney estimate (Probability) of the treatment effect has been presented. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 257 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1538 |
| Method | van Elteren test |
| Parameter estimate | Probability |
| Point estimate | 0.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.46 |
| upper limit | 0.61 |

## Secondary: Number of Participants Permanently Stopping Randomized Treatment Due to Meeting Rescue Criteria

| End point title | Number of Participants Permanently Stopping Randomized Treatment Due to Meeting Rescue Criteria |
|---|---|
| End point description: | |
| Number of participants permanently stopping randomized treatment due to meeting rescue criteria has been presented. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to Week 52 | |

| End point values | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 157[24] | 155[25] | | |
| Units: Participants | 5 | 5 | | |

Notes:
[24] - ITT Population
[25] - 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, dialysis type and dialysis start manner.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 312 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5348 |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.31 |
| upper limit | 3.66 |

### Secondary: Change from Baseline in Physical Component Score (PCS) using Short Form (SF)-36 Health-related Quality of Life (HRQoL) Questionnaire at Weeks 8, 12, 28, 52

| End point title | Change from Baseline in Physical Component Score (PCS) using Short Form (SF)-36 Health-related Quality of Life (HRQoL) Questionnaire at Weeks 8, 12, 28, 52 |
|---|---|

End point description:

SF-36 acute version2 is 36-item generic quality of life instrument designed to measure participant's level of performance in following 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/general health.Each domain is scored from 0(poorer health) to 100(better health). PCS is average score derived from 4domains(physical functioning,role-physical, bodily pain/general health) representing overall physical health.PCS ranges from 0 to 100;higher scores represent better health.Change from Baseline was calculated as post-dose visit value minus Baseline value.Baseline was defined as latest non-missing pre-dose assessment on or before randomization date. Only those participants with data available at indicated time points were analyzed (represented by n=X in the category titles)

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

End point timeframe:

Baseline (Day 1), Weeks 8, 12, 28 and 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88[26] | 88[27] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 8, n=88,86 | 0.79 (± 0.648) | 1.18 (± 0.658) | | |
| Week 12, n=88,88 | 1.67 (± 0.627) | 0.54 (± 0.631) | | |
| Week 28, n=80,74 | 0.94 (± 0.697) | 0.45 (± 0.725) | | |
| Week 52, n=67,65 | 0.61 (± 0.755) | 1.93 (± 0.774) | | |

Notes:

[26] - ITT Population.

[27] - ITT Population.

## Statistical analyses

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

Statistical analysis description:

SF-36 HRQoL PCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6641 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.22 |
| upper limit | 1.44 |

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

Statistical analysis description:

SF-36 HRQoL PCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.103 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 1.13 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.63 |
| upper limit | 2.89 |

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

Statistical analysis description:

SF-36 HRQoL PCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3157 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.51 |
| upper limit | 2.48 |

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

Statistical analysis description:

SF-36 HRQoL PCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8855 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.46 |
| upper limit | 0.84 |

## Secondary: Change from Baseline in Mental Component Score (MCS) using SF-36 HRQoL Questionnaire at Weeks 8, 12, 28, 52

| | |
|---|---|
| End point title | Change from Baseline in Mental Component Score (MCS) using |

| | |
|---|---|
| | SF-36 HRQoL Questionnaire at Weeks 8, 12, 28, 52 |

End point description:

SF-36 acute version2 is 36-item generic quality of life instrument designed to measure participant's level of performance in following 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/general health.Each domain is scored from 0(poorer health) to 100(better health). PCS is average score derived from 4domains(physical functioning,role-physical, bodily pain/general health) representing overall physical health.PCS ranges from 0 to 100;higher scores represent better health.Change from Baseline was calculated as post-dose visit value minus Baseline value.Baseline was defined as latest non-missing pre-dose assessment on or before randomization date. Only those participants with data available at indicated time points were analyzed (represented by n=X in the category titles).

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

End point timeframe:

Baseline (Day 1), Weeks 8, 12, 28 and 52

| **End point values** | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88[28] | 88[29] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 8, n=88,86 | 0.10 (± 0.822) | 0.76 (± 0.839) | | |
| Week 12, n=88,88 | 0.08 (± 0.813) | 1.60 (± 0.824) | | |
| Week 28, n=80,74 | -0.02 (± 0.905) | 0.30 (± 0.942) | | |
| Week 52, n=67,65 | -0.95 (± 1.029) | -0.72 (± 1.051) | | |

Notes:

[28] - ITT Population.

[29] - ITT Population.

## Statistical analyses

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

Statistical analysis description:

SF-36 HRQoL MCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7146 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.99 |
| upper limit | 1.66 |

| **Statistical analysis title** | Statistical analysis 2 |
|---|---|
| Statistical analysis description: | |
| SF-36 HRQoL MCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.905 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.82 |
| upper limit | 0.76 |

| **Statistical analysis title** | Statistical analysis 3 |
|---|---|
| Statistical analysis description: | |
| SF-36 HRQoL MCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.595 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.91 |
| upper limit | 2.28 |

| **Statistical analysis title** | Statistical analysis 4 |
|---|---|
| Statistical analysis description: | |
| SF-36 HRQoL MCS domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |

| | |
|---|---|
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5619 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.17 |
| upper limit | 2.7 |

## Secondary: Change from Baseline in SF-36 HRQoL Scores for Bodily Pain, General Health, Mental Health, Role-Emotional, Role-Physical, Social Functioning at Weeks 8, 12, 28, 52

| | |
|---|---|
| End point title | Change from Baseline in SF-36 HRQoL Scores for Bodily Pain, General Health, Mental Health, Role-Emotional, Role-Physical, Social Functioning at Weeks 8, 12, 28, 52 |

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 8 health domains: bodily pain, general health, mental health, role-emotional (role limitations caused by emotional problems), role-physical (role limitations caused by physical problems), social functioning, physical functioning and vitality. Each domain is scored from 0 (poorer health) to 100 (better health). Each domain score ranges from 0 to 100, higher score indicates a better health state and better functioning. Change from Baseline was calculated as post-dose visit value minus Baseline value. Baseline was defined as 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 (represented by n=X in the category titles).

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

End point timeframe:

Baseline (Day 1), Weeks 8, 12, 28 and 52

| **End point values** | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88[30] | 88[31] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Bodily pain: Week 8, n=88,86 | -0.41 (± 0.833) | -0.55 (± 0.843) | | |
| Bodily pain: Week 12, n=88,88 | -0.13 (± 0.892) | -0.06 (± 0.895) | | |
| Bodily pain: Week 28, n=80,74 | 1.08 (± 0.941) | -1.26 (± 0.976) | | |
| Bodily pain: Week 52, n=67,65 | -2.00 (± 1.084) | 0.61 (± 1.109) | | |
| General health: Week 8, n=88,86 | 0.80 (± 0.662) | 0.75 (± 0.674) | | |
| General health: Week 12, n=88,88 | 0.87 (± 0.651) | 0.59 (± 0.658) | | |
| General health: Week 28, n=80,74 | 0.63 (± 0.693) | 0.37 (± 0.720) | | |
| General health: Week 52, n=67,65 | 0.40 (± 0.823) | 0.58 (± 0.841) | | |

| | | | | |
|---|---|---|---|---|
| Mental health: Week 8, n=88,86 | -0.90 (± 0.825) | 0.25 (± 0.841) | | |
| Mental health: Week 12, n=88,88 | 0.01 (± 0.707) | 1.42 (± 0.712) | | |
| Mental health: Week 28, n=80,74 | -0.69 (± 0.866) | -0.21 (± 0.902) | | |
| Mental health: Week 52, n=67,65 | -0.53 (± 0.994) | -0.27 (± 1.013) | | |
| Role-emotional: Week 8, n=88,86 | 0.83 (± 0.880) | 0.50 (± 0.896) | | |
| Role-emotional: Week 12, n=88,88 | 0.55 (± 0.934) | -0.07 (± 0.946) | | |
| Role-emotional: Week 28, n=80,74 | 0.91 (± 0.929) | 0.39 (± 0.964) | | |
| Role-emotional: Week 52, n=67,65 | -1.60 (± 1.193) | -0.11 (± 1.216) | | |
| Role-physical: Week 8, n=88,86 | 1.34 (± 0.806) | 2.64 (± 0.818) | | |
| Role-physical: Week 12, n=88,88 | 2.39 (± 0.712) | 1.69 (± 0.716) | | |
| Role-physical: Week 28, n=80,74 | 0.62 (± 0.799) | 1.49 (± 0.829) | | |
| Role-physical: Week 52, n=67,65 | 1.49 (± 0.895) | 2.22 (± 0.913) | | |
| Social functioning: Week 8, n=88,86 | 0.52 (± 0.929) | 1.55 (± 0.947) | | |
| Social functioning: Week 12, n=88,88 | 0.98 (± 0.774) | 2.15 (± 0.783) | | |
| Social functioning: Week 28, n=80,74 | 1.03 (± 0.943) | 0.95 (± 0.980) | | |
| Social functioning: Week 52, n=67,65 | 0.39 (± 1.085) | -0.33 (± 1.105) | | |

Notes:

[30] - ITT Population.

[31] - ITT Population.

## Statistical analyses

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

Statistical analysis description:

SF-36 HRQoL bodily pain domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4523 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.21 |
| upper limit | 2.49 |

| **Statistical analysis title** | Statistical analysis 2 |
|---|---|

Statistical analysis description:

SF-36 HRQoL bodily pain domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |

| | |
|---|---|
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5222 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.57 |
| upper limit | 2.43 |

| **Statistical analysis title** | Statistical analysis 3 |
|---|---|
| Statistical analysis description: | |
| SF-36 HRQoL bodily pain domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.044 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 2.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.35 |
| upper limit | 5.02 |

| **Statistical analysis title** | Statistical analysis 4 |
|---|---|
| Statistical analysis description: | |
| SF-36 HRQoL bodily pain domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9523 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -2.61 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.68 |
| upper limit | 0.46 |

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

Statistical analysis description:

SF-36 HRQoL general health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4811 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.82 |
| upper limit | 1.91 |

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

Statistical analysis description:

SF-36 HRQoL general health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3834 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.56 |
| upper limit | 2.11 |

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

Statistical analysis description:

SF-36 HRQoL general health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3983 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.72 |
| upper limit | 2.24 |

| **Statistical analysis title** | Statistical analysis 8 |
|---|---|

Statistical analysis description:

SF-36 HRQoL general health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5617 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.51 |
| upper limit | 2.15 |

| **Statistical analysis title** | Statistical analysis 9 |
|---|---|

Statistical analysis description:

SF-36 HRQoL mental health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8336 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.15 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.48 |
| upper limit | 1.18 |

| **Statistical analysis title** | Statistical analysis 10 |
|---|---|

Statistical analysis description:

SF-36 HRQoL mental health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9188 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 0.57 |

| **Statistical analysis title** | Statistical analysis 11 |
|---|---|

Statistical analysis description:

SF-36 HRQoL mental health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6495 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.96 |
| upper limit | 1.99 |

| **Statistical analysis title** | Statistical analysis 12 |
|---|---|

Statistical analysis description:

SF-36 HRQoL mental health domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5737 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.09 |
| upper limit | 2.56 |

| **Statistical analysis title** | Statistical analysis 13 |
|---|---|

Statistical analysis description:

SF-36 HRQoL role-emotional domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3963 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.15 |
| upper limit | 2.82 |

| **Statistical analysis title** | Statistical analysis 14 |
|---|---|

Statistical analysis description:

SF-36 HRQoL role-emotional domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.322 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.62 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.01 |
| upper limit | 3.25 |

| **Statistical analysis title** | Statistical analysis 15 |
|---|---|

Statistical analysis description:

SF-36 HRQoL role-emotional domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3485 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.13 |
| upper limit | 3.18 |

| **Statistical analysis title** | Statistical analysis 16 |
|---|---|

Statistical analysis description:

SF-36 HRQoL role-emotional domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8064 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.87 |
| upper limit | 1.9 |

| **Statistical analysis title** | Statistical analysis 17 |
|---|---|

Statistical analysis description:

SF-36 HRQoL role-physical domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8687 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.57 |
| upper limit | 0.98 |

| **Statistical analysis title** | Statistical analysis 18 |
|---|---|

Statistical analysis description:

SF-36 HRQoL role-physical domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2435 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.29 |
| upper limit | 2.7 |

| **Statistical analysis title** | Statistical analysis 19 |
|---|---|

Statistical analysis description:

SF-36 HRQoL role-physical domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7747 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.87 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.15 |
| upper limit | 1.41 |

| **Statistical analysis title** | Statistical analysis 20 |
|---|---|
| Statistical analysis description: | |
| SF-36 HRQoL role-physical domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7141 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.26 |
| upper limit | 1.81 |

| **Statistical analysis title** | Statistical analysis 21 |
|---|---|
| Statistical analysis description: | |
| SF-36 HRQoL social functioning domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 8. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7803 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.65 |
| upper limit | 1.59 |

| **Statistical analysis title** | Statistical analysis 22 |
|---|---|

Statistical analysis description:

SF-36 HRQoL social functioning domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 12.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8556 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.35 |
| upper limit | 1 |

| **Statistical analysis title** | Statistical analysis 23 |
|---|---|

Statistical analysis description:

SF-36 HRQoL social functioning domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4763 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.61 |
| upper limit | 2.77 |

| **Statistical analysis title** | Statistical analysis 24 |
|---|---|

Statistical analysis description:

SF-36 HRQoL social functioning domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3208 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.73 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.35 |
| upper limit | 3.8 |

## Secondary: Change from Baseline in Vitality scores using SF-36 HRQoL Questionnaire at Weeks 28, 52

| End point title | Change from Baseline in Vitality scores using SF-36 HRQoL Questionnaire at Weeks 28, 52 |
|---|---|

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 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 health. Each domain is scored from 0 (poorer health) to 100 (better health). Vitality ranges from 0 to 100; higher scores represent better health. Change from Baseline was calculated as post-dose visit value minus Baseline value. Baseline was defined as 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 (represented by n=X in the category titles).

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

End point timeframe:

Baseline (Day 1), Weeks 28 and 52

| **End point values** | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80[32] | 74[33] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 28, n=80,74 | -0.08 (± 0.866) | 0.95 (± 0.902) | | |
| Week 52, n=67,65 | 0.16 (± 0.907) | 1.61 (± 0.925) | | |

Notes:

[32] - ITT Population.

[33] - ITT Population.

## Statistical analyses

| **Statistical analysis title** | Statistical analysis 2 |
|---|---|

Statistical analysis description:

SF-36 HRQoL vitality domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

| Comparison groups | Daprodustat v Darbepoetin alfa |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8648 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.03 |
| upper limit | 1.14 |

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

Statistical analysis description:

SF-36 HRQoL vitality domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.791 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.5 |
| upper limit | 1.46 |

## Secondary: Change from Baseline in Physical Functioning domain scores using SF-36 HRQoL Questionnaire at Weeks 28, 52

| End point title | Change from Baseline in Physical Functioning domain scores using SF-36 HRQoL Questionnaire at Weeks 28, 52 |
|---|---|

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 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 health. Each domain is scored from 0 (poorer health) to 100 (better health). Physical functioning ranges from 0 to 100; higher scores represent better health. Change from Baseline was calculated as post-dose visit value minus (-) Baseline value. Baseline was defined as 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 (represented by n=X in the category titles).

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

End point timeframe:

Baseline (Day 1), Weeks 28 and 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80[34] | 74[35] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 28, n=80,74 | 0.55 (± 0.863) | 0.83 (± 0.898) | | |
| Week 52, n=67,65 | 0.14 (± 0.947) | 1.58 (± 0.973) | | |

Notes:

[34] - ITT Population.

[35] - ITT Population.

## Statistical analyses

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

Statistical analysis description:

SF-36 HRQoL physical functioning domain scor was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 52.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8525 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.12 |
| upper limit | 1.26 |

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

Statistical analysis description:

SF-36 HRQoL physical functioning domain score was analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in LS means between arms at Week 28.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5879 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.28 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.75 |
| upper limit | 2.19 |

## Secondary: Change from Baseline in Health Utility EuroQol 5 Dimensions 5 Level (EQ-5D-5L) Questionnaire Score at Week 52

| End point title | Change from Baseline in Health Utility EuroQol 5 Dimensions 5 Level (EQ-5D-5L) Questionnaire Score at Week 52 |
|---|---|

End point description:

EQ-5D-5L consists of 2concepts–EQ-5D-5L descriptive system and EQ Visual Analogue Scale(EQ-VAS).EQ-5D-5L is self-assessment questionnaire,consisting of 5items covering 5dimensions(mobility,self care,usual activities,pain/discomfort and anxiety/depression).Each dimension is measured by 5-point Likert scale(no problems,slight problems,moderate problems,severe problems and extreme problems).Responses for 5 dimensions together formed a 5-figure description of health state(e.g.11111 indicates no problems in all 5dimensions).Each of these 5 figure health states were converted to a single index score by applying country-specific value set formula that attaches weights to dimensions and levels.Range for EQ-5D-5L index score is -0.594(worst health) to 1(full health),higher score better health status.Change from Baseline was calculated as post-dose visit value-Baseline value.Baseline was latest non-missing pre-dose assessment on or before randomization date.

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

End point timeframe:

Baseline (Day 1) and Week 52

| **End point values** | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24[36] | 25[37] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | 0.00 (± 0.041) | -0.03 (± 0.040) | | |

Notes:

[36] - ITT Population.

[37] - ITT Population.

### Statistical analyses

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

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

| Comparison groups | Daprodustat v Darbepoetin alfa |
|---|---|
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3154 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.03 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.09 |
| upper limit | 0.14 |

## Secondary: Change from Baseline in EQ Visual Analogue Scale (EQ-VAS) at Week 52

| End point title | Change from Baseline in EQ Visual Analogue Scale (EQ-VAS) at Week 52 |
|---|---|

End point description:

EQ-5D-5L consists of 2 concepts –EQ-5D-5L descriptive system and EQ-VAS. The EQ-5D-5L is a self-assessment questionnaire, consisting of 5 items covering five dimensions (mobility, self care, usual activities, pain/discomfort and anxiety/depression). Each dimension is measured by 5-point Likert scale (no problems, slight problems, moderate problems, severe problems, and extreme problems). The range for EQ-5D-5L index score is 0 to 1 with '0' is worst health and '1' is full health. EQ VAS records respondent's self-rated health on a vertical VAS, ranging from 0 to 100, where 0 represents worst health one can imagine and 100 represents best health one can imagine. Change from Baseline was calculated as post-dose visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the 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 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24[38] | 25[39] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | 3.4 (± 3.27) | 6.8 (± 3.28) | | |

Notes:

[38] - ITT Population.

[39] - ITT Population.

### Statistical analyses

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

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

| Comparison groups | Daprodustat v Darbepoetin alfa |
|---|---|
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7651 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -3.4 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.7 |
| upper limit | 5.9 |

## Secondary: Change from Baseline in Chronic Kidney Disease- Anemia Symptoms Questionnaire (CKD-AQ) at Week 52

| End point title | Change from Baseline in Chronic Kidney Disease- Anemia Symptoms Questionnaire (CKD-AQ) at Week 52 |
|---|---|

End point description:

CKD-AQ is 21-item patient reported outcome measure assessing symptoms/symptom impact in participants with anemia associated with CKD. It had 3domains:1.Tired/Low Energy/Weak scale consisting of 10 items;2.Chest Pain/Shortness of Breath scale consisting of 4items; 3.Cognitive scale consisting of 3 items. 4CKD-AQ single items are(shortness of breath, no activity),(severity-short breath, resting),(difficulty standing for long time)/(difficulty sleeping).Single-item were recorded based on 0-100 scoring with 0=worst possible;100=best possible score. 3 domains scores were calculated as average of items in each domain/ranged from 0-100;0=worst possible&100=best possible score.Change from Baseline was calculated as post-dose visit value minus Baseline value.Baseline was defined as latest non-missing pre-dose assessment on or before 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 52

| **End point values** | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 76[40] | 80[41] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Tired/Low energy/Weak domain | -2.36 (± 2.007) | 4.07 (± 1.990) | | |
| Chest pain/Shortness of breath domain | -1.83 (± 1.593) | 2.28 (± 1.557) | | |
| Cognitive domain | -4.17 (± 1.893) | 2.43 (± 1.852) | | |
| Shortness of breath, no activity | -1.90 (± 1.861) | 1.14 (± 1.826) | | |
| Severity-short breath, Resting | -4.16 (± 1.869) | 0.12 (± 1.836) | | |
| Difficulty standing for long time | -2.00 (± 2.812) | 3.30 (± 2.754) | | |
| Difficulty sleeping | -5.27 (± 2.667) | 1.26 (± 2.611) | | |

Notes:

[40] - ITT Population.

[41] - ITT Population.

### Statistical analyses

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

Statistical analysis description:

Tired/Low energy/Weak domain: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9875 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -6.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.05 |
| upper limit | -0.82 |

| **Statistical analysis title** | Statistical analysis 2 |
|---|---|

Statistical analysis description:

Chest pain/Shortness of breath domain: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9663 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -4.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.52 |
| upper limit | 0.3 |

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

Statistical analysis description:

Cognitive domain: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |

| | |
|---|---|
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.993 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -6.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.84 |
| upper limit | -1.35 |

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

Statistical analysis description:

Shortness of breath, no activity: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8765 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -3.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.19 |
| upper limit | 2.12 |

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

Statistical analysis description:

Severity-short breath, Resting: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9464 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -4.27 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.48 |
| upper limit | 0.94 |

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

Statistical analysis description:

Difficulty standing for long time: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9101 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -5.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.09 |
| upper limit | 2.47 |

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

Statistical analysis description:

Difficulty sleeping: MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9586 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -6.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.9 |
| upper limit | 0.86 |

## 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 value. Baseline was defined as 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 (represented by n=X in the category titles).

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

End point timeframe:

Baseline (Day 1), Weeks 8, 12, 28 and 52

| **End point values** | Daprodustat | Darbepoetin alfa | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 100[42] | 103[43] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 8, n=100,100 | 0.16 (± 0.091) | -0.11 (± 0.092) | | |
| Week 12, n=100,103 | 0.02 (± 0.077) | -0.03 (± 0.077) | | |
| Week 28, n=92,85 | 0.09 (± 0.086) | -0.07 (± 0.089) | | |
| Week 52, n=75,77 | 0.22 (± 0.106) | 0.04 (± 0.105) | | |

Notes:

[42] - ITT Population.

[43] - ITT Population.

## Statistical analyses

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

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 8 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

| Comparison groups | Daprodustat v Darbepoetin alfa |
|---|---|
| Number of subjects included in analysis | 203 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.981 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.02 |
| upper limit | 0.53 |

| **Statistical analysis title** | Statistical analysis 2 |
|---|---|

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 12 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 203 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6743 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.17 |
| upper limit | 0.26 |

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

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 28 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 203 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8997 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.09 |
| upper limit | 0.4 |

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

Statistical analysis description:

MMRM model was fitted from Baseline up to Week 52 with factors for treatment, time, dialysis type, dialysis start manner, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|---|
| Comparison groups | Daprodustat v Darbepoetin alfa |

| | |
|---|---|
| Number of subjects included in analysis | 203 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8835 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.12 |
| upper limit | 0.47 |

## Secondary: Plasma Concentration of Daprodustat (GSK1278863) and its Metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13)

| | |
|---|---|
| End point title | Plasma Concentration of Daprodustat (GSK1278863) and its Metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13) |

End point description:

Pharmacokinetic samples were collected at pre-dose, 0.5, 1, 2 and 3 hours post-dose on Week 4 or 8 or 12 for pharmacokinetic (PK) analysis of daprodustat (GSK1278863) and its metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13). GSK2391220, GSK2506104 and GSK2531401 are the metabolites of Daprodustat (GSK1278863). Protocol allowed participants to provide pharmacokinetic samples on Week 4 or 8 or 12. Pharmacokinetic Population comprised of participants for whom a pharmacokinetic sample was obtained and analyzed. Only those participants with data available at the indicated time points were analyzed (represented by n=X in the category titles). Blood samples were not collected for PK analysis of daprodustat 12, 16 and 24 mg arms. 99999 indicates, Standard deviation could not be calculated for single participant. 88888 indicates, data is not available.

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

End point timeframe:

Pre-dose, 0.5, 1, 2 and 3 hours post-dose; each pharmacokinetic sample was taken at Week 4 or 8 or 12

| End point values | Daprodustat 1 mg | Daprodustat 2 mg | Daprodustat 4 mg | Daprodustat 6 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19[44] | 26[45] | 20[46] | 18[47] |
| Units: Nanogram per milliliter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Daprodustat: Pre-Dose, n=19,26,20,18,1,1 | 2.118 (± 5.0030) | 1.015 (± 3.1451) | 0.5787 (± 1.5718) | 2.867 (± 6.6142) |
| Daprodustat: 0.5 hour, n=19,26,20,18,0,1 | 5.675 (± 8.4998) | 4.664 (± 8.7508) | 10.27 (± 20.425) | 12.58 (± 23.742) |
| Daprodustat: 1 hour, n=19,26,20,18,1,1 | 12.34 (± 13.435) | 21.45 (± 42.160) | 36.78 (± 62.497) | 45.48 (± 48.765) |
| Daprodustat: 2 hours, n=19,26,20,18,1,1 | 12.74 (± 9.9019) | 20.36 (± 22.210) | 54.68 (± 80.284) | 55.62 (± 51.471) |
| Daprodustat: 3 hours, n=19,26,19,18,1,1 | 7.719 (± 5.9144) | 15.58 (± 13.694) | 43.34 (± 66.295) | 56.49 (± 74.357) |
| GSK2391220: Pre-Dose, n=19,26,20,18,1,1 | 0.7106 (± 0.64028) | 2.124 (± 2.8721) | 2.087 (± 2.1371) | 3.560 (± 4.2255) |

| | | | | |
|---|---|---|---|---|
| GSK2391220: 0.5 hour, n=19,25,20,18,1,1 | 0.7602 (± 0.67950) | 1.807 (± 2.2007) | 1.822 (± 2.1355) | 2.410 (± 2.8243) |
| GSK2391220: 1 hour, n=18,26,20,18,1,1 | 1.123 (± 0.76920) | 1.752 (± 1.8589) | 1.965 (± 2.2830) | 3.140 (± 2.4856) |
| GSK2391220: 2 hours, n=19,26,20,18,1,1 | 1.745 (± 1.3160) | 2.969 (± 2.4659) | 4.008 (± 4.4522) | 6.336 (± 4.3723) |
| GSK2391220: 3 hours, n=19,26,19,18,1,1 | 1.911 (± 1.2274) | 3.535 (± 2.7203) | 5.553 (± 6.5157) | 9.372 (± 6.6452) |
| GSK2506104: Pre-Dose, n=19,26,20,18,1,1 | 1.270 (± 0.96071) | 3.508 (± 4.2066) | 3.879 (± 3.4207) | 5.921 (± 5.8981) |
| GSK2506104: 0.5 hour, n=19,26,20,18,1,1 | 1.197 (± 0.85104) | 2.788 (± 2.9893) | 3.315 (± 3.4249) | 4.015 (± 3.7385) |
| GSK2506104: 1 hour, n=19,26,20,18,1,1 | 1.364 (± 0.96292) | 2.610 (± 2.4761) | 3.268 (± 3.4808) | 4.333 (± 3.0505) |
| GSK2506104: 2 hours, n=19,26,20,18,1,1 | 1.966 (± 1.3440) | 3.583 (± 2.8427) | 4.989 (± 5.2109) | 7.130 (± 4.5105) |
| GSK2506104: 3 hours, n=19,26,19,18,1,1 | 2.190 (± 1.3898) | 4.145 (± 3.1757) | 6.503 (± 7.5130) | 9.942 (± 7.0616) |
| GSK2531401: Pre-Dose, n=19,26,20,18,1,1 | 1.642 (± 1.4836) | 2.729 (± 1.8934) | 3.750 (± 3.8006) | 5.111 (± 4.0632) |
| GSK2531401: 0.5 hour, n=19,26,20,18,1,1 | 1.427 (± 1.2870) | 2.170 (± 1.6621) | 3.263 (± 3.8737) | 3.800 (± 2.8722) |
| GSK2531401: 1 hour, n=19,26,20,18,1,1 | 1.399 (± 1.4595) | 1.979 (± 1.6316) | 3.146 (± 4.0334) | 3.776 (± 3.4411) |
| GSK2531401: 2 hours, n=19,26,20,18,1,1 | 1.690 (± 1.6309) | 2.338 (± 2.1467) | 3.711 (± 5.0223) | 4.892 (± 4.7877) |
| GSK2531401: 3 hours, n=19,26,19,18,1,1 | 1.847 (± 1.7376) | 2.734 (± 2.6846) | 4.715 (± 7.2788) | 6.631 (± 7.1049) |

Notes:

[44] - Pharmacokinetic Population.

[45] - Pharmacokinetic Population.

[46] - Pharmacokinetic Population.

[47] - Pharmacokinetic Population.

| **End point values** | Daprodustat 8 mg | Daprodustat 10 mg | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1[48] | 1[49] | | |
| Units: Nanogram per milliliter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Daprodustat: Pre-Dose, n=19,26,20,18,1,1 | 0.1030 (± 99999) | 0.1090 (± 99999) | | |
| Daprodustat: 0.5 hour, n=19,26,20,18,0,1 | 88888 (± 88888) | 145.0 (± 99999) | | |
| Daprodustat: 1 hour, n=19,26,20,18,1,1 | 0.9120 (± 99999) | 79.60 (± 99999) | | |
| Daprodustat: 2 hours, n=19,26,20,18,1,1 | 32.00 (± 99999) | 27.60 (± 99999) | | |
| Daprodustat: 3 hours, n=19,26,19,18,1,1 | 25.30 (± 99999) | 11.00 (± 99999) | | |
| GSK2391220: Pre-Dose, n=19,26,20,18,1,1 | 4.450 (± 99999) | 6.560 (± 99999) | | |
| GSK2391220: 0.5 hour, n=19,25,20,18,1,1 | 3.950 (± 99999) | 6.740 (± 99999) | | |
| GSK2391220: 1 hour, n=18,26,20,18,1,1 | 3.900 (± 99999) | 10.00 (± 99999) | | |
| GSK2391220: 2 hours, n=19,26,20,18,1,1 | 4.700 (± 99999) | 16.20 (± 99999) | | |
| GSK2391220: 3 hours, n=19,26,19,18,1,1 | 6.090 (± 99999) | 16.60 (± 99999) | | |

| | | | | |
|---|---|---|---|---|
| GSK2506104: Pre-Dose, n=19,26,20,18,1,1 | 8.710 (± 99999) | 9.500 (± 99999) | | |
| GSK2506104: 0.5 hour, n=19,26,20,18,1,1 | 7.740 (± 99999) | 8.110 (± 99999) | | |
| GSK2506104: 1 hour, n=19,26,20,18,1,1 | 7.460 (± 99999) | 12.40 (± 99999) | | |
| GSK2506104: 2 hours, n=19,26,20,18,1,1 | 8.930 (± 99999) | 19.60 (± 99999) | | |
| GSK2506104: 3 hours, n=19,26,19,18,1,1 | 10.10 (± 99999) | 22.00 (± 99999) | | |
| GSK2531401: Pre-Dose, n=19,26,20,18,1,1 | 5.660 (± 99999) | 7.760 (± 99999) | | |
| GSK2531401: 0.5 hour, n=19,26,20,18,1,1 | 4.960 (± 99999) | 6.460 (± 99999) | | |
| GSK2531401: 1 hour, n=19,26,20,18,1,1 | 4.810 (± 99999) | 6.630 (± 99999) | | |
| GSK2531401: 2 hours, n=19,26,20,18,1,1 | 5.190 (± 99999) | 8.290 (± 99999) | | |
| GSK2531401: 3 hours, n=19,26,19,18,1,1 | 5.760 (± 99999) | 10.20 (± 99999) | | |

Notes:

[48] - Pharmacokinetic Population.

[49] - Pharmacokinetic Population.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Observed concentration at Dosing Interval (Ctau) of Daprodustat (GSK1278863) and its Metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13)

| | |
|---|---|
| End point title | Observed concentration at Dosing Interval (Ctau) of Daprodustat (GSK1278863) and its Metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13) |

End point description:

Pharmacokinetic samples were collected at pre-dose, 0.5, 1, 2 and 3 hours post-dose on Week 4 or 8 or 12 for pharmacokinetic analysis of daprodustat (GSK1278863) and its metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13). GSK2391220, GSK2506104 and GSK2531401 are the metabolites of Daprodustat (GSK1278863). Protocol allowed participants to provide pharmacokinetic samples on Week 4 or 8 or 12. Only those participants with data available at the indicated time points were analyzed. Blood samples were not collected for PK analysis of daprodustat 12, 16 and 24 mg arms. 99999 indicates, Standard deviation could not be calculated for single participant.

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

End point timeframe:

Pre-Dose, 0.5, 1, 2 and 3 hours post-dose; each pharmacokinetic sample was taken at Week 4 or 8 or 12

| End point values | Daprodustat 1 mg | Daprodustat 2 mg | Daprodustat 4 mg | Daprodustat 6 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19[50] | 26[51] | 20[52] | 18[53] |
| Units: Nanogram per milliliter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Daprodustat | 2.118 (± 5.0030) | 1.015 (± 3.1451) | 0.5787 (± 1.5718) | 2.867 (± 6.6142) |

| | | | | |
|---|---|---|---|---|
| GSK2391220 | 0.7106 (± 0.64028) | 2.124 (± 2.8721) | 2.087 (± 2.1371) | 3.560 (± 4.2255) |
| GSK2506104 | 1.270 (± 0.96071) | 3.508 (± 4.2066) | 3.879 (± 3.4207) | 5.921 (± 5.8981) |
| GSK2531401 | 1.642 (± 1.4836) | 2.729 (± 1.8934) | 3.750 (± 3.8006) | 5.111 (± 4.0632) |

Notes:

[50] - Pharmacokinetic Population.

[51] - Pharmacokinetic Population.

[52] - Pharmacokinetic Population.

[53] - Pharmacokinetic Population.

| **End point values** | Daprodustat 8 mg | Daprodustat 10 mg | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1[54] | 1[55] | | |
| Units: Nanogram per milliliter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Daprodustat | 0.1030 (± 99999) | 0.1090 (± 99999) | | |
| GSK2391220 | 4.450 (± 99999) | 6.560 (± 99999) | | |
| GSK2506104 | 8.710 (± 99999) | 9.500 (± 99999) | | |
| GSK2531401 | 5.660 (± 99999) | 7.760 (± 99999) | | |

Notes:

[54] - Pharmacokinetic Population.

[55] - Pharmacokinetic Population.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Observed Concentration (Cmax) of Daprodustat (GSK1278863) and its Metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13)

| | |
|---|---|
| End point title | Maximum Observed Concentration (Cmax) of Daprodustat (GSK1278863) and its Metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13) |

End point description:

Pharmacokinetic samples were collected at pre-dose, 0.5, 1, 2 and 3 hours post-dose on Week 4 or 8 or 12 for pharmacokinetic analysis of daprodustat (GSK1278863) and its metabolites GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13). GSK2391220, GSK2506104 and GSK2531401 are the metabolites of Daprodustat (GSK1278863). Protocol allowed participants to provide pharmacokinetic samples on Week 4 or 8 or 12. Only those participants with data available at the indicated time points were analyzed. Blood samples were not collected for PK analysis of daprodustat 12, 16 and 24 mg arms. 99999 indicates, Standard deviation could not be calculated for single participant.

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

End point timeframe:

Pre-Dose, 0.5, 1, 2 and 3 hours post-dose; each pharmacokinetic sample was taken at Week 4 or 8 or 12

| End point values | Daprodustat 1 mg | Daprodustat 2 mg | Daprodustat 4 mg | Daprodustat 6 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19[56] | 26[57] | 20[58] | 18[59] |
| Units: Nanogram per milliliter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Daprodustat | 21.74 (± 10.998) | 32.29 (± 40.166) | 76.92 (± 81.867) | 100.2 (± 74.086) |
| GSK2391220 | 2.160 (± 1.2596) | 4.139 (± 3.3561) | 5.780 (± 6.2840) | 10.36 (± 6.3377) |
| GSK2506104 | 2.477 (± 1.3625) | 5.212 (± 4.5562) | 7.075 (± 7.1313) | 11.60 (± 6.8731) |
| GSK2531401 | 2.283 (± 1.8210) | 3.565 (± 2.6091) | 5.328 (± 6.9034) | 7.836 (± 6.6199) |

Notes:

[56] - Pharmacokinetic Population.

[57] - Pharmacokinetic Population.

[58] - Pharmacokinetic Population.

[59] - Pharmacokinetic Population.

| End point values | Daprodustat 8 mg | Daprodustat 10 mg | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1[60] | 1[61] | | |
| Units: Nanogram per milliliter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Daprodustat | 32.00 (± 99999) | 145.0 (± 99999) | | |
| GSK2391220 | 6.090 (± 99999) | 16.60 (± 99999) | | |
| GSK2506104 | 10.10 (± 99999) | 22.00 (± 99999) | | |
| GSK2531401 | 5.760 (± 99999) | 10.20 (± 99999) | | |

Notes:

[60] - Pharmacokinetic Population.

[61] - Pharmacokinetic Population.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All-cause mortality, treatment emergent non-serious adverse events and serious adverse events were collected up to follow-up visit (Week 58)

Adverse event reporting additional description:

Safety Population comprised of all randomized participants who received at least one dose of randomized treatment.

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

### Dictionary used

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

### Reporting groups

| | |
|---|---|
| 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, and 24 milligrams (mg) orally once daily for up to 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 grams per deciliter [g/dL]).

| | |
|---|---|
| Reporting group title | Darbepoetin alfa |

Reporting group description:

Participants received darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection with 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 120, 160, 200, 300 and 400 microgram (mcg) for 52 weeks. Study treatment was dose-titrated to achieve and maintain hemoglobin in the target range (10 to 11 g/dL).

| Serious adverse events | Daprodustat | Darbepoetin alfa | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 52 / 157 (33.12%) | 51 / 155 (32.90%) | |
| number of deaths (all causes) | 17 | 12 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer metastatic | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thyroid cancer stage I | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 157 (1.27%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive emergency | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive urgency | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphocele | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Steal syndrome | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| 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 | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 2 / 155 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Pyrexia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 2 / 157 (1.27%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metrorrhagia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (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 | | | |
| Chronic obstructive pulmonary disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 2 / 155 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 2 / 155 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Asthma | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device malfunction | | | |
| subjects affected / exposed | 4 / 157 (2.55%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 2 / 155 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Arteriovenous fistula thrombosis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 4 / 155 (2.58%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous fistula site complication | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 2 / 155 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia postoperative | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous graft thrombosis | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inadequate haemodialysis | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Open globe injury | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritoneal dialysate leakage | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritoneal dialysis complication | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Unintentional medical device removal | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular access malfunction | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Hypertrophic cardiomyopathy | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 3 / 155 (1.94%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 2 / 155 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 2 / 155 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 2 / 157 (1.27%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (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 | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive heart disease | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus bradycardia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Nervous system disorders** | | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 2 / 155 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive encephalopathy | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uraemic encephalopathy | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (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 | | | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Retinopathy hypertensive | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 3 / 155 (1.94%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Volvulus | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bloody peritoneal effluent | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (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 / 157 (0.64%) | 0 / 155 (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 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hydrocholecystis | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| 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 | | | |
| Diabetic foot | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Azotaemia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 157 (2.55%) | 7 / 155 (4.52%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Peritonitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 157 (0.64%) | 3 / 155 (1.94%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 2 / 157 (1.27%) | 2 / 155 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Post procedural infection | | | |
| subjects affected / exposed | 3 / 157 (1.91%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 3 / 155 (1.94%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 157 (1.27%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiolitis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Clostridial sepsis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related bacteraemia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia infection | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (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 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Helicobacter gastritis | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected skin ulcer | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leptospirosis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (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 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal infection | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 155 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Fluid overload | | | |
| subjects affected / exposed | 5 / 157 (3.18%) | 3 / 155 (1.94%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 157 (1.27%) | 2 / 155 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 157 (0.00%) | 3 / 155 (1.94%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 155 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Daprodustat | Darbepoetin alfa | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 76 / 157 (48.41%) | 74 / 155 (47.74%) | |
| Injury, poisoning and procedural complications | | | |
| Arteriovenous fistula site complication | | | |
| subjects affected / exposed | 4 / 157 (2.55%) | 8 / 155 (5.16%) | |
| occurrences (all) | 4 | 13 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 27 / 157 (17.20%) | 24 / 155 (15.48%) | |
| occurrences (all) | 51 | 35 | |
| Dialysis hypotension | | | |
| subjects affected / exposed | 21 / 157 (13.38%) | 15 / 155 (9.68%) | |
| occurrences (all) | 34 | 22 | |
| Hypotension | | | |
| subjects affected / exposed | 7 / 157 (4.46%) | 9 / 155 (5.81%) | |
| occurrences (all) | 8 | 9 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 12 / 157 (7.64%) | 9 / 155 (5.81%) | |
| occurrences (all) | 14 | 10 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 14 / 157 (8.92%) | 10 / 155 (6.45%) | |
| occurrences (all) | 17 | 10 | |

| | | | |
|---|---|---|---|
| Vomiting | | | |
| subjects affected / exposed | 11 / 157 (7.01%) | 5 / 155 (3.23%) | |
| occurrences (all) | 16 | 5 | |
| Nausea | | | |
| subjects affected / exposed | 8 / 157 (5.10%) | 6 / 155 (3.87%) | |
| occurrences (all) | 13 | 6 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 7 / 157 (4.46%) | 9 / 155 (5.81%) | |
| occurrences (all) | 12 | 12 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 157 (4.46%) | 9 / 155 (5.81%) | |
| occurrences (all) | 12 | 9 | |
| Catheter site infection | | | |
| subjects affected / exposed | 5 / 157 (3.18%) | 8 / 155 (5.16%) | |
| occurrences (all) | 5 | 11 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 157 (4.46%) | 11 / 155 (7.10%) | |
| occurrences (all) | 9 | 12 | |
| Metabolism and nutrition disorders | | | |
| Fluid overload | | | |
| subjects affected / exposed | 9 / 157 (5.73%) | 6 / 155 (3.87%) | |
| occurrences (all) | 9 | 7 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 06 October 2017 | Amendment 1:<br>Updated time period of planning to start dialysis from the screening to 6 weeks, when appropriate; Removed number of screening participants and stated only an approximate number of randomized participants required; Modified PD inclusion criteria to allow participants on >=4 times/week PD including an incremental schedule; Removed France country specific requirement for Informed Consent process from inclusion criteria; Broadened exclusion to include participation in an interventional study with an investigational agent or device; Removed option to have Early Treatment Discontinuation visit supersede the scheduled visit; Added a provision that in unexpected circumstances where the supply to the site is interrupted, local SOC for anemia management during this time period may be considered; Added direction regarding randomized treatment and study continuation for participants who will be away from the research site for an extended period of time; Added new darbepoetin alfa dose strengths (not available in all countries); Clarified timeframe for iron management criteria; Clarified timing of designated study visits for participants who have not yet initiated dialysis and for participants on dialysis; Shortened visit window for week 2 and 4; Changed time point for blinded data cut need for psychometric validation of the CKD Questionnaire; Revised statistical section to change from 2-sided testing at the 5% level to 1-sided testing at the 2.5% level; for secondary endpoints, to change significance levels to p-values and to correct the time point for various PRO;Provision for possible adjustment to the Dose Adjustment Algorithm triggers for Hgb values 7.5 grams per deciliter (g/dL) to <9.5 g/dL based on review of blinded instream Hgb data; Updated FSH level to confirm menopause in Appendix 5, Female Eligibility Criteria |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported