



Clinical trial results:

A phase 3 randomized, open-label (sponsor-blind), active-controlled, parallel-group, multi-center, event driven study in non-dialysis subjects with anemia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to darbepoetin alfa

Summary

| | |
|--------------------------|---|
| EudraCT number | 2016-000542-65 |
| Trial protocol | HU BE GB DK AT CZ DE PT SE ES NL BG GR FR PL IT |
| Global end of trial date | 19 April 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v2 (current) |
| This version publication date | 28 April 2022 |
| First version publication date | 08 March 2022 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 200808 |
|-----------------------|--------|

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 | 02 August 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 19 April 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To compare daprodustat to darbepoetin alfa for cardiovascular (CV) safety (non-inferiority)
- To compare daprodustat to darbepoetin alfa for hemoglobin (Hgb) efficacy (non-inferiority)

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 27 September 2016 |
| 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 | Hong Kong: 29 |
| Country: Number of subjects enrolled | India: 144 |
| Country: Number of subjects enrolled | Korea, Republic of: 323 |
| Country: Number of subjects enrolled | Malaysia: 71 |
| Country: Number of subjects enrolled | Philippines: 79 |
| Country: Number of subjects enrolled | Singapore: 18 |
| Country: Number of subjects enrolled | Taiwan: 120 |
| Country: Number of subjects enrolled | Thailand: 64 |
| Country: Number of subjects enrolled | Viet Nam: 140 |
| Country: Number of subjects enrolled | Bulgaria: 128 |
| Country: Number of subjects enrolled | Czechia: 40 |
| Country: Number of subjects enrolled | Estonia: 5 |
| Country: Number of subjects enrolled | Hungary: 90 |
| Country: Number of subjects enrolled | Poland: 51 |
| Country: Number of subjects enrolled | Romania: 49 |
| Country: Number of subjects enrolled | Russian Federation: 82 |
| Country: Number of subjects enrolled | South Africa: 25 |
| Country: Number of subjects enrolled | Turkey: 19 |
| Country: Number of subjects enrolled | Ukraine: 198 |
| Country: Number of subjects enrolled | Australia: 72 |
| Country: Number of subjects enrolled | Belgium: 43 |
| Country: Number of subjects enrolled | Canada: 29 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Denmark: 15 |
| Country: Number of subjects enrolled | France: 42 |
| Country: Number of subjects enrolled | Germany: 17 |
| Country: Number of subjects enrolled | Greece: 143 |
| Country: Number of subjects enrolled | Israel: 37 |
| Country: Number of subjects enrolled | Italy: 21 |
| Country: Number of subjects enrolled | Netherlands: 6 |
| Country: Number of subjects enrolled | New Zealand: 34 |
| Country: Number of subjects enrolled | Portugal: 41 |
| Country: Number of subjects enrolled | Spain: 56 |
| Country: Number of subjects enrolled | Sweden: 3 |
| Country: Number of subjects enrolled | United Kingdom: 67 |
| Country: Number of subjects enrolled | Argentina: 146 |
| Country: Number of subjects enrolled | Brazil: 128 |
| Country: Number of subjects enrolled | Colombia: 37 |
| Country: Number of subjects enrolled | Mexico: 279 |
| Country: Number of subjects enrolled | United States: 981 |
| Worldwide total number of subjects | 3872 |
| EEA total number of subjects | 750 |

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) | 1678 |
| From 65 to 84 years | 1971 |
| 85 years and over | 223 |

Subject disposition

Recruitment

Recruitment details:

This was a multicenter study conducted across 39 countries. Participants were randomized to receive either daprodustat or darbepoetin alfa.

Pre-assignment

Screening details:

A total of 3872 participants were enrolled in the study.

Period 1

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

Arms

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

Arm description:

Participants received placebo tablets orally once daily in run-in period from Week-4 up to randomization (Day 1) and subsequently received treatment with daprodustat film-coated tablets at dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 and 24 milligrams (mg) orally once daily up to 51.1 month. 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:

Daprodustat was given orally once daily at dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 and 24 milligrams (mg).

| | |
|--|----------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo was administered orally, one tablet daily.

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

Arm description:

Participants received placebo tablets orally once daily in run-in period from Week-4 up to randomization (Day 1) and subsequently received treatment with darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection at 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 100, 150, 200, 300 and 400 microgram (mcg) up to 51.1 month. Darbepoetin alfa IV injection was administered to participants undergoing hemodialysis. 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 | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo was administered orally, one tablet daily.

| | |
|--|---|
| Investigational medicinal product name | Darbepoetin alfa |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection, Solution for injection in pre-filled syringe |
| Routes of administration | Intravenous use, Subcutaneous use |

Dosage and administration details:

Darbepoetin alfa was administered subcutaneously (SC) or as intravenous (IV) injection with 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 100, 150, 200, 300 and 400 microgram (mcg).

| Number of subjects in period 1 | Daprodustat | Darbepoetin alfa |
|---------------------------------------|-------------|------------------|
| Started | 1937 | 1935 |
| Completed | 1873 | 1870 |
| Not completed | 64 | 65 |
| Consent withdrawn by subject | 32 | 23 |
| Unknown | 1 | - |
| Investigator Site Closed | 6 | 13 |
| Lost to follow-up | 25 | 29 |

Baseline characteristics

Reporting groups

| | |
|--|------------------|
| Reporting group title | Daprodustat |
| Reporting group description: | |
| Participants received placebo tablets orally once daily in run-in period from Week-4 up to randomization (Day 1) and subsequently received treatment with daprodustat film-coated tablets at dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 and 24 milligrams (mg) orally once daily up to 51.1 month. 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 placebo tablets orally once daily in run-in period from Week-4 up to randomization (Day 1) and subsequently received treatment with darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection at 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 100, 150, 200, 300 and 400 microgram (mcg) up to 51.1 month. Darbepoetin alfa IV injection was administered to participants undergoing hemodialysis. 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 | 1937 | 1935 | 3872 |
| Age categorical Units: Participants | | | |
| 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) | 836 | 842 | 1678 |
| From 65-84 years | 994 | 977 | 1971 |
| 85 years and over | 107 | 116 | 223 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 64.8 | 64.9 | - |
| standard deviation | ± 14.03 | ± 13.83 | - |
| Sex: Female, Male Units: Participants | | | |
| Female | 1102 | 1071 | 2173 |
| Male | 835 | 864 | 1699 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| American Indian or Alaskan Native | 88 | 100 | 188 |
| Asian - Central/South Asian Heritage | 58 | 71 | 129 |
| Asian - East Asian Heritage | 245 | 232 | 477 |
| Asian - Japanese Heritage | 5 | 3 | 8 |
| Asian - South East Asian Heritage | 216 | 229 | 445 |
| Black or African American | 183 | 185 | 368 |
| Native Hawaiian or Other Pacific Islander | 7 | 7 | 14 |

| | | | |
|---|------|------|------|
| White - Arabic/North African Heritage | 19 | 18 | 37 |
| White - White/Caucasian/European Heritage | 1079 | 1037 | 2116 |
| Mixed Asian Race | 1 | 2 | 3 |
| Mixed Race | 36 | 51 | 87 |

End points

End points reporting groups

| | |
|--|------------------|
| Reporting group title | Daprodustat |
| Reporting group description: | |
| Participants received placebo tablets orally once daily in run-in period from Week-4 up to randomization (Day 1) and subsequently received treatment with daprodustat film-coated tablets at dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 and 24 milligrams (mg) orally once daily up to 51.1 month. 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 placebo tablets orally once daily in run-in period from Week-4 up to randomization (Day 1) and subsequently received treatment with darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection at 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 100, 150, 200, 300 and 400 microgram (mcg) up to 51.1 month. Darbepoetin alfa IV injection was administered to participants undergoing hemodialysis. Study treatment was dose-titrated to achieve and maintain Hgb in the target range (10 to 11 g/dL). | |

Primary: Time to first occurrence of adjudicated major adverse cardiovascular event (MACE) during cardiovascular (CV) events follow-up time period (non-inferiority analysis)

| | |
|--|--|
| End point title | Time to first occurrence of adjudicated major adverse cardiovascular event (MACE) during cardiovascular (CV) events follow-up time period (non-inferiority analysis) |
| End point description: | |
| Time to MACE defined as time to first occurrence of Clinical Events Committee(CEC)adjudicated MACE (composite of all-cause mortality,non-fatal myocardial infarction[MI],non-fatal stroke)was analyzed using Cox proportional hazards regression model with treatment group,current erythropoiesis-stimulating agents(ESA)use at randomization and region as covariates.Time to first occurrence was computed as (event date minus randomization date)+1.Incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% confidence interval(CI). First event person years=(cumulative total time to first event for participants who have the event+cumulative total of censored time for participants without event)/365.25,based on CV follow-up time period.All Randomized (Intent-to-treat[ITT]) Population comprised of all randomized participants. Participants were analyzed according to treatment to which they were randomized. | |
| End point type | Primary |
| End point timeframe: | |
| Up to 4.3 person-years for CV follow-up time period | |

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[1] | 1935 ^[2] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 10.86 (9.80 to 12.02) | 10.63 (9.58 to 11.77) | | |

Notes:

[1] - All Randomized (ITT) Population.

[2] - All Randomized (ITT) Population.

Statistical analyses

| Statistical analysis title | Statistical analysis |
|--|--------------------------------|
| Statistical analysis description: Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[3] |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.89 |
| upper limit | 1.19 |

Notes:

[3] - Non-inferiority was achieved if the upper limit of the two-sided 95% CI for the hazard ratio was below the pre-specified non-inferiority margin of 1.25.

Primary: Mean Change from Baseline in Hgb levels over the Evaluation Period (Week 28 to Week 52)

| | |
|-----------------|---|
| End point title | Mean Change from Baseline in Hgb levels over the Evaluation Period (Week 28 to Week 52) |
|-----------------|---|

End point description:

Blood samples were collected from participants for Hgb measurements. 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 imputation methods. Change from Baseline was defined as post-Baseline value minus (-) Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Analysis was performed using the Analysis of covariance (ANCOVA) model with terms for treatment, Baseline Hgb, current ESA use and region.

| | |
|----------------|---------|
| 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 | 1937 ^[4] | 1935 ^[5] | | |
| Units: Grams per deciliter | | | | |
| least squares mean (standard error) | 0.74 (± 0.019) | 0.66 (± 0.019) | | |

Notes:

[4] - All Randomized (ITT) Population.

[5] - All Randomized (ITT) Population.

Statistical analyses

| Statistical analysis title | Statistical analysis |
|----------------------------|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[6] |
| Parameter estimate | Least square (LS) mean difference |
| Point estimate | 0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.03 |
| upper limit | 0.13 |

Notes:

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

Secondary: Time to first occurrence of adjudicated MACE during CV events follow-up time period (Superiority analysis)

| | |
|-----------------|--|
| End point title | Time to first occurrence of adjudicated MACE during CV events follow-up time period (Superiority analysis) |
|-----------------|--|

End point description:

Time to MACE defined as the time to first occurrence of CEC adjudicated MACE was analyzed using a Cox proportional hazards regression model with treatment group, current ESA use at randomization, and region as covariate. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period. This endpoint was adjusted for multiplicity using the Holm-Bonferonni method.

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

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[7] | 1935 ^[8] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 10.86 (9.80 to 12.02) | 10.63 (9.58 to 11.77) | | |

Notes:

[7] - All Randomized (ITT) Population.

[8] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates.

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

| | |
|---|---------------------------|
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.670884 ^[9] |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.89 |
| upper limit | 1.19 |

Notes:

[9] - The p-value was compared against 0.008333 based on the Holm-Bonferonni adjustment.

Secondary: Time to first occurrence of adjudicated MACE or thromboembolic event during CV events follow-up time period

| | |
|-----------------|---|
| End point title | Time to first occurrence of adjudicated MACE or thromboembolic event during CV events follow-up time period |
|-----------------|---|

End point description:

Time to first occurrence of adjudicated MACE or thromboembolic event (vascular access thrombosis, symptomatic deep vein thrombosis or symptomatic pulmonary embolism) was analyzed using a Cox proportional hazards regression model with treatment group, current ESA use at randomization, and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period. This endpoint was adjusted for multiplicity using the Holm-Bonferonni method.

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

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[10] | 1935 ^[11] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 12.34 (11.19 to 13.57) | 11.77 (10.65 to 12.98) | | |

Notes:

[10] - All Randomized (ITT) Population.

[11] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates.

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

| | |
|---|----------------------------|
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.800813 ^[12] |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 1.22 |

Notes:

[12] - The p-value was compared against 0.012500 based on the Holm-Bonferonni adjustment.

Secondary: Time to first occurrence of adjudicated MACE or hospitalization for heart failure during CV events follow-up time period

| | |
|-----------------|--|
| End point title | Time to first occurrence of adjudicated MACE or hospitalization for heart failure during CV events follow-up time period |
|-----------------|--|

End point description:

Time to first occurrence of adjudicated MACE or hospitalization for heart failure was analyzed using a Cox proportional hazards regression model with treatment group, current ESA use at randomization, and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period. This endpoint was adjusted for multiplicity using the Holm-Bonferonni method.

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

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[13] | 1935 ^[14] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 13.16 (11.97 to 14.44) | 12.22 (11.08 to 13.46) | | |

Notes:

[13] - All Randomized (ITT) Population.

[14] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates.

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

| | |
|---|----------------------------|
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.886195 ^[15] |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 1.24 |

Notes:

[15] - The p-value was compared against 0.025000 based on the Holm-Bonferonni adjustment.

Secondary: Time to First Occurrence of chronic kidney disease (CKD) Progression during CV events follow-up time period

| | |
|-----------------|---|
| End point title | Time to First Occurrence of chronic kidney disease (CKD) Progression during CV events follow-up time period |
|-----------------|---|

End point description:

Progression of CKD defined as:40% decline in eGFR from Baseline or ESRD as defined by either initiating chronic dialysis for >=90 days or not initiating chronic dialysis when dialysis is indicated or kidney transplantation.Time to first occurrence of CKD progression was analyzed using Fine and Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use and region as covariates.Time to first occurrence was computed as(event date minus randomization date) +1.Incidence rate per 100 person years calculated as(100*number of participants with at least 1 event)/first event person-years).First event person years=(cumulative total time to first event for participants who have event+cumulative total of censored time for participants without event)/365.25,based on CV follow-up time period.Only those participants with data available at indicated time points were analyzed.This analysis population was restricted to those with a Baseline eGFR

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

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1220 ^[16] | 1265 ^[17] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 17.55 (15.74 to 19.51) | 17.76 (15.97 to 19.70) | | |

Notes:

[16] - All Randomized (ITT) Population.

[17] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Subdistribution hazard ratio was estimated using Fine and Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use, and region as covariates.

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

| | |
|---|------------------------------|
| Number of subjects included in analysis | 2485 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.36947 |
| Method | Wald test |
| Parameter estimate | Subdistribution hazard ratio |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.84 |
| upper limit | 1.13 |

Secondary: Time to First occurrence of Adjudicated All-Cause Mortality during Vital Status for follow-up time period

| | |
|------------------------|---|
| End point title | Time to First occurrence of Adjudicated All-Cause Mortality during Vital Status for follow-up time period |
| End point description: | Time to first occurrence of adjudicated all-cause mortality was analyzed using a Cox proportional hazards regression model with treatment group, current ESA use at randomization, and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the vital status follow-up time period. |
| End point type | Secondary |
| End point timeframe: | Up to 4.3 person-years for vital status follow-up time period |

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[18] | 1935 ^[19] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 8.35 (7.43 to 9.35) | 8.27 (7.35 to 9.26) | | |

Notes:

[18] - All Randomized (ITT) Population.

[19] - All Randomized (ITT) Population.

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical analysis |
| Statistical analysis description: | Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates. |
| Comparison groups | Daprodustat v Darbepoetin alfa |

| | |
|---|-------------------|
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6197 |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.2 |

Secondary: Time to First occurrence of Adjudicated CV Mortality during CV events follow-up time period

| | |
|-----------------|---|
| End point title | Time to First occurrence of Adjudicated CV Mortality during CV events follow-up time period |
|-----------------|---|

End point description:

Time to first occurrence of adjudicated CV mortality was analyzed using a Cox proportional hazards regression model with treatment group, current ESA use at randomization, and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

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

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[20] | 1935 ^[21] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 3.02 (2.48 to 3.65) | 2.55 (2.06 to 3.13) | | |

Notes:

[20] - All Randomized (ITT) Population.

[21] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates.

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

| | |
|---|-------------------|
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8976 |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 1.58 |

Secondary: Time to First occurrence of Adjudicated Myocardial Infarction (MI) (Fatal and Non-Fatal) during CV events follow-up time period

| | |
|-----------------|---|
| End point title | Time to First occurrence of Adjudicated Myocardial Infarction (MI) (Fatal and Non-Fatal) during CV events follow-up time period |
|-----------------|---|

End point description:

Time to first occurrence of adjudicated MI (fatal and non-fatal) was analyzed using a Cox proportional hazards regression model with treatment group, current ESA use at randomization, and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

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

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[22] | 1935 ^[23] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 2.94 (2.40 to 3.56) | 2.76 (2.24 to 3.36) | | |

Notes:

[22] - All Randomized (ITT) Population.

[23] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates.

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

| | |
|---|-------------------|
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6581 |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.4 |

Secondary: Time to First occurrence of Adjudicated Stroke (Fatal and Non-Fatal) during CV events follow-up time period

| | |
|--|---|
| End point title | Time to First occurrence of Adjudicated Stroke (Fatal and Non-Fatal) during CV events follow-up time period |
| End point description: | |
| Time to first occurrence of adjudicated stroke (fatal and non-fatal) was analyzed using a Cox proportional hazards regression model with treatment group, current ESA use at randomization, and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 4.3 person-years for CV follow-up time period | |

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[24] | 1935 ^[25] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 1.26 (0.92 to 1.69) | 0.95 (0.66 to 1.33) | | |

Notes:

[24] - All Randomized (ITT) Population.

[25] - All Randomized (ITT) Population.

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis |
| Statistical analysis description: | |
| Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |

| | |
|---|-------------------|
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.894 |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 2.07 |

Secondary: Number of Participants with Adjudicated MACE or Hospitalization for Heart Failure (Recurrent events analysis)

| | |
|------------------------|--|
| End point title | Number of Participants with Adjudicated MACE or Hospitalization for Heart Failure (Recurrent events analysis) |
| End point description: | Number of participants with adjudicated MACE or hospitalization for heart failure (recurrent events analysis) is presented, categorized by number of occurrences of adjudicated MACE or hospitalization for heart failure per participant. |
| End point type | Secondary |
| End point timeframe: | Up to 4.3 person-years for CV follow-up time period |

| End point values | Daprodustat | Darbepoetin alfa | | |
|--------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[26] | 1935 ^[27] | | |
| Units: Participants | | | | |
| Occurrences per participant: 0 | 1493 | 1518 | | |
| Occurrences per participant: 1 | 318 | 317 | | |
| Occurrences per participant: 2 | 76 | 64 | | |
| Occurrences per participant: 3 | 26 | 22 | | |
| Occurrences per participant: 4 | 14 | 9 | | |
| Occurrences per participant: 5 | 5 | 3 | | |
| Occurrences per participant: 6 | 1 | 0 | | |
| Occurrences per participant: 7 | 4 | 1 | | |
| Occurrences per participant: 8 | 0 | 1 | | |

Notes:

[26] - All Randomized (ITT) Population.

[27] - All Randomized (ITT) Population.

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | Overall HR is presented using Model 1. Model 1 assumed a common treatment effect, regardless of |

number of events experienced. HR was estimated using a Prentice, Williams and Peterson(PWP) model, with treatment, dialysis type and region as covariates.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9422 |
| Method | Chi-squared |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.98 |
| upper limit | 1.23 |

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

Statistical analysis description:

First Event Hazard ratio is presented using Model 2. Model 2 assumed treatment effect differs by number of events experienced. Hazard Ratio (HR) was estimated using a PWP model, with treatment, dialysis type and region as covariates.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8862 |
| Method | Chi-squared |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 1.24 |

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

Statistical analysis description:

Second Event Hazard ratio is presented using Model 2. Model 2 assumed treatment effect differs by number of events experienced. HR was estimated using a PWP model, with treatment, dialysis type and region as covariates.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6789 |
| Method | Chi-squared |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.07 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 1.39 |

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

Statistical analysis description:

Third Event Hazard ratio is presented using Model 2. Model 2 assumed treatment effect differs by number of events experienced. HR was estimated using a PWP model, with treatment, dialysis type and region as covariates.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9016 |
| Method | Chi-squared |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 2.19 |

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

Statistical analysis description:

First Event Hazard ratio is presented using Model 3. Model 3 assumed treatment effect for first event differs from a common effect for subsequent events. HR was estimated using a PWP model, with treatment, dialysis type and region as covariates.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8862 |
| Method | Chi-squared |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 1.24 |

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

Statistical analysis description:

Subsequent Event Hazard ratio is presented using Model 3. Model 3 assumed treatment effect for first event differs from a common effect for subsequent events. HR was estimated using a PWP model, with treatment, dialysis type and region as covariates.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8989 |
| Method | Chi-squared |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 1.46 |

Secondary: Time to First Occurrence of Adjudicated CV Mortality or Non-Fatal MI during CV events follow-up time period

| | |
|-----------------|---|
| End point title | Time to First Occurrence of Adjudicated CV Mortality or Non-Fatal MI during CV events follow-up time period |
|-----------------|---|

End point description:

Time to first occurrence of adjudicated CV mortality or non-fatal MI was analyzed using a Cox proportional hazards regression model with treatment group, current ESA use at randomization, and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

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

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[28] | 1935 ^[29] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 5.36 (4.62 to 6.18) | 4.98 (4.27 to 5.77) | | |

Notes:

[28] - All Randomized (ITT) Population.

[29] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group,

current ESA use at randomization, and region as covariates.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7673 |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.33 |

Secondary: Time to First Occurrence of All-Cause Hospitalization during CV events follow-up time period

| | |
|-----------------|--|
| End point title | Time to First Occurrence of All-Cause Hospitalization during CV events follow-up time period |
|-----------------|--|

End point description:

All-cause hospitalization events were hospital admissions recorded on the hospitalization electronic case report form (eCRF) form with a hospitalization duration ≥ 24 hours. Time to first occurrence of all-cause hospitalization was analyzed using a Cox proportional hazards regression model with treatment group, current ESA use at randomization, and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as $(100 \times \text{number of participants with at least 1 event}) / (\text{first event person-years})$ is presented along with 95% CI. First event person years = $(\text{cumulative total time to first event for participants who have the event} + \text{cumulative total of censored time for participants without the event}) / 365.25$, based on the CV follow-up time period.

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

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[30] | 1935 ^[31] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 41.13 (38.59 to 43.80) | 38.99 (36.54 to 41.56) | | |

Notes:

[30] - All Randomized (ITT) Population.

[31] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8601 |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.96 |
| upper limit | 1.15 |

Secondary: Time to First Occurrence of All-Cause Hospital Re-admission within 30 Days during CV events follow-up time period

| | |
|-----------------|---|
| End point title | Time to First Occurrence of All-Cause Hospital Re-admission within 30 Days during CV events follow-up time period |
|-----------------|---|

End point description:

All-cause hospital re-admissions within 30days are defined as hospital admissions recorded on hospitalization electronic case record form with hospitalization duration of ≥ 24 hours and admission date within 30days following previous discharge date of all-cause hospitalization event, where previous hospitalization was ≥ 24 hours. Time to first occurrence of all-cause hospital re-admission within 30days was analyzed using Cox proportional hazards regression model with treatment group, current ESA use at randomization and region as covariates. Time to the first occurrence was computed as (event date - randomization date) + 1. Incidence rate per 100 person years calculated as $(100 \times \text{number of participants with at least 1 event}) / \text{first event person-years}$ is presented along with 95% CI. First event person years = (cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event) / 365.25, based on the CV follow-up time period.

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

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[32] | 1935 ^[33] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 7.78 (6.87 to 8.79) | 7.55 (6.65 to 8.55) | | |

Notes:

[32] - All Randomized (ITT) Population.

[33] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates.

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

| | |
|---|-------------------|
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6207 |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.22 |

Secondary: Time to First Occurrence of Adjudicated MACE or Hospitalization for Heart Failure or Thromboembolic events during CV events follow-up time period

| | |
|-----------------|---|
| End point title | Time to First Occurrence of Adjudicated MACE or Hospitalization for Heart Failure or Thromboembolic events during CV events follow-up time period |
|-----------------|---|

End point description:

Time to first occurrence of adjudicated MACE or hospitalization for heart failure or thromboembolic events were analyzed using a Cox proportional hazards regression model with treatment group, current ESA use at randomization, and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

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

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[34] | 1935 ^[35] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 14.60 (13.33 to 15.96) | 13.32 (12.11 to 14.61) | | |

Notes:

[34] - All Randomized (ITT) Population.

[35] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates.

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

| | |
|---|-------------------|
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9393 |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.97 |
| upper limit | 1.26 |

Secondary: Time to First Occurrence of Adjudicated Hospitalization for Heart Failure during CV events follow-up time period

| | |
|-----------------|--|
| End point title | Time to First Occurrence of Adjudicated Hospitalization for Heart Failure during CV events follow-up time period |
|-----------------|--|

End point description:

Time to first occurrence of adjudicated hospitalization for heart failure was analyzed using a Cox proportional hazards regression model with treatment group, current ESA use at randomization, and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period.

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

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[36] | 1935 ^[37] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 4.05 (3.41 to 4.78) | 3.30 (2.73 to 3.96) | | |

Notes:

[36] - All Randomized (ITT) Population.

[37] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates.

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

| | |
|---|-------------------|
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9412 |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 1.56 |

Secondary: Time to First Occurrence of Adjudicated Thromboembolic Events during CV events follow-up time period

| | |
|------------------------|--|
| End point title | Time to First Occurrence of Adjudicated Thromboembolic Events during CV events follow-up time period |
| End point description: | Time to first occurrence of adjudicated thromboembolic events were analyzed using a Cox proportional hazards regression model with treatment group, current ESA use at randomization, and region as covariates. Time to the first occurrence was computed as (event date minus randomization date) + 1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period. |
| End point type | Secondary |
| End point timeframe: | Up to 4.3 person-years for CV follow-up time period |

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[38] | 1935 ^[39] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 1.81 (1.39 to 2.31) | 1.43 (1.07 to 1.89) | | |

Notes:

[38] - All Randomized (ITT) Population.

[39] - All Randomized (ITT) Population.

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical analysis |
| Statistical analysis description: | Hazard ratio was estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates. |
| Comparison groups | Daprodustat v Darbepoetin alfa |

| | |
|---|-------------------|
| Number of subjects included in analysis | 3872 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8994 |
| Method | Wald test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.84 |

Secondary: Time to First Occurrence of Confirmed 40% Decline in eGFR during CV events follow-up time period

| | |
|-----------------|--|
| End point title | Time to First Occurrence of Confirmed 40% Decline in eGFR during CV events follow-up time period |
|-----------------|--|

End point description:

Time to first occurrence of confirmed 40% decline in eGFR was analyzed using a Fine & Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use and region as covariates. Time to the first occurrence was computed as (event date minus randomization date)+1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1220 ^[40] | 1265 ^[41] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 8.21 (7.04 to 9.52) | 8.90 (7.69 to 10.24) | | |

Notes:

[40] - All Randomized (ITT) Population.

[41] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Subdistribution hazard ratio was estimated using Fine & Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use, and region as covariates.

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

| | |
|---|------------------------------|
| Number of subjects included in analysis | 2485 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2073 |
| Method | Wald test |
| Parameter estimate | Subdistribution hazard ratio |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.13 |

Secondary: Time to First Occurrence of Chronic Dialysis during CV events follow-up time period

| | |
|------------------------|---|
| End point title | Time to First Occurrence of Chronic Dialysis during CV events follow-up time period |
| End point description: | Time to first occurrence of chronic dialysis was analyzed using a Fine & Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use and region as covariates. Chronic dialysis is defined by either initiating dialysis for ≥ 90 days or not initiating chronic dialysis when dialysis is indicated. Time to the first occurrence was computed as (event date minus randomization date)+1. The incidence rate per 100 person years calculated as $(100 \times \text{number of participants with at least 1 event}) / \text{first event person-years}$ is presented along with 95% CI. First event person years = $(\text{cumulative total time to first event for participants who have the event} + \text{cumulative total of censored time for participants without the event}) / 365.25$, based on the CV follow-up time period. Only those participants with data available at the indicated time points were analyzed. |
| End point type | Secondary |
| End point timeframe: | Up to 4.3 person-years for CV follow-up time period |

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1220 ^[42] | 1265 ^[43] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 12.20 (10.74 to 13.81) | 12.06 (10.63 to 13.62) | | |

Notes:

[42] - All Randomized (ITT) Population.

[43] - All Randomized (ITT) Population.

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical analysis |
| Statistical analysis description: | Subdistribution hazard ratio was estimated using Fine & Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use, and region as covariates. |
| Comparison groups | Daprodustat v Darbepoetin alfa |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 2485 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5068 |
| Method | Wald test |
| Parameter estimate | Subdistribution hazard ratio |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.84 |
| upper limit | 1.19 |

Secondary: Time to First Occurrence of Kidney Transplant during CV events follow-up time period

| | |
|-----------------|--|
| End point title | Time to First Occurrence of Kidney Transplant during CV events follow-up time period |
|-----------------|--|

End point description:

Time to first occurrence of kidney transplant were analyzed using a Fine & Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use and region as covariates. Time to the first occurrence was computed as (event date minus randomization date)+1. The incidence rate per 100 person years calculated as (100*number of participants with at least 1 event)/first event person-years) is presented along with 95% CI. First event person years=(cumulative total time to first event for participants who have the event + cumulative total of censored time for participants without the event)/365.25, based on the CV follow-up time period. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

Up to 4.3 person-years for CV follow-up time period

| End point values | Daprodustat | Darbepoetin alfa | | |
|------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1220 ^[44] | 1265 ^[45] | | |
| Units: Events per 100 person years | | | | |
| number (confidence interval 95%) | 1.00 (0.63 to 1.50) | 1.14 (0.75 to 1.66) | | |

Notes:

[44] - All Randomized (ITT) Population.

[45] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Subdistribution hazard ratio was estimated using Fine & Gray's proportional subdistribution hazard regression model with treatment group, Baseline ESA use, and region as covariates.

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

| | |
|---|------------------------------|
| Number of subjects included in analysis | 2485 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3285 |
| Method | Wald test |
| Parameter estimate | Subdistribution hazard ratio |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 1.54 |

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

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

End point description:

Blood samples were collected from participants for Hgb measurements. Change from Baseline was defined as post-randomization value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Analysis was performed using mixed model repeated measures (MMRM) model fitted from Baseline up to Week 52, excluding values collected during the stabilization period, with factors for treatment, time, current ESA use, region, Baseline Hgb and Baseline Hgb by time and treatment by time interactions. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

Baseline (Pre-dose on Day 1) and Week 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1557 ^[46] | 1556 ^[47] | | |
| Units: Grams per deciliter | | | | |
| least squares mean (standard error) | 0.76 (± 0.029) | 0.73 (± 0.029) | | |

Notes:

[46] - All Randomized (ITT) Population.

[47] - All Randomized (ITT) Population.

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | Statistical analysis |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3113 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[48] |
| Parameter estimate | LS mean difference |
| Point estimate | 0.03 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.11 |

Notes:

[48] - 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 in the Hgb Analysis Range (10 to 11.5 Grams/Deciliter) During Evaluation Period (Week 28 to Week 52)

| | |
|-----------------|---|
| End point title | Number of Hgb Responders in the Hgb Analysis Range (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 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:

Week 28 to Week 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1491 ^[49] | 1520 ^[50] | | |
| Units: Participants | 1167 | 1063 | | |

Notes:

[49] - All Randomized (ITT) Population.

[50] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test adjusted for current ESA use and region was used to compare the number of responders between the treatment groups.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3011 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in response rate |
| Point estimate | 8.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.2 |
| upper limit | 11.4 |

Secondary: Percentage of Time With Hgb in the Analysis Range (10 to 11.5 Grams/Deciliter) During Evaluation Period (Week 28 to Week 52): Non-inferiority analysis

| | |
|-----------------|--|
| End point title | Percentage of Time With Hgb in the Analysis Range (10 to 11.5 Grams/Deciliter) 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 in the analysis range during evaluation period is calculated as time in range during the evaluation period / [Earlier of (Date of the last evaluable Hgb value, Week 52 visit date) – Later of (Date of the first evaluable Hgb value that between Week 16 and Week 52 inclusive, Week 28 visit date)]. Only those participants with data available at the indicated time points were analyzed.

| | |
|----------------------|--------------------|
| End point type | Secondary |
| End point timeframe: | Week 28 to Week 52 |

| End point values | Daprodustat | Darbepoetin alfa | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1461 ^[51] | 1483 ^[52] | | |
| Units: Percentage of days | | | | |
| median (full range (min-max)) | 70.5 (0.0 to 100.0) | 63.2 (0.0 to 100.0) | | |

Notes:

[51] - All Randomized (ITT) Population.

[52] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Hodges-Lehmann estimate of the treatment difference (daprodustat-darbepoetin alfa) and associated two-sided asymptotic 95% CI is presented.

| | |
|---|---------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2944 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[53] |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.04 |
| upper limit | 7.11 |

Notes:

[53] - 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 With Hgb in the Analysis Range (10 to 11.5 Grams/Deciliter) During Evaluation Period (Week 28 to Week 52): Superiority analysis

| | |
|-----------------|--|
| End point title | Percentage of Time With Hgb in the Analysis Range (10 to 11.5 Grams/Deciliter) 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 in the analysis range during evaluation period is calculated as time in range during the evaluation period / [Earlier of (Date of the last evaluable Hgb value, Week 52 visit date) – Later of (Date of the first evaluable Hgb value that between Week 16 and Week 52 inclusive, Week 28 visit date)]. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

Week 28 to Week 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1461 ^[54] | 1483 ^[55] | | |
| Units: Percentage of days | | | | |
| median (full range (min-max)) | 70.5 (0.0 to 100.0) | 63.2 (0.0 to 100.0) | | |

Notes:

[54] - All Randomized (ITT) Population.

[55] - All Randomized (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 | 2944 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | van Elteren test |
| Parameter estimate | Probability |
| Point estimate | 0.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.53 |
| upper limit | 0.57 |

Secondary: Percentage of Time With Hgb in the Analysis Range (10 to 11.5 Grams/Deciliter) During Maintenance Period (Week 28 to End of study): Non-

inferiority analysis

| | |
|-----------------|--|
| End point title | Percentage of Time With Hgb in the Analysis Range (10 to 11.5 Grams/Deciliter) During Maintenance Period (Week 28 to End of study): 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 maintenance period (Week 28 to end of study), including any unscheduled evaluable Hgb values that were taken during this time period was calculated. Percentage of time in the analysis range during maintenance period is calculated as time in range during the maintenance period / [Earlier of (Date of the last evaluable Hgb value, End of study date)– Later of (Date of the first evaluable Hgb value that is on or after week 16, Week 28 visit date)]. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

Week 28 to end of study (4.3 person-years for follow-up time period)

| | | | | |
|-------------------------------|----------------------|----------------------|--|--|
| End point values | Daprodustat | Darbepoetin alfa | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1469 ^[56] | 1489 ^[57] | | |
| Units: Percentage of days | | | | |
| median (full range (min-max)) | 66.1 (0.0 to 100.0) | 62.1 (0.0 to 100.0) | | |

Notes:

[56] - All Randomized (ITT) Population.

[57] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Hodges-Lehmann estimate of the treatment difference (daprodustat-darbepoetin alfa) and associated two-sided asymptotic 95% CI is presented.

| | |
|---|----------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2958 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[58] |
| Parameter estimate | Median difference (final values) |
| Point estimate | 3.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.9 |
| upper limit | 5.91 |

Notes:

[58] - 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 With Hemoglobin in the Analysis Range (10 to 11.5 Grams/Deciliter) During Maintenance Period (Week 28 to End of study): Superiority analysis

| | |
|-----------------|--|
| End point title | Percentage of Time With Hemoglobin in the Analysis Range (10 to 11.5 Grams/Deciliter) During Maintenance Period (Week 28 |
|-----------------|--|

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 maintenance period (Week 28 to end of study), including any unscheduled evaluable Hgb values that were taken during this time period was calculated. Percentage of time in the analysis range during maintenance period is calculated as time in range during the maintenance period / [Earlier of (Date of the last evaluable Hgb value, End of study date)– Later of (Date of the first evaluable Hgb value that is on or after week 16, Week 28 visit date)]. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

| |
|--|
| Week 28 to end of study (4.3 person-years for follow-up time period) |
|--|

| End point values | Daprodustat | Darbepoetin alfa | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1469 ^[59] | 1489 ^[60] | | |
| Units: Percentage of days | | | | |
| median (full range (min-max)) | 66.1 (0.0 to 100.0) | 62.1 (0.0 to 100.0) | | |

Notes:

[59] - All Randomized (ITT) Population.

[60] - All Randomized (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 | 2958 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | van Elteren test |
| Parameter estimate | Probability |
| Point estimate | 0.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 0.56 |

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

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

End point description:

SBP, DBP and MAP were measured in a seated position after at least a 5-minutes of rest. MAP is the

average (BP) in an individual's arteries during a single cardiac cycle. Change from Baseline was calculated as on-treatment visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Analysis was performed using MMRM model with treatment group + time + current ESA use at randomization + region + Baseline value + Baseline value*time + treatment group*time, using an unstructured covariance matrix. Data for post-dialysis BP measurements have been presented. 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 (Week -4) and Week 52 | |

| End point values | Daprodustat | Darbepoetin alfa | | |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1913 ^[61] | 1884 ^[62] | | |
| Units: Millimeter of mercury | | | | |
| least squares mean (standard error) | | | | |
| SBP, n=1913, 1884 | -0.62 (± 0.488) | -1.17 (± 0.479) | | |
| DBP, n=1912, 1884 | 0.06 (± 0.267) | -0.59 (± 0.262) | | |
| MAP, n=1912, 1884 | -0.17 (± 0.300) | -0.77 (± 0.294) | | |

Notes:

[61] - All Randomized (ITT) Population.

[62] - All Randomized (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 | 3797 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7916 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.79 |
| upper limit | 1.9 |

| 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 | 3797 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9241 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.22 |
| upper limit | 1.43 |

| | |
|-----------------------------------|------------------------|
| 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 | 3797 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9581 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.09 |
| upper limit | 1.38 |

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 seated position 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 on-treatment visit value minus Baseline value. Baseline was defined as the latest non-missing pre-dose assessment on or before the randomization date. Analysis was performed using ANCOVA model with terms for treatment group, current ESA use at randomization, region and Baseline value. Data for post-dialysis BP measurements have been presented. 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 (Week -4) and 51.1 months

| End point values | Daprodustat | Darbepoetin alfa | | |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1919 ^[63] | 1884 ^[64] | | |
| Units: Millimeter of mercury | | | | |
| least squares mean (standard error) | | | | |
| SBP, n=1919, 1884 | -1.19 (± 0.395) | -1.10 (± 0.398) | | |
| DBP, n=1918, 1884 | -0.26 (± 0.229) | -0.38 (± 0.231) | | |
| MAP, n=1918, 1884 | -0.57 (± 0.248) | -0.62 (± 0.251) | | |

Notes:

[63] - All Randomized (ITT) Population.

[64] - All Randomized (ITT) Population.

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|--------------------------------|
| Statistical analysis description: | |
| For SBP: Treatment group comparisons were based on an ANCOVA model with terms for treatment group, current ESA use at randomization, region and Baseline value. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3803 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.442 |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.18 |
| upper limit | 1.02 |

| Statistical analysis title | Statistical analysis 2 |
|---|--------------------------------|
| Statistical analysis description: | |
| For DBP: Treatment group comparisons were based on an ANCOVA model with terms for treatment group, current ESA use at randomization, region and Baseline value. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3803 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6369 |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | 0.11 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.52 |
| upper limit | 0.75 |

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

Statistical analysis description:

For MAP: Treatment group comparisons were based on an ANCOVA model with terms for treatment group, current ESA use at randomization, region and Baseline value.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3803 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.549 |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | 0.04 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.65 |
| upper limit | 0.74 |

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

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

End point description:

BP exacerbation event (based on post-dialysis) was defined as: SBP \geq 25 millimeter of mercury (mmHg) increased from Baseline or SBP \geq 180 mmHg; DBP \geq 15 mmHg increased from Baseline or DBP \geq 110 mmHg. The BP exacerbation events per 100 participant years was estimated using the negative binomial model with treatment, current ESA use at randomization and region as covariates and the logarithm of time on-treatment as an offset variable. Data for post-dialysis BP measurements have been presented. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

Day 1 to end of treatment (51.1 months)

| | | | | |
|---|---------------------------|---------------------------|--|--|
| End point values | Daprodustat | Darbepoetin alfa | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1919 ^[65] | 1884 ^[66] | | |
| Units: Events per 100 participant years | | | | |
| number (confidence interval 95%) | 138.50 (128.58 to 149.18) | 157.35 (146.30 to 169.23) | | |

Notes:

[65] - All Randomized (ITT) Population.

[66] - All Randomized (ITT) Population.

Statistical analyses

| Statistical analysis title | Statistical analysis |
|--|--------------------------------|
| Statistical analysis description: | |
| Ratio of model estimated exacerbation rates and CIs were estimated using a negative binomial model with treatment, current ESA use at randomization, and region as covariates and logarithm of time on treatment as an offset variable for the treatment group comparison. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 3803 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0074 |
| Method | Negative binomial model |
| Parameter estimate | Ratio of exacerbation rate |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 0.98 |

Secondary: Number of Participants with at Least one BP Exacerbation Event During Study

| | |
|--|---|
| End point title | Number of Participants with at Least one BP Exacerbation Event During Study |
| End point description: | |
| BP exacerbation was defined as: SBP \geq 25 mmHg increased from Baseline or SBP \geq 180 mmHg; DBP \geq 15 mmHg increased from Baseline or DBP \geq 110 mmHg. Number of participants with at least one BP exacerbation event is presented. Only those participants with data available at the indicated time points were analyzed. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 to end of treatment (51.1 months) | |

| End point values | Daprodustat | Darbepoetin alfa | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1919 ^[67] | 1884 ^[68] | | |
| Units: Participants | 939 | 1012 | | |

Notes:

[67] - All Randomized (ITT) Population.

[68] - All Randomized (ITT) Population.

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Percentage of Participants Permanently Stopping Randomized Treatment Due to Meeting Rescue Criteria |
|-----------------|---|

End point description:

Percentage of participants permanently stopping randomized treatment due to meeting rescue criteria has been presented.

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

End point timeframe:

Day 1 to 51.1 months

| End point values | Daprodustat | Darbepoetin alfa | | |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1937 ^[69] | 1935 ^[70] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 2.0 | 3.3 | | |

Notes:

[69] - All Randomized (ITT) Population.

[70] - All Randomized (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, current ESA use and region.

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

| | |
|---|------|
| Number of subjects included in analysis | 3872 |
|---|------|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

| | |
|---------|----------|
| P-value | = 0.0113 |
|---------|----------|

| | |
|--------|-----------|
| Method | Wald test |
|--------|-----------|

| | |
|--------------------|-------------------|
| Parameter estimate | Hazard ratio (HR) |
|--------------------|-------------------|

| | |
|----------------|------|
| Point estimate | 0.63 |
|----------------|------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|------|
| lower limit | 0.42 |
|-------------|------|

| | |
|-------------|------|
| upper limit | 0.94 |
|-------------|------|

Secondary: Change from Baseline in On-treatment 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 On-treatment 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 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). The PCS is an average score derived from 4 domains (physical functioning, role-physical, bodily pain and general health) representing overall physical health. PCS ranges from 0 to 100; higher score represents better health. Change from Baseline was calculated as on-treatment 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 (Pre-dose on 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 | 1238 ^[71] | 1227 ^[72] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 8, n=1238,1187 | 0.42 (± 0.169) | 0.78 (± 0.172) | | |
| Week 12, n=1237,1227 | 0.60 (± 0.171) | 0.71 (± 0.172) | | |
| Week 28, n=968,956 | 0.16 (± 0.197) | 0.04 (± 0.198) | | |
| Week 52, n=804,780 | -0.32 (± 0.218) | -0.12 (± 0.221) | | |

Notes:

[71] - All Randomized (ITT) Population.

[72] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Week8: Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, Baseline value and Baseline value by time and treatment by time interactions

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

| | |
|---|--------------------|
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.932 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.83 |
| upper limit | 0.11 |

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

Statistical analysis description:

Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6761 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.59 |
| upper limit | 0.36 |

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

Statistical analysis description:

Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3335 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.12 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.43 |
| upper limit | 0.67 |

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

Statistical analysis description:

Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7423 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.81 |
| upper limit | 0.41 |

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

| | |
|-----------------|--|
| End point title | Change from Baseline in On-treatment Mental Component Score (MCS) using SF-36 HRQoL Questionnaire 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: 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). MCS is an average score derived from 4 domains (vitality, social functioning, role-emotional and mental health) representing overall mental health. MCS ranges from 0 to 100; higher scores represent better health. Change from Baseline was calculated as on-treatment 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 (Pre-dose on 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 | 1238 ^[73] | 1227 ^[74] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 8, n=1238,1187 | 0.08 (± 0.217) | 0.37 (± 0.221) | | |
| Week 12, n=1237,1227 | 0.02 (± 0.223) | 0.18 (± 0.224) | | |
| Week 28, n=968,956 | -0.35 (± 0.244) | -0.02 (± 0.245) | | |
| Week 52, n=804,780 | -0.71 (± 0.290) | -0.35 (± 0.294) | | |

Notes:

[73] - All Randomized (ITT) Population.

[74] - All Randomized (ITT) Population.

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|--------------------------------|
| Statistical analysis description: | |
| Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8268 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0.32 |

| Statistical analysis title | Statistical analysis 2 |
|--|--------------------------------|
| Statistical analysis description: | |
| Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6851 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.15 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.77 |
| upper limit | 0.47 |

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

Statistical analysis description:

Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8316 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.01 |
| upper limit | 0.35 |

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

Statistical analysis description:

Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented,with factors for treatment, time,current ESA use at randomization, region, Baseline value and Baseline value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8032 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.16 |
| upper limit | 0.46 |

Secondary: Change from Baseline in On-treatment 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 On-treatment 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 (b pain), general health (GH), mental health (MH), role-emotional (RE) (role limitations caused by emotional problems), role-physical (RP) (role limitations caused by physical problems), social functioning (SF), 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 (BL) was calculated as on-treatment 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 (Pre-dose on 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 | 1238 ^[75] | 1227 ^[76] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Bodily pain: Week 8, n=1238,1187 | 0.11 (± 0.221) | 0.45 (± 0.225) | | |
| Bodily pain: Week 12, n=1237,1227 | 0.35 (± 0.223) | 0.50 (± 0.224) | | |
| Bodily pain: Week 28, n=968,956 | -0.48 (± 0.261) | 0.02 (± 0.263) | | |
| Bodily pain: Week 52, n=804,780 | -0.34 (± 0.283) | 0.13 (± 0.288) | | |
| General health: Week 8, n=1238,1187 | 0.36 (± 0.171) | 0.43 (± 0.174) | | |
| General health: Week 12, n=1237,1227 | 0.28 (± 0.174) | 0.48 (± 0.175) | | |
| General health: Week 28, n=968,956 | 0.14 (± 0.200) | 0.04 (± 0.201) | | |
| General health: Week 52, n=804,780 | -0.27 (± 0.220) | -0.19 (± 0.224) | | |
| Mental health: Week 8, n=1238,1187 | -0.19 (± 0.204) | 0.12 (± 0.208) | | |
| Mental health: Week 12, n=1237,1227 | -0.07 (± 0.210) | -0.09 (± 0.211) | | |
| Mental health: Week 28, n=968,956 | -0.67 (± 0.231) | -0.37 (± 0.232) | | |
| Mental health: Week 52, n=804,780 | -0.85 (± 0.271) | -0.61 (± 0.275) | | |
| Role-emotional: Week 8, n=1238,1187 | 0.45 (± 0.253) | 0.54 (± 0.258) | | |
| Role-emotional: Week 12, n=1237,1227 | 0.17 (± 0.258) | 0.43 (± 0.259) | | |
| Role-emotional: Week 28, n=968,956 | -0.30 (± 0.290) | 0.07 (± 0.292) | | |
| Role-emotional: Week 52, n=804,780 | -0.90 (± 0.339) | -0.38 (± 0.344) | | |
| Role-physical: Week 8, n=1238,1187 | 0.33 (± 0.202) | 0.83 (± 0.205) | | |
| Role-physical: Week 12, n=1237,1227 | 0.40 (± 0.203) | 0.73 (± 0.204) | | |
| Role-physical: Week 28, n=968,956 | 0.06 (± 0.230) | 0.00 (± 0.232) | | |

| | | | | |
|--|----------------------|----------------------|--|--|
| Role-physical: Week 52, n=804,780 | -0.63 (\pm 0.259) | -0.44 (\pm 0.263) | | |
| Social functioning: Week 8, n=1238,1187 | 0.19 (\pm 0.224) | 0.82 (\pm 0.228) | | |
| Social functioning: Week 12, n=1237,1227 | 0.21 (\pm 0.224) | 0.53 (\pm 0.225) | | |
| Social functioning: Week 28, n=968,956 | 0.04 (\pm 0.247) | 0.17 (\pm 0.249) | | |
| Social functioning: Week 52, n=804,780 | -0.58 (\pm 0.282) | -0.20 (\pm 0.286) | | |

Notes:

[75] - All Randomized (ITT) Population.

[76] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

B pain, Week8: Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8562 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.95 |
| upper limit | 0.28 |

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

Statistical analysis description:

B pain, Week12: Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6849 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.77 |
| upper limit | 0.47 |

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 3 |
| Statistical analysis description: | |
| B pain,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9074 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.22 |
| upper limit | 0.24 |

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Statistical analysis description: | |
| B pain,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8765 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.26 |
| upper limit | 0.32 |

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 5 |
| Statistical analysis description: | |
| GH,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions | |
| Comparison groups | Daprodustat v Darbepoetin alfa |

| | |
|---|--------------------|
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6252 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.56 |
| upper limit | 0.4 |

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

Statistical analysis description:

GH,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7852 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.68 |
| upper limit | 0.29 |

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

Statistical analysis description:

GH,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3614 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.46 |
| upper limit | 0.66 |

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

Statistical analysis description:

GH,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5991 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.54 |

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

Statistical analysis description:

MH,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8526 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.88 |
| upper limit | 0.27 |

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

Statistical analysis description:

MH,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4673 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.56 |
| upper limit | 0.61 |

Statistical analysis title

Statistical analysis 11

Statistical analysis description:

MH,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8262 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.95 |
| upper limit | 0.33 |

Statistical analysis title

Statistical analysis 12

Statistical analysis description:

MH,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

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

| | |
|---|--------------------|
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.738 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.51 |

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

Statistical analysis description:

RE,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5997 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.62 |

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

Statistical analysis description:

RE,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7649 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.26 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.98 |
| upper limit | 0.45 |

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

Statistical analysis description:

RE,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8175 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.18 |
| upper limit | 0.43 |

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

Statistical analysis description:

RE,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8591 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.47 |
| upper limit | 0.43 |

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

Statistical analysis description:

RP,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9588 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.06 |
| upper limit | 0.06 |

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

Statistical analysis description:

RP,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8761 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0.23 |

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

Statistical analysis description:

RP,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

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

| | |
|---|--------------------|
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4293 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.58 |
| upper limit | 0.7 |

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 20 |
|-----------------------------------|-------------------------|

Statistical analysis description:

RP,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6983 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.92 |
| upper limit | 0.53 |

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 21 |
|-----------------------------------|-------------------------|

Statistical analysis description:

SF,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9743 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.62 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.25 |
| upper limit | 0 |

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

Statistical analysis description:

SF,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time,current ESA use at randomization, region,BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8405 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.94 |
| upper limit | 0.31 |

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

Statistical analysis description:

SF,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6459 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.82 |
| upper limit | 0.56 |

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

Statistical analysis description:

SF, Week 52: Model was fitted from Baseline up to Week 52 and model adjusted Week 52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8272 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.17 |
| upper limit | 0.41 |

Secondary: Change from Baseline in On-treatment Vitality scores using SF-36 HRQoL Questionnaire at Weeks 8, 12, 28, 52

| | |
|-----------------|---|
| End point title | Change from Baseline in On-treatment Vitality scores using SF-36 HRQoL Questionnaire 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: 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 score ranges from 0 to 100; higher scores represent better health. Change from Baseline was calculated as on-treatment 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 (Pre-dose on 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 | 1238 ^[77] | 1227 ^[78] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 8, n=1238,1187 | 0.35 (± 0.192) | 0.90 (± 0.195) | | |
| Week 12, n=1237,1227 | 0.62 (± 0.200) | 0.74 (± 0.201) | | |
| Week 28, n=968,956 | 0.22 (± 0.222) | 0.32 (± 0.223) | | |
| Week 52, n=804,780 | -0.14 (± 0.250) | 0.35 (± 0.253) | | |

Notes:

[77] - All Randomized (ITT) Population.

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|--------------------------------|
| Statistical analysis description: | |
| Week 8: Model was fitted from Baseline up to Week 52 and model adjusted Week 8 data has been presented,with factors for treatment, time,current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9786 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.09 |
| upper limit | -0.02 |

| Statistical analysis title | Statistical analysis 2 |
|---|--------------------------------|
| Statistical analysis description: | |
| Week 12: Model was fitted from Baseline up to Week 52 and model adjusted Week 12 data has been presented,with factors for treatment, time,current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6642 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.68 |
| upper limit | 0.44 |

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

Statistical analysis description:

Week 28: Model was fitted from Baseline up to Week 52 and model adjusted Week 28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6261 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.72 |
| upper limit | 0.52 |

Statistical analysis title

Statistical analysis 4

Statistical analysis description:

Week 52: Model was fitted from Baseline up to Week 52 and model adjusted Week 52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9161 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.19 |
| upper limit | 0.21 |

Secondary: Change from Baseline in On-treatment Physical Functioning domain scores using SF-36 HRQoL Questionnaire at Weeks 8, 12, 28, 52

| | |
|-----------------|--|
| End point title | Change from Baseline in On-treatment Physical Functioning domain scores using SF-36 HRQoL Questionnaire 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: 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 score ranges from 0 to 100; higher scores represent better health. Change from Baseline was calculated as on-treatment 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 (Pre-dose on 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 | 1238 ^[79] | 1227 ^[80] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 8, n=1238,1187 | 0.51 (± 0.200) | 0.83 (± 0.203) | | |
| Week 12, n=1237,1227 | 0.65 (± 0.195) | 0.52 (± 0.196) | | |
| Week 28, n=968,956 | 0.05 (± 0.224) | -0.10 (± 0.225) | | |
| Week 52, n=804,780 | -0.69 (± 0.262) | -0.37 (± 0.266) | | |

Notes:

[79] - All Randomized (ITT) Population.

[80] - All Randomized (ITT) Population.

Statistical analyses

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

Statistical analysis description:

Week 8: Model was fitted from Baseline up to Week 52 and model adjusted Week 8 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8703 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.88 |
| upper limit | 0.24 |

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

Statistical analysis description:

Week 12: Model was fitted from Baseline up to Week 52 and model adjusted Week 12 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

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

| | |
|---|--------------------|
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3167 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.41 |
| upper limit | 0.67 |

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

Statistical analysis description:

Week 28: Model was fitted from Baseline up to Week 52 and model adjusted Week 28 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3155 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.47 |
| upper limit | 0.78 |

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

Statistical analysis description:

Week 52: Model was fitted from Baseline up to Week 52 and model adjusted Week 52 data has been presented, with factors for treatment, time, current ESA use at randomization, region, BL value and BL value by time & treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8069 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.32 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.06 |
| upper limit | 0.41 |

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

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

End point description:

EQ-5D-5L is self-assessment questionnaire, consisting of 5 items covering 5 dimensions (mobility, self care, usual activities, pain/discomfort and anxiety/depression). Each dimension is measured by 5-point Likert scale (1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems and 5=extreme problems). Responses for 5 dimensions together formed a 5-figure description of health state (e.g.11111 indicates no problems in all 5 dimensions). 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 state). Change from Baseline was calculated as on-treatment visit value minus Baseline value. Baseline was 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 (Pre-dose on Day 1) and Week 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 443 ^[81] | 399 ^[82] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | -0.0253 (± 0.00842) | -0.0018 (± 0.00883) | | |

Notes:

[81] - All Randomized (ITT) Population.

[82] - All Randomized (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, current ESA use, region, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 842 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9724 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.0234 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.0474 |
| upper limit | 0.0005 |

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

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

End point description:

The EQ VAS records the respondent's self-rated health on a vertical VAS, ranging from 0 to 100, where 0 represents the worst imaginable health and 100 represents the best imaginable health. Change from Baseline was calculated as on-treatment 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. Only those participants with data available at the indicated time points were analyzed.

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

End point timeframe:

Baseline (Pre-dose on Day 1) and Week 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 443 ^[83] | 399 ^[84] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | -0.7 (± 0.78) | -1.4 (± 0.82) | | |

Notes:

[83] - All Randomized (ITT) Population.

[84] - All Randomized (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, current ESA use, region, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 842 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2687 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.7 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.5 |
| upper limit | 2.9 |

Secondary: Change from Baseline in On-treatment Chronic Kidney Disease- Anemia Symptoms Questionnaire (CKD-AQ) at Weeks 8, 12, 28, 52

| | |
|-----------------|--|
| End point title | Change from Baseline in On-treatment Chronic Kidney Disease- Anemia Symptoms Questionnaire (CKD-AQ) at Weeks 8, 12, 28, 52 |
|-----------------|--|

End point description:

CKD-AQ is 21-item PRO measure assessing symptoms and symptom impact in participants with anemia associated with CKD. It had 3 domains: 1. Tired/Low Energy (LE)/Weak scale consisting of 10 items; 2. Chest Pain (CP)/Shortness of Breath (SOB) scale consisting of 4 items; 3. Cognitive (Cog) scale consisting of 3 items. 4 CKD-AQ single items are: SOB, no activity; severity-short breath (S-SB), resting; difficulty standing (diff. std.) for long time (LT) and difficulty sleeping (diff sleep). Single-item were recorded based on a 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 where 0=worst possible; 100=best possible score. Change from Baseline was calculated as on-treatment visit value-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 category

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

End point timeframe:

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

| End point values | Daprodustat | Darbepoetin alfa | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1341 ^[85] | 1360 ^[86] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Tired/Low energy/Weak domain: Week 8, n=1340,1294 | 1.72 (± 0.424) | 2.94 (± 0.429) | | |
| Tired/Low energy/Weak domain: Week 12, n=1341,1360 | 2.11 (± 0.437) | 3.08 (± 0.434) | | |
| Tired/Low energy/Weak domain: Week 28, n=1053,1047 | 1.27 (± 0.495) | 1.87 (± 0.496) | | |
| Tired/Low energy/Weak domain: Week 52, n=870,865 | 0.20 (± 0.554) | 1.77 (± 0.556) | | |
| Chest pain/SOB domain: Week 8, n=1340,1294 | 0.63 (± 0.358) | 1.83 (± 0.363) | | |
| Chest pain/ SOB domain: Week 12, n=1341,1360 | 0.88 (± 0.370) | 1.53 (± 0.368) | | |
| Chest pain/ SOB domain: Week 28, n=1053,1047 | 0.01 (± 0.424) | 0.53 (± 0.425) | | |
| Chest pain/ SOB domain: Week 52, n=870,865 | -0.71 (± 0.471) | 0.47 (± 0.473) | | |
| Cognitive domain: Week 8, n=1340,1294 | 0.13 (± 0.413) | 0.89 (± 0.419) | | |
| Cognitive domain: Week 12, n=1341,1360 | -0.17 (± 0.414) | 1.01 (± 0.412) | | |

| | | | | |
|--|-----------------|-----------------|--|--|
| Cognitive domain: Week 28,n=1053,1047 | -0.40 (± 0.468) | 0.37 (± 0.469) | | |
| Cognitive domain: Week 52,n=870,865 | -2.00 (± 0.526) | -0.35 (± 0.527) | | |
| SOB, no activity: Week 8,n=1340,1294 | -0.1 (± 0.42) | 1.0 (± 0.42) | | |
| SOB, no activity: Week 12,n=1341,1360 | 0.1 (± 0.43) | 0.4 (± 0.42) | | |
| SOB, no activity: Week 28,n=1053,1047 | -1.1 (± 0.50) | -0.2 (± 0.50) | | |
| SOB, no activity: Week 52,n=870,865 | -1.7 (± 0.57) | -1.6 (± 0.57) | | |
| Severity-short breath, Resting: Week 8,n=1340,1294 | -0.3 (± 0.40) | 0.8 (± 0.40) | | |
| Severity-short breath, Resting:Week 12,n=1341,1360 | -0.3 (± 0.42) | 0.0 (± 0.42) | | |
| Severity-short breath, Resting:Week 28,n=1053,1047 | -1.1 (± 0.48) | -0.7 (± 0.48) | | |
| Severity-short breath, Resting:Week 52,n=870,865 | -2.0 (± 0.53) | -0.5 (± 0.53) | | |
| Diff std for long time: Week 8,n=1340,1294 | 1.0 (± 0.62) | 2.5 (± 0.63) | | |
| Diff std for long time: Week 12,n=1341,1360 | 0.7 (± 0.63) | 1.6 (± 0.62) | | |
| Diff std for long time: Week 28,n=1053,1047 | 0.4 (± 0.71) | 1.7 (± 0.71) | | |
| Diff std for long time: Week 52,n=870,865 | -2.1 (± 0.76) | 1.2 (± 0.76) | | |
| Difficulty sleeping: Week 8,n=1340,1294 | 1.6 (± 0.60) | 1.1 (± 0.61) | | |
| Difficulty sleeping: Week 12,n=1341,1360 | 0.5 (± 0.60) | 2.0 (± 0.59) | | |
| Difficulty sleeping: Week 28,n=1053,1047 | -0.7 (± 0.69) | -0.3 (± 0.70) | | |
| Difficulty sleeping: Week 52,n=870,865 | -2.6 (± 0.78) | -0.3 (± 0.78) | | |

Notes:

[85] - All Randomized (ITT) Population.

[86] - All Randomized (ITT) Population.

Statistical analyses

| Statistical analysis title | Statistical analysis 2 |
|---|--------------------------------|
| Statistical analysis description: | |
| Tired/LE/Weak domain,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.943 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.18 |
| upper limit | 0.23 |

| | |
|--|--------------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: Tired/LE/Weak domain,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.978 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.4 |
| upper limit | -0.03 |

| | |
|--|--------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Statistical analysis description: Tired/LE/Weak domain,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.977 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.11 |
| upper limit | -0.03 |

| | |
|--|--------------------------------|
| Statistical analysis title | Statistical analysis 3 |
| Statistical analysis description: Tired/LE/Weak domain,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |

| | |
|---|--------------------|
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8042 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.98 |
| upper limit | 0.77 |

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

Statistical analysis description:

CP/SOB,Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8939 |
| Method | LS mean difference |
| Parameter estimate | LS mean difference |
| Point estimate | -0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.67 |
| upper limit | 0.37 |

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

Statistical analysis description:

CP/SOB,Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9905 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | -0.2 |

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

Statistical analysis description:

CP/SOB,Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9615 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.49 |
| upper limit | 0.13 |

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

Statistical analysis description:

CP/SOB,Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.807 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.7 |
| upper limit | 0.66 |

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

Statistical analysis description:

Cog domain, Week8: Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9015 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.91 |
| upper limit | 0.39 |

Statistical analysis title

Statistical analysis 10

Statistical analysis description:

Cog domain, Week12: Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9781 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.32 |
| upper limit | -0.03 |

Statistical analysis title

Statistical analysis 12

Statistical analysis description:

Cog domain, Week52: Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

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

| | |
|---|--------------------|
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9864 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.11 |
| upper limit | -0.19 |

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

Statistical analysis description:

Cog domain, Week28: Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8778 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.07 |
| upper limit | 0.53 |

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

Statistical analysis description:

SOB, no activity, Week8: Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9725 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.3 |
| upper limit | 0 |

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

Statistical analysis description:

SOB, no activity, Week12: Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7188 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.5 |
| upper limit | 0.8 |

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

Statistical analysis description:

SOB, no activity, Week28: Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8903 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.3 |
| upper limit | 0.5 |

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

Statistical analysis description:

SOB, no activity, Week52: Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5011 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | 1.6 |

Statistical analysis title

Statistical analysis 17

Statistical analysis description:

S-SB, Resting, Week8: Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9716 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | 0 |

Statistical analysis title

Statistical analysis 18

Statistical analysis description:

S-SB, Resting, Week12: Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

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

| | |
|---|--------------------|
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6908 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4 |
| upper limit | 0.9 |

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

Statistical analysis description:

S-SB,Resting, Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7462 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.8 |
| upper limit | 0.9 |

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 20 |
|-----------------------------------|-------------------------|

Statistical analysis description:

S-SB,Resting, Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.977 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.5 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.9 |
| upper limit | 0 |

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

Statistical analysis description:

Diff std for LT, Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.833 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.6 |
| upper limit | 0.9 |

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 21 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Diff std for LT, Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9471 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.2 |
| upper limit | 0.3 |

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

Statistical analysis description:

Diff std for LT, Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9986 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.4 |
| upper limit | -1.1 |

Statistical analysis title

Statistical analysis 23

Statistical analysis description:

Diff std for LT, Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8918 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.2 |
| upper limit | 0.7 |

Statistical analysis title

Statistical analysis 25

Statistical analysis description:

Diff sleep, Week8:Model was fitted from Baseline up to Week52 and model adjusted Week8 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

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

| | |
|---|--------------------|
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3035 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 2.1 |

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 26 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Diff sleep, Week12:Model was fitted from Baseline up to Week52 and model adjusted Week12 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9563 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.1 |
| upper limit | 0.2 |

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 27 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Diff sleep, Week28:Model was fitted from Baseline up to Week52 and model adjusted Week28 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6548 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.4 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.3 |
| upper limit | 1.5 |

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 28 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Diff sleep, Week52:Model was fitted from Baseline up to Week52 and model adjusted Week52 data has been presented, with factors for treatment, time, current ESA use, region, BL value and BL value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2701 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9832 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -2.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.5 |
| upper limit | -0.2 |

Secondary: Change from Baseline in On-treatment Patient Global Impression of Severity (PGI-S) at Weeks 8, 12, 28, 52

| | |
|-----------------|---|
| End point title | Change from Baseline in On-treatment Patient Global Impression of Severity (PGI-S) at Weeks 8, 12, 28, 52 |
|-----------------|---|

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 more disease severity. Change from Baseline was calculated as on-treatment 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 (Pre-dose on 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 | 1341 ^[87] | 1362 ^[88] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 8, n=1341,1295 | 0.00 (± 0.022) | -0.02 (± 0.022) | | |
| Week 12, n=1341,1362 | 0.03 (± 0.022) | -0.02 (± 0.022) | | |
| Week 28, n=1054,1051 | 0.05 (± 0.025) | 0.09 (± 0.025) | | |
| Week 52, n=871,865 | 0.11 (± 0.028) | 0.06 (± 0.029) | | |

Notes:

[87] - All Randomized (ITT) Population.

[88] - All Randomized (ITT) Population.

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|--------------------------------|
| Statistical analysis description: | |
| Week 8: Model was fitted from Baseline up to Week52 and model adjusted Week 8 data has been presented, with factors for treatment, time, current ESA use, region, Baseline value and Baseline value by time and treatment by time interactions. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2703 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6917 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.08 |

| Statistical analysis title | Statistical analysis 2 |
|---|--------------------------------|
| Statistical analysis description: | |
| Week 12: Model was fitted from Baseline up to Week52 and model adjusted Week 12 data has been presented, with factors for treatment, time, current ESA use, region, Baseline value and Baseline value by time and treatment by time interactions. | |
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2703 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.951 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.05 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.01 |
| upper limit | 0.11 |

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

Statistical analysis description:

Week 28: Model was fitted from Baseline up to Week52 and model adjusted Week 28 data has been presented, with factors for treatment, time, current ESA use, region, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2703 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1136 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.11 |
| upper limit | 0.03 |

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

Statistical analysis description:

Week 52: Model was fitted from Baseline up to Week52 and model adjusted Week 52 data has been presented, with factors for treatment, time, current ESA use, region, Baseline value and Baseline value by time and treatment by time interactions.

| | |
|---|--------------------------------|
| Comparison groups | Daprodustat v Darbepoetin alfa |
| Number of subjects included in analysis | 2703 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8859 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03 |
| upper limit | 0.13 |

Secondary: Change from Baseline in Post-randomization estimated Glomerular

Filtration Rate (eGFR) at Week 52

| | |
|-----------------|---|
| End point title | Change from Baseline in Post-randomization estimated Glomerular Filtration Rate (eGFR) at Week 52 |
|-----------------|---|

End point description:

Blood samples were collected to analyze estimated glomerular filtration rate. Change from Baseline was calculated as post-Baseline 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 (Pre-dose on Day 1) and Week 52

| End point values | Daprodustat | Darbepoetin alfa | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1869 ^[89] | 1868 ^[90] | | |
| Units: mL per minute per 1.73 square meter | | | | |
| least squares mean (standard error) | -2.88 (± 0.193) | -2.67 (± 0.193) | | |

Notes:

[89] - All Randomized (ITT) Population.

[90] - All Randomized (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, current ESA use at randomization, region, Baseline value and Baseline value by time and treatment by time interactions.

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

| | |
|---|------|
| Number of subjects included in analysis | 3737 |
|---|------|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

| | |
|---------|----------|
| P-value | = 0.7716 |
|---------|----------|

| | |
|--------|------|
| Method | MMRM |
|--------|------|

| | |
|--------------------|--------------------|
| Parameter estimate | LS mean difference |
|--------------------|--------------------|

| | |
|----------------|------|
| Point estimate | -0.2 |
|----------------|------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|-------|
| lower limit | -0.74 |
|-------------|-------|

| | |
|-------------|------|
| upper limit | 0.33 |
|-------------|------|

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week -4 to randomization(Day1) in Run-in period and from Day1 to 4.3 person-years for CV follow-up time period.2 participants in All Randomized(ITT)Population did not receive treatment and were excluded from Safety Population.

Adverse event reporting additional description:

All-cause mortality/Placebo run-in used All Randomized(ITT)Population consisting of all randomized participants/analyzed based on treatment to which were randomized.TESAEs/non-serious TEAEs during treatment period used SafetyPopulation,included all randomized participants who received at least1 dose of treatment,analyzed based on treatment received

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Participants received treatment with daprodustat film-coated tablets at dose levels ranging from 1, 2, 4, 6, 8, 10, 12, 16 and 24 milligrams (mg) orally once daily from randomization (Day 1) up to 51.1 month. 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 treatment with darbepoetin alfa as prefilled syringes (PFS) for subcutaneous or intravenous (IV) injection at 4-weekly total dose levels ranging from 20, 30, 40, 60, 80, 100, 150, 200, 300 and 400 microgram (mcg) from randomization (Day 1) up to 51.1 month. Darbepoetin alfa IV injection was administered to participants undergoing hemodialysis. Study treatment was dose-titrated to achieve and maintain Hgb in the target range (10 to 11 g/dL).

| | |
|-----------------------|------------------------|
| Reporting group title | Run-in Period: Placebo |
|-----------------------|------------------------|

Reporting group description:

Participants received placebo tablets orally once daily in run-in period from Week-4 up to randomization (Day 1).

| Serious adverse events | Daprodustat | Darbepoetin alfa | Run-in Period: Placebo |
|---|---------------------|---------------------|------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 850 / 1937 (43.88%) | 703 / 1933 (36.37%) | 63 / 3872 (1.63%) |
| number of deaths (all causes) | 301 | 298 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 5 / 1937 (0.26%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 5 / 1937 (0.26%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 4 / 1933 (0.21%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma pancreas | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign neoplasm of bladder | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder cancer | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder cancer recurrent | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chondrosarcoma | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Colon adenoma | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diffuse large B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial cancer stage 0 | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematological malignancy | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic cancer | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hodgkin's disease | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lip and/or oral cavity cancer | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma stage I | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm of unknown primary site | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Meningioma | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to bone | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Monoclonal gammopathy | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myeloproliferative neoplasm | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cancer | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic neoplasm | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parathyroid tumour benign | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer recurrent | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatic adenoma | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Refractory anaemia with an excess of blasts | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cancer | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cancer recurrent | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retroperitoneal neoplasm | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of the vulva | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thyroid adenoma | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteric cancer | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 15 / 1937 (0.77%) | 11 / 1933 (0.57%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 16 | 1 / 14 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 8 / 1937 (0.41%) | 8 / 1933 (0.41%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 8 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive urgency | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 9 / 1933 (0.47%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |

| | | | |
|---|-------------------|------------------|------------------|
| subjects affected / exposed | 10 / 1937 (0.52%) | 5 / 1933 (0.26%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive emergency | | | |
| subjects affected / exposed | 6 / 1937 (0.31%) | 8 / 1933 (0.41%) | 2 / 3872 (0.05%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 8 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 8 / 1933 (0.41%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 8 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 5 / 1937 (0.26%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic stenosis | | | |
| subjects affected / exposed | 5 / 1937 (0.26%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematoma | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Intermittent claudication | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 1937 (0.15%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic aneurysm | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dialysis hypotension | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Extremity necrosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant hypertension | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Accelerated hypertension | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic dissection | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic intramural haematoma | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriosclerosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Arteriovenous fistula | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic vascular disorder | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Giant cell arteritis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Internal haemorrhage | | | |

| | | | |
|--|-------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Phlebitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian artery stenosis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 13 / 1937 (0.67%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 13 | 1 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 13 | 1 / 4 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 9 / 1937 (0.46%) | 6 / 1933 (0.31%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 8 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 7 / 1937 (0.36%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 6 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 2 / 1933 (0.10%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised oedema | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 4 / 1933 (0.21%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 1 / 1933 (0.05%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired healing | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Cardiac death | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Catheter site extravasation | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site inflammation | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Complication associated with device | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Discomfort | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gait inability | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inflammation | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrobiosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic mass | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden cardiac death | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Vascular device occlusion | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal transplant failure | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemophagocytic lymphohistiocytosis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Kidney transplant rejection | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anti-neutrophil cytoplasmic antibody positive vasculitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Social circumstances | | | |
| Immobile | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast mass | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Heavy menstrual bleeding | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intermenstrual bleeding | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Scrotal swelling | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine polyp | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 11 / 1937 (0.57%) | 11 / 1933 (0.57%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 13 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 13 / 1937 (0.67%) | 7 / 1933 (0.36%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 9 / 1937 (0.46%) | 11 / 1933 (0.57%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 12 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 12 / 1933 (0.62%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 14 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 5 / 1937 (0.26%) | 7 / 1933 (0.36%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 7 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 6 / 1937 (0.31%) | 5 / 1933 (0.26%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 6 / 1937 (0.31%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 6 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary congestion | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 3 / 1933 (0.16%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthma | | | |
| subjects affected / exposed | 5 / 1937 (0.26%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiectasis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Apnoea | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic respiratory disease | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrothorax | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Painful respiration | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngeal haemorrhage | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hypertensive crisis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary mass | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory alkalosis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 4 / 1933 (0.21%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delirium | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anxiety | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device malfunction | | | |
| subjects affected / exposed | 9 / 1937 (0.46%) | 9 / 1933 (0.47%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 12 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device occlusion | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 60 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis in device | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device failure | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lead dislodgement | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute hepatic failure | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Biliary obstruction | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cryptogenic cirrhosis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Haemobilia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic cytolysis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic mass | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-alcoholic steatohepatitis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 1 / 1933 (0.05%) | 2 / 3872 (0.05%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Troponin increased | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anticoagulation drug level above therapeutic | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acid base balance abnormal | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Blood glucose increased | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coagulation test abnormal | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrocardiogram QRS complex prolonged | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic enzymes increased | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus test positive | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|------------------|-------------------|------------------|
| Femur fracture | | | |
| subjects affected / exposed | 8 / 1937 (0.41%) | 12 / 1933 (0.62%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 12 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 9 / 1937 (0.46%) | 6 / 1933 (0.31%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Arteriovenous fistula thrombosis | | | |
| subjects affected / exposed | 5 / 1937 (0.26%) | 9 / 1933 (0.47%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 10 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 6 / 1933 (0.31%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 6 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 5 / 1937 (0.26%) | 5 / 1933 (0.26%) | 2 / 3872 (0.05%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 6 / 1933 (0.31%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriovenous fistula site complication | | | |
| subjects affected / exposed | 6 / 1937 (0.31%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic fracture | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 5 / 1937 (0.26%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Peritoneal dialysis complication | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Craniocerebral injury | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemodialysis complication | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriovenous fistula site haemorrhage | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Contusion | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibula fracture | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foot fracture | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue injury | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular access malfunction | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular graft thrombosis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular pseudoaneurysm ruptured | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Accidental overdose | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acetabulum fracture | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriovenous fistula maturation failure | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriovenous fistula occlusion | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriovenous fistula site haematoma | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriovenous fistula site pseudoaneurysm | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriovenous graft thrombosis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Comminuted fracture | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Complications of transplanted kidney | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis radiation | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Heart injury | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament rupture | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple fractures | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Nasal injury | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nerve root injury lumbar | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periprosthetic fracture | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural complication | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haematoma | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haematuria | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural inflammation | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative ileus | | | |

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|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural vomiting | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skull fracture | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stress fracture | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic intracranial haemorrhage | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ulna fracture | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention postoperative | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular access complication | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular access site thrombosis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular graft complication | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular graft occlusion | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound dehiscence | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound secretion | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Congenital cystic kidney disease | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syringomyelia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 37 / 1937 (1.91%) | 26 / 1933 (1.35%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 2 / 40 | 0 / 28 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 3 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 29 / 1937 (1.50%) | 20 / 1933 (1.03%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 1 / 43 | 0 / 23 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 28 / 1937 (1.45%) | 14 / 1933 (0.72%) | 2 / 3872 (0.05%) |
| occurrences causally related to treatment / all | 1 / 35 | 0 / 17 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |

| | | | |
|---|-------------------|-------------------|------------------|
| Angina unstable | | | |
| subjects affected / exposed | 13 / 1937 (0.67%) | 15 / 1933 (0.78%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 15 | 0 / 17 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 10 / 1937 (0.52%) | 11 / 1933 (0.57%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 12 | 0 / 11 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 10 / 1937 (0.52%) | 9 / 1933 (0.47%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 11 / 1937 (0.57%) | 8 / 1933 (0.41%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 9 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 14 / 1937 (0.72%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 2 / 14 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 9 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 10 / 1937 (0.52%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 5 | 0 / 4 | 0 / 0 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 9 / 1937 (0.46%) | 5 / 1933 (0.26%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Acute left ventricular failure | | | |
| subjects affected / exposed | 12 / 1937 (0.62%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 6 / 1937 (0.31%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 3 / 1933 (0.16%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 6 / 1937 (0.31%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardiorenal syndrome | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 1937 (0.15%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Palpitations | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis uraemic | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiomyopathy | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diastolic dysfunction | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive heart disease | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradyarrhythmia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic left ventricular failure | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic cardiomyopathy | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mitral valve prolapse | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocarditis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nodal arrhythmia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Right ventricular failure | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stress cardiomyopathy | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular extrasystoles | | | |

| | | | |
|---|-------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bifascicular block | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 0 / 1933 (0.00%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 13 / 1937 (0.67%) | 8 / 1933 (0.41%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 8 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 6 / 1937 (0.31%) | 9 / 1933 (0.47%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic encephalopathy | | | |
| subjects affected / exposed | 6 / 1937 (0.31%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 4 / 1937 (0.21%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Toxic encephalopathy | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aphasia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uraemic encephalopathy | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebellar stroke | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Dementia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Diabetic neuropathy | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness postural | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive encephalopathy | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxic-ischaemic encephalopathy | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Intercostal neuralgia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intracranial haematoma | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiculopathy | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Altered state of consciousness | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basilar artery occlusion | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain stem haemorrhage | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Brain stem infarction | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haematoma | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidotic hyperglycaemic coma | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dystonic tremor | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolic stroke | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised tonic-clonic seizure | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gliositis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| IIIrd nerve paresis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intracranial aneurysm | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lacunar infarction | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar radiculopathy | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbosacral radiculopathy | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Monoparesis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myasthenia gravis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral sensorimotor neuropathy | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Putamen haemorrhage | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertigo CNS origin | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 33 / 1937 (1.70%) | 31 / 1933 (1.60%) | 3 / 3872 (0.08%) |
| occurrences causally related to treatment / all | 2 / 34 | 0 / 34 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 5 / 1937 (0.26%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrogenic anaemia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune thrombocytopenia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune haemolytic anaemia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood loss anaemia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coagulopathy | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Evans syndrome | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-immune heparin associated thrombocytopenia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sideroblastic anaemia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vestibular disorder | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Vitreous haemorrhage | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cataract | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal detachment | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angle closure glaucoma | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye haemorrhage | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eyelid ptosis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glaucoma | | | |

| | | | |
|---|-------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhegmatogenous retinal detachment | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulcerative keratitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vitreoretinal traction syndrome | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 12 / 1937 (0.62%) | 7 / 1933 (0.36%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 12 / 1937 (0.62%) | 6 / 1933 (0.31%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 6 / 1937 (0.31%) | 5 / 1933 (0.26%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 4 / 1937 (0.21%) | 5 / 1933 (0.26%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 5 / 1933 (0.26%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 6 / 1937 (0.31%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 5 / 1933 (0.26%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 6 / 1937 (0.31%) | 1 / 1933 (0.05%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 5 / 1933 (0.26%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 3 / 1933 (0.16%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer haemorrhage | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 1937 (0.15%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 3 / 1933 (0.16%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis erosive | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal perforation | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic gastroparesis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Food poisoning | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal vascular malformation haemorrhagic | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic erosive gastritis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incarcerated umbilical hernia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumoperitoneum | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retroperitoneal haemorrhage | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uraemic gastropathy | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal wall haematoma | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute abdomen | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis microscopic | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic gastropathy | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulum intestinal | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenitis haemorrhagic | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric perforation | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal inflammation | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gingival bleeding | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal haemorrhage | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mesenteric vascular insufficiency | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic disorder | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peptic ulcer | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Proctitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic foot | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 5 / 1933 (0.26%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 7 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 6 / 1933 (0.31%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug reaction with eosinophilia and systemic symptoms | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic skin ulcer | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Actinic keratosis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angioedema | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cutaneous calcification | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Diabetic ulcer | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erythrodermic psoriasis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peau d'orange | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psoriasis | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin necrosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxic skin eruption | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 86 / 1937 (4.44%) | 49 / 1933 (2.53%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 90 | 0 / 52 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 6 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 70 / 1937 (3.61%) | 47 / 1933 (2.43%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 76 | 0 / 53 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Azotaemia | | | |
| subjects affected / exposed | 54 / 1937 (2.79%) | 35 / 1933 (1.81%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 56 | 0 / 35 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 7 | 0 / 2 | 0 / 0 |
| End stage renal disease | | | |
| subjects affected / exposed | 48 / 1937 (2.48%) | 36 / 1933 (1.86%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 50 | 0 / 37 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| Renal impairment | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 20 / 1937 (1.03%) | 11 / 1933 (0.57%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 21 | 0 / 11 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 15 / 1937 (0.77%) | 11 / 1933 (0.57%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 16 | 0 / 11 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| Nephropathy | | | |
| subjects affected / exposed | 6 / 1937 (0.31%) | 6 / 1933 (0.31%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cyst haemorrhage | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephropathy toxic | | | |

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|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anuria | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic end stage renal disease | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Diabetic nephropathy | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glomerulonephritis chronic | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glomerulonephritis membranous | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| IgA nephropathy | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intercapillary glomerulosclerosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lupus nephritis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstructive nephropathy | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oliguria | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal tubular necrosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal artery occlusion | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 0 / 1933 (0.00%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal artery stenosis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 0 / 1933 (0.00%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 0 / 1933 (0.00%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Hyperparathyroidism secondary | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperparathyroidism | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperprolactinaemia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parathyroid hyperplasia | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Systemic lupus erythematosus | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Costochondritis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gouty arthritis | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mobility decreased | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal stenosis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bursitis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gouty tophus | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemarthrosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle twitching | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myositis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteolysis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sacroiliitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sarcopenia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue necrosis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 78 / 1937 (4.03%) | 75 / 1933 (3.88%) | 3 / 3872 (0.08%) |
| occurrences causally related to treatment / all | 0 / 90 | 0 / 81 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 10 | 0 / 4 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 39 / 1937 (2.01%) | 33 / 1933 (1.71%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 39 | 0 / 33 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 10 | 0 / 4 | 0 / 0 |
| Urinary tract infection | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 33 / 1937 (1.70%) | 36 / 1933 (1.86%) | 2 / 3872 (0.05%) |
| occurrences causally related to treatment / all | 0 / 34 | 0 / 38 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 19 / 1937 (0.98%) | 14 / 1933 (0.72%) | 3 / 3872 (0.08%) |
| occurrences causally related to treatment / all | 0 / 22 | 0 / 15 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 14 / 1937 (0.72%) | 19 / 1933 (0.98%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 15 | 0 / 19 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 5 | 0 / 1 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 21 / 1937 (1.08%) | 10 / 1933 (0.52%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 28 | 0 / 15 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 10 / 1933 (0.52%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 10 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 10 / 1933 (0.52%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 11 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| Osteomyelitis | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 8 / 1933 (0.41%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 5 / 1937 (0.26%) | 10 / 1933 (0.52%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 10 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 7 / 1937 (0.36%) | 7 / 1933 (0.36%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 10 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gangrene | | | |
| subjects affected / exposed | 8 / 1937 (0.41%) | 6 / 1933 (0.31%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 8 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 6 / 1933 (0.31%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| Device related sepsis | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 5 / 1933 (0.26%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 5 / 1933 (0.26%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 7 / 1933 (0.36%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 7 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 7 / 1933 (0.36%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 6 / 1933 (0.31%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suspected COVID-19 | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 1937 (0.10%) | 6 / 1933 (0.31%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess limb | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 5 / 1933 (0.26%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 5 / 1937 (0.26%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Post procedural infection | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis chronic | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Streptococcal bacteraemia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriovenous fistula site infection | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis bacterial | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis acute | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute hepatitis B | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 1937 (0.15%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endophthalmitis | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 0 / 1933 (0.00%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal bacteraemia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiolitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related bacteraemia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic foot infection | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterobacter sepsis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia infection | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fungal peritonitis | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infected skin ulcer | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver abscess | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis bacterial | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue infection | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendiceal abscess | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis perforated | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriovenous graft site infection | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain abscess | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis staphylococcal | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic sinusitis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium bacteraemia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colonic abscess | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis klebsiella | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Dengue haemorrhagic fever | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis intestinal haemorrhagic | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis intestinal perforated | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eczema infected | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Emphysematous pyelonephritis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Empyema | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis infectious | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterococcal sepsis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis Escherichia coli | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis bacillus | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Groin abscess | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic cyst infection | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes ophthalmic | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incision site abscess | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infected fistula | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infective tenosynovitis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral discitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Kidney infection | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Listeria sepsis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis viral | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metapneumovirus infection | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ophthalmic herpes zoster | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orchitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parotitis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perineal abscess | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia adenoviral | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia escherichia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia influenzal | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia viral | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomembranous colitis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonas bronchitis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyonephrosis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal abscess | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cyst infection | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal graft infection | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis syndrome | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic arthritis staphylococcal | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Serratia sepsis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis fungal | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord infection | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sphingomonas paucimobilis infection | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tuberculosis | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tubo-ovarian abscess | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteritis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection pseudomonal | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection staphylococcal | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular access site infection | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular graft infection | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 0 / 1933 (0.00%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 26 / 1937 (1.34%) | 25 / 1933 (1.29%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 26 | 0 / 26 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Fluid overload | | | |
| subjects affected / exposed | 25 / 1937 (1.29%) | 23 / 1933 (1.19%) | 2 / 3872 (0.05%) |
| occurrences causally related to treatment / all | 0 / 27 | 0 / 24 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 16 / 1937 (0.83%) | 13 / 1933 (0.67%) | 2 / 3872 (0.05%) |
| occurrences causally related to treatment / all | 0 / 20 | 0 / 16 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 10 / 1937 (0.52%) | 16 / 1933 (0.83%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 20 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 5 / 1933 (0.26%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 7 / 1937 (0.36%) | 3 / 1933 (0.16%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gout | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 5 / 1933 (0.26%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 4 / 1933 (0.21%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 3 / 1933 (0.16%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 6 / 1933 (0.31%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 4 / 1937 (0.21%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypervolaemia | | | |
| subjects affected / exposed | 4 / 1937 (0.21%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 3 / 1933 (0.16%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemia | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 2 / 1933 (0.10%) | 1 / 3872 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemic hyperosmolar nonketotic syndrome | | | |
| subjects affected / exposed | 3 / 1937 (0.15%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iron deficiency | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 2 / 1933 (0.10%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic metabolic decompensation | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Failure to thrive | | | |
| subjects affected / exposed | 2 / 1937 (0.10%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Fluid retention | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abnormal loss of weight | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acidosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperammonaemia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperinsulinaemic hypoglycaemia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemic syndrome | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic syndrome | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudohyponatraemia | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Refeeding syndrome | | | |
| subjects affected / exposed | 0 / 1937 (0.00%) | 1 / 1933 (0.05%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Starvation ketoacidosis | | | |
| subjects affected / exposed | 1 / 1937 (0.05%) | 0 / 1933 (0.00%) | 0 / 3872 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Daprodustat | Darbepoetin alfa | Run-in Period: Placebo |
|---|------------------------|------------------------|---------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 851 / 1937 (43.93%) | 825 / 1933 (42.68%) | 0 / 3872 (0.00%) |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 104 / 1937 (5.37%) | 88 / 1933 (4.55%) | 0 / 3872 (0.00%) |
| occurrences (all) | 128 | 119 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 247 / 1937 (12.75%) | 264 / 1933 (13.66%) | 0 / 3872 (0.00%) |
| occurrences (all) | 317 | 339 | 0 |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 198 / 1937 (10.22%) | 162 / 1933 (8.38%) | 0 / 3872 (0.00%) |
| occurrences (all) | 239 | 199 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 149 / 1937 (7.69%) | 139 / 1933 (7.19%) | 0 / 3872 (0.00%) |
| occurrences (all) | 181 | 172 | 0 |
| Constipation | | | |
| subjects affected / exposed | 127 / 1937 (6.56%) | 88 / 1933 (4.55%) | 0 / 3872 (0.00%) |
| occurrences (all) | 150 | 96 | 0 |
| Nausea | | | |
| subjects affected / exposed | 103 / 1937 (5.32%) | 84 / 1933 (4.35%) | 0 / 3872 (0.00%) |
| occurrences (all) | 120 | 101 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 82 / 1937 (4.23%) | 105 / 1933 (5.43%) | 0 / 3872 (0.00%) |
| occurrences (all) | 95 | 110 | 0 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 164 / 1937 (8.47%) | 153 / 1933 (7.92%) | 0 / 3872 (0.00%) |
| occurrences (all) | 245 | 199 | 0 |

| | | | |
|---|---------------------------|---------------------------|-----------------------|
| Nasopharyngitis subjects affected / exposed occurrences (all) | 118 / 1937 (6.09%) 163 | 133 / 1933 (6.88%) 180 | 0 / 3872 (0.00%) 0 |
| Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all) | 128 / 1937 (6.61%) 148 | 122 / 1933 (6.31%) 141 | 0 / 3872 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 20 September 2016 | Amendment 1 (Austria, Belgium, Czech Republic, Denmark, Estonia, Germany, Hungary, Italy, Poland, Portugal, Romania, Spain, Sweden and the United Kingdom): Clarified end of the study timing; removed requirement to reduce ESA dose if Week -8 Hgb is >11.5 g/dL; further iron management guidance; new exploratory objective for delayed graft function after deceased donor kidney transplantation |
| 12 October 2016 | Amendment 2 (Key changes): Applied changes from Amendment 1; added new timepoints at Week -4 and Week 2 for collection of iron therapy and at Week 52 for Kt/Vurea; changes to ambulatory blood pressure monitoring (ABPM) assessments; clarification for those randomized to rhEPO who transition from HD to PD will change from epoetin alfa to darbepoetin alfa; added country-specific requirements for France and Czech Republic |
| 08 February 2017 | Amendment 2/France-01: Added France only requirements for additional ultrasound added to end of study and for participants who transition to dialysis to permanently discontinue randomized treatment. |
| 05 October 2017 | Amendment 3 (Key changes): Added retest for Hgb and TSAT for entry; broadened exclusion to include participation in interventional study with investigational agent or device; added provisions for use of local standard of care; revised statistical section to change from two-sided testing at the 5% level to one-sided testing at the 2.5% level; correct the comparator for the Null and Alternative hypotheses; changed significance levels to p-values; added description of the adjustments to statistical model; updated hyporesponder analyses; added text regarding the interim analysis process; added exploratory endpoints around Hgb variability, iron parameters, transfusions and dose adjustment scheme; added provision for possible change to Dose Adjustment Algorithm based review of blinded instream aggregate Hgb data; updated Risk Assessment to align with Investigator's Brochure, version 8; simplified ABPM sub-study |
| 09 October 2017 | Amendment 3/France-01: Apply changes from global amendment 3 |
| 16 August 2019 | Amendment 4: Added retest values for Hgb entry at Day 1, an additional retest opportunity for TSAT for eligibility at W-8, and revised the definition of current uncontrolled hypertension; added autosomal dominant polycystic kidney disease (ADPKD) risk information and requirements for patients with ADPKD; added new adverse event of special interest of worsening of hypertension; added secondary objective/endpoint to assess renal progression via change in eGFR; updated Risk Assessment to align with Investigator's Brochure, version 10; stated recruitment in the ABPM sub-study is closed; PK sub-study entry criteria to exclude patients transitioning or already transitioned to dialysis |
| 16 August 2019 | Amendment 4/France-01: Apply changes from global amendment 4 plus update France administrative considerations |
| 30 July 2020 | Amendment 5: Revised MACE NI margin and target MACE as a result of the NI margin change; updated analysis of the Hgb co-primary endpoint and multiplicity adjustment strategy from Hommel to Holm-Bonferroni based on FDA feedback; updated pregnancy reporting timelines to align with revised Sponsor timings |
| 30 July 2020 | Amendment No. 05/FRA-01: Apply changes from global amendment 4 |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported