



Clinical trial results:

A 24-week, Phase IIB, Randomized, Controlled, Parallel group, Multi-center Study to Evaluate the Safety and Efficacy of GSK1278863 in Subjects with Anemia Associated with Chronic Kidney Diseases who are not on Dialysis.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-002681-39 |
| Trial protocol | ES SE GB CZ HU DK |
| Global end of trial date | 14 May 2015 |

Results information

| | |
|--------------------------------|-------------|
| Result version number | v1 |
| This version publication date | 15 May 2016 |
| First version publication date | 15 May 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 113747 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01977573 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Middlesex, Brentford, United Kingdom, |
| Public contact | GlaxoSmithKline, GlaxoSmithKline, +1 8664357343, |
| Scientific contact | GlaxoSmithKline, GlaxoSmithKline, +1 8664357343, |

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 | 07 August 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 May 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This study will be conducted in approximately 228 subjects with anemia associated with CKD who are not on dialysis. Two groups of subjects will be enrolled into the study: Group 1: recombinant human erythropoietin (rhEPO) naive subjects; Group 2: rhEPO users, who are currently receiving rhEPO. Subjects who are rhEPO naive will be randomized to receive either GSK1278863 once daily (QD) or rhEPO in a 3:1 fashion; subjects who are receiving an rhEPO before enrolling (rhEPO users) will be randomized in a 1:1 fashion to GSK1278863 QD or to the control arm. For those randomized to the control arm, the decision around whether the subject requires rhEPO, the selection of the type of rhEPO (if needed) and the choice of rhEPO dose to achieve and maintain Hgb concentrations within the target range should be based on Investigator clinical judgment, with the historical rhEPO dose and the current Hgb value being considered.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 31 October 2013 |
| 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 | Australia: 8 |
| Country: Number of subjects enrolled | Canada: 14 |
| Country: Number of subjects enrolled | Czech Republic: 20 |
| Country: Number of subjects enrolled | Denmark: 3 |
| Country: Number of subjects enrolled | France: 7 |
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | Hungary: 6 |
| Country: Number of subjects enrolled | Korea, Republic of: 19 |
| Country: Number of subjects enrolled | Poland: 4 |
| Country: Number of subjects enrolled | Russian Federation: 38 |
| Country: Number of subjects enrolled | Spain: 24 |
| Country: Number of subjects enrolled | Sweden: 5 |
| Country: Number of subjects enrolled | United Kingdom: 7 |
| Country: Number of subjects enrolled | United States: 45 |
| Country: Number of subjects enrolled | Japan: 42 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 252 |
| EEA total number of subjects | 86 |

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) | 93 |
| From 65 to 84 years | 149 |
| 85 years and over | 10 |

Subject disposition

Recruitment

Recruitment details:

Two groups of participants (par.) were enrolled in this study. Group 1 consisted of recombinant human erythropoietin (rhEPO)-naive par. whereas Group 2 consisted of rhEPO users.

Pre-assignment

Screening details:

Post screening, eligible par. were randomized to receive either GSK1278863 once a day (QD) or to the Control arm in a 3:1 fashion in Group 1 and 1:1 fashion in Group 2.

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 | rhEPO-Naive GSK1278863 |

Arm description:

RhEPO-naive participants were randomly assigned to receive GSK1278863 QD for 24 weeks. Participants were blinded to the dose-level they received throughout the study. At Week 24, participants stopped taking GSK1278863, and returned for the follow-up visit at Week 28.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | GSK1278863 tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received GSK1278863 once daily for 24 weeks and were blinded to the dose-level they received throughout the study. Blinding was maintained by providing the required dose in an appropriate combination of GSK1278863 and/or placebo tablets.

| | |
|--|------------------------------------|
| Investigational medicinal product name | Placebo to match GSK1278863 tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received GSK1278863 once daily for 24 weeks and were blinded to the dose-level they received throughout the study. Blinding was maintained by providing the required dose in an appropriate combination of GSK1278863 and/or placebo tablets.

| | |
|------------------|---------------------|
| Arm title | rhEPO-Naive Control |
|------------------|---------------------|

Arm description:

RhEPO-naive participants were randomly assigned to receive open-label rhEPO (epoetins or their biosimilars, or darbepoetin) as necessary per standard of care, based on the Investigator's clinical judgment, for 24 weeks. At Week 24, participants stopped taking rhEPO (if applicable) and remained off rhEPO or other Erythropoiesis Stimulating Agents (ESA) until at least the follow-up visit at Week 28.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|--|
| Investigational medicinal product name | Standard of care including RhEPO if needed |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Cutaneous use, Intravenous use |
| Dosage and administration details: Standard of care provided accordingly. | |
| Arm title | rhEPO-User GSK1278863 |

Arm description:

RhEPO users were randomly assigned to receive GSK1278863 QD for 24 weeks. Participants were blinded to the dose-level they received throughout the study. At Week 24, participants stopped taking GSK1278863 and did not re-start rhEPO or other ESAs until after the follow-up visit at Week 28 (except in cases where there was a compelling clinical reason [based on Investigator's opinion] to start rhEPO therapy).

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | GSK1278863 tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received GSK1278863 once daily for 24 weeks and were blinded to the dose-level they received throughout the study. Blinding was maintained by providing the required dose in an appropriate combination of GSK1278863 and/or placebo tablets.

| | |
|--|------------------------------------|
| Investigational medicinal product name | Placebo to match GSK1278863 tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received GSK1278863 once daily for 24 weeks and were blinded to the dose-level they received throughout the study. Blinding was maintained by providing the required dose in an appropriate combination of GSK1278863 and/or placebo tablets.

| | |
|------------------|--------------------|
| Arm title | rhEPO-User Control |
|------------------|--------------------|

Arm description:

RhEPO users were randomly assigned to receive rhEPO (epoetins or their biosimilars, or darbepoetin) as necessary per standard of care, based on the Investigator clinical judgment, for 24 weeks. Participants were allowed to continue rhEPO therapy between Week 24 and 28.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Standard of care include RhEPO if needed |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Cutaneous use, Intravascular use |

Dosage and administration details:

Standard of care provided accordingly.

| Number of subjects in period 1 | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 |
|---------------------------------------|---------------------------|---------------------|--------------------------|
| Started | 136 | 44 | 36 |
| Completed | 116 | 41 | 32 |
| Not completed | 20 | 3 | 4 |
| Consent withdrawn by subject | 6 | 1 | 1 |
| Physician decision | 1 | - | - |
| Adverse event, non-fatal | 7 | - | 2 |
| Lost to follow-up | 1 | - | - |
| Protocol deviation | 3 | 1 | - |
| reached defined stopping criteria | 2 | 1 | - |
| Protocol-Defined Stopping Criteria | - | - | 1 |

| Number of subjects in period 1 | rhEPO-User Control |
|---------------------------------------|--------------------|
| Started | 36 |
| Completed | 33 |
| Not completed | 3 |
| Consent withdrawn by subject | 1 |
| Physician decision | - |
| Adverse event, non-fatal | 1 |
| Lost to follow-up | 1 |
| Protocol deviation | - |
| reached defined stopping criteria | - |
| Protocol-Defined Stopping Criteria | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | rhEPO-Naive GSK1278863 |
|-----------------------|------------------------|

Reporting group description:

RhEPO-naive participants were randomly assigned to receive GSK1278863 QD for 24 weeks. Participants were blinded to the dose-level they received throughout the study. At Week 24, participants stopped taking GSK1278863, and returned for the follow-up visit at Week 28.

| | |
|-----------------------|---------------------|
| Reporting group title | rhEPO-Naive Control |
|-----------------------|---------------------|

Reporting group description:

RhEPO-naive participants were randomly assigned to receive open-label rhEPO (epoetins or their biosimilars, or darbepoetin) as necessary per standard of care, based on the Investigator's clinical judgment, for 24 weeks. At Week 24, participants stopped taking rhEPO (if applicable) and remained off rhEPO or other Erythropoiesis Stimulating Agents (ESA) until at least the follow-up visit at Week 28.

| | |
|-----------------------|-----------------------|
| Reporting group title | rhEPO-User GSK1278863 |
|-----------------------|-----------------------|

Reporting group description:

RhEPO users were randomly assigned to receive GSK1278863 QD for 24 weeks. Participants were blinded to the dose-level they received throughout the study. At Week 24, participants stopped taking GSK1278863 and did not re-start rhEPO or other ESAs until after the follow-up visit at Week 28 (except in cases where there was a compelling clinical reason [based on Investigator's opinion] to start rhEPO therapy).

| | |
|-----------------------|--------------------|
| Reporting group title | rhEPO-User Control |
|-----------------------|--------------------|

Reporting group description:

RhEPO users were randomly assigned to receive rhEPO (epoetins or their biosimilars, or darbepoetin) as necessary per standard of care, based on the Investigator clinical judgment, for 24 weeks. Participants were allowed to continue rhEPO therapy between Week 24 and 28.

| Reporting group values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 |
|------------------------------------|---------------------------|---------------------|--------------------------|
| Number of subjects | 136 | 44 | 36 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Age continuous Units: years arithmetic mean standard deviation | 67.7 ± 12.39 | 64.5 ± 14.11 | 61.9 ± 14.65 |
| Gender categorical Units: Subjects | | | |
| Female | 56 | 20 | 17 |
| Male | 80 | 24 | 19 |
| Race, customized Units: Subjects | | | |
| White | 89 | 30 | 25 |
| African American | 14 | 2 | 2 |
| Asian | 33 | 12 | 9 |

| Reporting group values | rhEPO-User Control | Total | |
|------------------------------------|--------------------|-------|--|
| Number of subjects | 36 | 252 | |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-----------------|-----|--|
| Age continuous Units: years arithmetic mean standard deviation | 66.7 ± 12.89 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 13 | 106 | |
| Male | 23 | 146 | |
| Race, customized Units: Subjects | | | |
| White | 19 | 163 | |
| African American | 4 | 22 | |
| Asian | 13 | 67 | |

End points

End points reporting groups

| | |
|---|------------------------|
| Reporting group title | rhEPO-Naive GSK1278863 |
| Reporting group description: RhEPO-naive participants were randomly assigned to receive GSK1278863 QD for 24 weeks. Participants were blinded to the dose-level they received throughout the study. At Week 24, participants stopped taking GSK1278863, and returned for the follow-up visit at Week 28. | |
| Reporting group title | rhEPO-Naive Control |
| Reporting group description: RhEPO-naive participants were randomly assigned to receive open-label rhEPO (epoetins or their biosimilars, or darbepoetin) as necessary per standard of care, based on the Investigator's clinical judgment, for 24 weeks. At Week 24, participants stopped taking rhEPO (if applicable) and remained off rhEPO or other Erythropoiesis Stimulating Agents (ESA) until at least the follow-up visit at Week 28. | |
| Reporting group title | rhEPO-User GSK1278863 |
| Reporting group description: RhEPO users were randomly assigned to receive GSK1278863 QD for 24 weeks. Participants were blinded to the dose-level they received throughout the study. At Week 24, participants stopped taking GSK1278863 and did not re-start rhEPO or other ESAs until after the follow-up visit at Week 28 (except in cases where there was a compelling clinical reason [based on Investigator's opinion] to start rhEPO therapy). | |
| Reporting group title | rhEPO-User Control |
| Reporting group description: RhEPO users were randomly assigned to receive rhEPO (epoetins or their biosimilars, or darbepoetin) as necessary per standard of care, based on the Investigator clinical judgment, for 24 weeks. Participants were allowed to continue rhEPO therapy between Week 24 and 28. | |

Primary: Summary of hemoglobin (Hgb) concentration at Week 24

| | |
|---|---|
| End point title | Summary of hemoglobin (Hgb) concentration at Week 24 ^[1] |
| End point description: The original Hgb target range was 9.0 to 10.5 g/dL for Group 1- rhEPO naive participants with a stable baseline Hgb of 8.0-10.0 g/dL and for Group 2- rhEPO users with a stable baseline Hgb of 9.0-10.5. The amended Hgb target range was 10.0 to 11.5 g/dL for Group 1- rhEPO naive participants with a stable baseline Hgb of 8.0-11.0 g/dL and Group 2- rhEPO users with a stable baseline Hgb of 9.0-11.5 g/dL. Data are presented for those participants following the original criteria ("Original") and those following the amended ("Amended") criteria. Intent-to-Treat (ITT): The ITT population consisted of all randomized participants who received at least one dose of study drug, had a Baseline and at least one corresponding on-treatment assessment. Only participants who were available at the indicated time point were analyzed. | |
| End point type | Primary |
| End point timeframe: Week 24 | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There was no statistical information to present for this outcome measure.

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|--------------------------------------|------------------------|---------------------|-----------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 123 | 43 | 33 | 36 |
| Units: grams per deciliter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Original n=45,15,19,13 | 10.2 (± 0.906) | 10.64 (± 0.664) | 10.03 (± 0.522) | 10.66 (± 0.62) |

| | | | | |
|-----------------------|-----------------|-----------------|-----------------|-----------------|
| Amended n=61,21,11,17 | 10.96 (± 1.044) | 11.05 (± 1.144) | 10.42 (± 0.827) | 10.86 (± 1.182) |
|-----------------------|-----------------|-----------------|-----------------|-----------------|

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with hemoglobin (Hgb) in the target range at Week 24

| | |
|--|---|
| End point title | Number of participants with hemoglobin (Hgb) in the target range at Week 24 |
| End point description: Target range is defined as: Original Hgb Criteria of 9.0 to 10.5 gram/deciliter (g/dL), and Amended Hgb Criteria of 10.0 to 11.5 g/dL. Sites in the USA used 9.0 to 10.5 g/dL. ITT population. Only participants who were available at the indicated time point were analyzed. | |
| End point type | Secondary |
| End point timeframe: Week 24 | |

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|-----------------------------|------------------------|---------------------|-----------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 106 | 36 | 30 | 30 |
| Units: participants | | | | |
| number (not applicable) | 78 | 20 | 22 | 19 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants reaching pre-defined Hgb stopping criteria

| | |
|---|---|
| End point title | Number of participants reaching pre-defined Hgb stopping criteria |
| End point description: The Hgb stopping criteria was a value of <7.5 mg/dL obtained on-site via a validated point-of-care Hgb measurement device, which necessitated permanent discontinuation of the study medication. None of the participants met the stopping criteria therefore there is no data to present for this outcome measure. ITT population. | |
| End point type | Secondary |
| End point timeframe: Over a period of 24 Weeks | |

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|-----------------------------|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 136 | 44 | 36 | 36 |
| Units: Participants | | | | |
| number (not applicable) | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline in hepcidin concentration at Week 24

| | |
|-----------------|---|
| End point title | Percent change from Baseline in hepcidin concentration at Week 24 |
|-----------------|---|

End point description:

Baseline is the last pre-dose hepcidin value. Percent change was calculated as 100 multiplied by (exponential of mean change on log scale minus 1). Change was calculated by subtracting the Baseline value from the Week 24 value. Intent-to-Treat (ITT) population consisted all randomized participants who received at least one dose of study drug, had a Baseline and at least one corresponding on-treatment assessment. Only participants with available hepcidin values at Baseline and Week 24 were analyzed.

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

End point timeframe:

Baseline and Week 24

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|--|---------------------------|------------------------|--------------------------|-------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 106 | 35 | 30 | 29 |
| Units: percent change in Hepcidin | | | | |
| geometric mean (confidence interval 95%) | -19.27 (-28.1 to -9.36) | 6.67 (-13.62 to 31.72) | -9.87 (-28.59 to 13.76) | -17.12 (-33.22 to 2.86) |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean maximum observed change from Baseline in serum erythropoietin (EPO)

| | |
|-----------------|--|
| End point title | Mean maximum observed change from Baseline in serum erythropoietin (EPO) |
|-----------------|--|

End point description:

Baseline is the last pre-dose EPO value. Change from Baseline in EPO at each visit was calculated and maximum change from baseline was recorded. Change from Baseline is the post-dose EPO value minus the Baseline EPO value. ITT population. Only participants having a Baseline EPO measurement and at least one post-baseline EPO measurement were analyzed

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

End point timeframe:

Baseline to Week 24

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|--------------------------------------|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 123 | 42 | 33 | 36 |
| Units: International Units per liter | | | | |
| arithmetic mean (standard deviation) | 7.27 (± 12.744) | 27.05 (± 94.999) | 3.69 (± 20.554) | 25.85 (± 38.89) |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed percent change from Baseline in Vascular Endothelial Growth Factor (VEGF)

| | |
|-----------------|--|
| End point title | Maximum observed percent change from Baseline in Vascular Endothelial Growth Factor (VEGF) |
|-----------------|--|

End point description:

Baseline is the last pre-dose VEGF value. Change from Baseline in VEGF was calculated for each visit by subtracting the Baseline value from each post-dose value. Percent change from Baseline was calculated for each visit as 100 multiplied by (exponential of mean change on log scale minus 1). The maximum observed percent change from Baseline was recorded.

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

End point timeframe:

Baseline and up to Week 24

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|---|---------------------------|------------------------|--------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 123 ^[2] | 42 ^[3] | 33 ^[4] | 3 ^[5] |
| Units: percent change in VEGF concentration | | | | |
| geometric mean (confidence interval 95%) | 76.36 (59.46 to 95.06) | 26.84 (1.73 to 58.15) | 49.99 (28.28 to 75.39) | 40.85 (19.14 to 66.52) |

Notes:

[2] - ITT population. Only pars with data available at Baseline and a maximum observed change analyzed

[3] - ITT population. Only pars with data available at Baseline and a maximum observed change analyzed

[4] - ITT population. Only pars with data available at Baseline and a maximum observed change analyzed

[5] - ITT population. Only pars with data available at Baseline and a maximum observed change analyzed

Statistical analyses

Secondary: Percentage of time within, below, and above hemoglobin (Hgb) target range, between Weeks 12 and 24

| | |
|-----------------|--|
| End point title | Percentage of time within, below, and above hemoglobin (Hgb) target range, between Weeks 12 and 24 |
|-----------------|--|

End point description:

The number of days a participant's Hgb was within target range was calculated by estimating (using linear interpolation) the number of days within target range between two scheduled Hgb visits. Percentage of time within range for a participant was calculated by dividing the total number of days that Hgb was within range during Weeks 12 to 24 by the total number of days the participant remained on treatment during Weeks 12 to 24. Similarly, percent of time above and below Hgb target range was calculated. Target range was defined as: Original Hgb Criteria of 9.0 to 10.5 g/dL, and Amended Hgb Criteria of 10.0 to 11.5 g/dL. Sites in the USA used 9.0 to 10.5 g/dL. ITT population. Only participants with data available at specific time points were analyzed.

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

End point timeframe:

Weeks 12 to 24

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|--|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 112 | 38 | 30 | 32 |
| Units: percentage of days | | | | |
| arithmetic mean (standard deviation) | | | | |
| Percentage of time within target range | 68.99 (± 34.612) | 51.01 (± 41.403) | 75.06 (± 32.485) | 61.29 (± 43.352) |
| Percentage of time above target range | 22.84 (± 33.825) | 45.1 (± 42.579) | 17.96 (± 28.809) | 31.1 (± 41.683) |
| Percentage of time below target range | 8.17 (± 20.301) | 3.89 (± 16.175) | 6.98 (± 21.118) | 7.61 (± 25.113) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ferritin concentration at Week 24

| | |
|-----------------|---|
| End point title | Change from Baseline in ferritin concentration at Week 24 |
|-----------------|---|

End point description:

Baseline is the last pre-dose ferritin value. Change was calculated by subtracting the Baseline value from the Week 24 value. ITT population. Only participants with data available at specific time point were analyzed. ITT population. Only participants with data available at specific time point were analyzed.

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

End point timeframe:

Baseline and Week 24

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|--------------------------------------|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 108 | 36 | 30 | 30 |
| Units: micrograms per liter | | | | |
| arithmetic mean (standard deviation) | -30.8 (± 110.5) | -2.4 (± 77.06) | -63.4 (± 141.93) | -20.4 (± 63.38) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in transferrin concentration at Week 24

| | |
|---|--|
| End point title | Change from Baseline in transferrin concentration at Week 24 |
| End point description: Baseline is the last pre-dose transferrin value. Change from Baseline in transferrin was calculated by subtracting the Baseline value from the Week 24 value. ITT population. Only participants with data available at specific time point were analyzed. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 24 | |

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|--------------------------------------|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 107 | 36 | 30 | 30 |
| Units: grams per liter | | | | |
| arithmetic mean (standard deviation) | 0.077 (± 0.3577) | -0.008 (± 0.2694) | 0.171 (± 0.4124) | 0.018 (± 0.2395) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline in transferrin saturation at Week 24

| | |
|--|---|
| End point title | Percent change from Baseline in transferrin saturation at Week 24 |
| End point description: Transferrin saturation is measured as a percentage; it is a ratio of serum iron and total iron-binding capacity. Baseline is the last pre-dose transferrin saturation value. Percent change was calculated as 100 multiplied by (exponential of mean change on log scale minus 1). Change was calculated by subtracting the Baseline value from the post-dose value. ITT population. Only participants with data available at specific time point were analyzed. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 24 | |

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|--|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 106 | 35 | 30 | 30 |
| Units: percent change | | | | |
| geometric mean (confidence interval 95%) | -1.1 (-8 to 6.4) | 12.3 (2.2 to 23.3) | -15.7 (-26.8 to -3) | 11.4 (-14.7 to 45.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in total iron at Week 24

| | |
|---|---|
| End point title | Change from Baseline in total iron at Week 24 |
| End point description: Baseline is the last pre-dose total iron value. Change from Baseline was calculated by subtracting the Baseline value from the Week 24 value. ITT population. Only participants with available total iron values at Baseline and Week 24 were analyzed. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 24 | |

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|--------------------------------------|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 107 | 36 | 30 | 30 |
| Units: micromoles per liter | | | | |
| arithmetic mean (standard deviation) | 1 (± 5.01) | 2.5 (± 5.98) | -1.8 (± 5.54) | 0.7 (± 8.36) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in total iron binding capacity (TIBC) at Week 24

| | |
|--|---|
| End point title | Change from Baseline in total iron binding capacity (TIBC) at Week 24 |
| End point description: TIBC measures the blood's capacity to bind iron with transferrin. Baseline is the last pre-dose TIBC value. Change from Baseline in TIBC was calculated by subtracting the Baseline value from the Week 24 value. ITT population. Only participants with data available at specific timepoint were analyzed. | |
| End point type | Secondary |

End point timeframe:
Baseline and Week 24

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|--------------------------------------|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 106 | 35 | 30 | 30 |
| Units: micromoles per liter | | | | |
| arithmetic mean (standard deviation) | 3.2 (± 6.46) | 0.1 (± 5.17) | 3 (± 9.44) | -1 (± 6.69) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in reticulocyte hemoglobin (CHr) at Week 24

| | |
|-----------------|--|
| End point title | Change from Baseline in reticulocyte hemoglobin (CHr) at Week 24 |
|-----------------|--|

End point description:

Reticulocytes are slightly immature red blood cells. Reticulocyte Hgb content is used to differentiate iron deficiency from other causes of anemia. Baseline is the last pre-dose CHr value. Change from Baseline in reticulocyte Hgb was calculated by subtracting the Baseline value from the post-dose value. ITT population. Only participants with data available at specific timepoint were analyzed.

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

End point timeframe:

Baseline and Week 24

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|--------------------------------------|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 108 | 35 | 30 | 30 |
| Units: picogram | | | | |
| arithmetic mean (standard deviation) | -0.19 (± 1.109) | -0.33 (± 1.085) | -0.32 (± 0.864) | -0.19 (± 1.546) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematocrit at Week 24

| | |
|-----------------|---|
| End point title | Change from Baseline in hematocrit at Week 24 |
|-----------------|---|

End point description:

Baseline is the last pre-dose hematocrit value. Change from Baseline was calculated by subtracting the Baseline value from the Week 24 value. ITT population. Only participants with data available at specific timepoint were analyzed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 24 | |

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|---|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 111 | 36 | 30 | 30 |
| Units: percentage change in Fraction of 1 | | | | |
| arithmetic mean (standard deviation) | 2.64 (± 3.389) | 3.13 (± 3.245) | -0.66 (± 3.074) | 2.09 (± 3.243) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in red blood cell count at Week 24

| | |
|---|---|
| End point title | Change from Baseline in red blood cell count at Week 24 |
| End point description: | |
| Baseline is the last pre-dose red blood cell count. Change from Baseline in red blood cell count was calculated by subtracting the Baseline count from the post-dose count. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 24 | |

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|---|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 111 ^[6] | 36 ^[7] | 30 ^[8] | 30 ^[9] |
| Units: 10 ¹² cells per liter | | | | |
| arithmetic mean (standard deviation) | 0.28 (± 0.377) | 0.34 (± 0.365) | -0.08 (± 0.312) | 0.22 (± 0.318) |

Notes:

[6] - ITT population. Only participants with data available at specific time point were analyzed.

[7] - ITT population. Only participants with data available at specific time point were analyzed.

[8] - ITT population. Only participants with data available at specific time point were analyzed.

[9] - ITT population. Only participants with data available at specific time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in reticulocyte cell count at Week 24

| | |
|-----------------|--|
| End point title | Change from Baseline in reticulocyte cell count at Week 24 |
|-----------------|--|

End point description:

Reticulocyte count is a blood test that measures the percentage of reticulocytes in the blood. Reticulocytes are slightly immature red blood cells. Baseline is the last pre-dose red reticulocyte count. Change from Baseline in reticulocyte cell count was calculated by subtracting the Baseline count from the Week 24 count. ITT population. Only participants with data available at specific timepoint were analyzed.

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

End point timeframe:

Baseline and Week 24

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|--------------------------------------|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 111 | 36 | 30 | 31 |
| Units: percentage of reticulocytes | | | | |
| arithmetic mean (standard deviation) | -0.02 (± 0.551) | -0.12 (± 0.648) | 0.27 (± 0.892) | -0.09 (± 0.755) |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of GSK1278863 and relevant metabolites as a population pharmacokinetic endpoint

| | |
|-----------------|---|
| End point title | Concentration of GSK1278863 and relevant metabolites as a population pharmacokinetic endpoint ^[10] |
|-----------------|---|

End point description:

Blood samples were collected for individual plasma GSK1278863 and metabolite (GSK2391220, GSK2487818, GSK2506102, GSK2531398, GSK2531401, and GSK2531403) concentration measurement on Day 1 (pre-dose), Wk 4 (6-12 hour, 7-13 hour, 8-14 hour, 9-15 hour post-dose), and Wk 20 (pre-dose, 1 hour, 2 hour, 3 hour post-dose). Participants available in each arm at the specified time points have been presented. Pharmacokinetics (PK) population: All participants from whom a PK sample was obtained and analyzed. This population did not include participants from the control groups.

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

End point timeframe:

Day 1 (pre-dose), Week (Wk) 4 (6-12 hour, 7-13 hour, 8-14 hour, 9-15 hour post-dose), and Wk 20 (pre-dose, 1 hour, 2 hour, 3 hour post-dose)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Control groups were not measured for this endpoint, so there are not statistics to present.

| End point values | rhEPO-Naive GSK1278863 | rhEPO-User GSK1278863 | | |
|--|---------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 35 | | |
| Units: nanograms per milliliter | | | | |
| arithmetic mean (standard deviation) | | | | |
| GSK1278863, Day 1, Pre-Dose, n=128, 35 | 0 (± 0) | 0 (± 0) | | |

| | | | | |
|--|----------------|----------------|--|--|
| GSK1278863, Wk 4, 6-12 hour Post-Dose, n=116, 31 | 2 (± 5.18) | 1.1 (± 1.69) | | |
| GSK1278863, Wk 4, 7-13 hour Post-Dose, n=117, 31 | 2.3 (± 7.06) | 0.8 (± 1.22) | | |
| GSK1278863, Wk 4, 8-14 hour Post-Dose, n=116, 31 | 1.6 (± 4.93) | 1.6 (± 5.49) | | |
| GSK1278863, Wk 4, 9-15 hour Post-Dose, n=116, 31 | 1.4 (± 4.52) | 1.6 (± 4.6) | | |
| GSK1278863, Wk 20, Pre-Dose, n=111, 29 | 0.6 (± 3.07) | 0.3 (± 0.92) | | |
| GSK1278863, Wk 20, 1 hour Post-Dose, n=110, 28 | 22.8 (± 35.93) | 19.8 (± 19.66) | | |
| GSK1278863, Wk 20, 2 hour Post-Dose, n=109, 29 | 17 (± 28.57) | 19.4 (± 21.92) | | |
| GSK1278863, Wk 20, 3 hour Post-Dose, n=109, 29 | 11.6 (± 19.56) | 13.9 (± 19.12) | | |
| GSK2391220, Day 1, Pre-Dose, n=128, 35 | 0 (± 0) | 0 (± 0) | | |
| GSK2391220, Wk 4, 6-12 hour Post-Dose, n=116, 31 | 3.2 (± 5.21) | 3.7 (± 2.89) | | |
| GSK2391220, Wk 4, 7-13 hour Post-Dose, n=117, 31 | 3.1 (± 5.67) | 3.2 (± 2.43) | | |
| GSK2391220, Wk 4, 8-14 hour Post-Dose, n=116, 31 | 2.8 (± 5.01) | 2.9 (± 2.54) | | |
| GSK2391220, Wk 4, 9-15 hour Post-Dose, n=116, 31 | 2.6 (± 4.89) | 3.1 (± 2.76) | | |
| GSK2391220, Wk 20, Pre-Dose, n=111, 29 | 1 (± 2.06) | 0.8 (± 0.98) | | |
| GSK2391220, Wk 20, 1 hour Post-Dose, n=110, 28 | 2.1 (± 3.52) | 1.6 (± 1.39) | | |
| GSK2391220, Wk 20, 2 hour Post-Dose, n=109, 29 | 3.8 (± 5.08) | 3.7 (± 2.98) | | |
| GSK2391220, Wk 20, 3 hour Post-Dose, n=109, 29 | 4.5 (± 5.43) | 4.7 (± 3.53) | | |
| GSK2487818, Day 1, Pre-Dose, n=128, 35 | 0 (± 0) | 0 (± 0) | | |
| GSK2487818, Wk 4, 6-12 hour Post-Dose, n=116, 31 | 1.2 (± 3.87) | 1 (± 0.96) | | |
| GSK2487818, Wk 4, 7-13 hour Post-Dose, n=116, 31 | 1.1 (± 4.11) | 0.7 (± 0.7) | | |
| GSK2487818, Wk 4, 8-14 hour Post-Dose, n=116, 31 | 1 (± 4.48) | 0.6 (± 0.66) | | |
| GSK2487818, Wk 4, 9-15 hour Post-Dose, n=116, 31 | 0.9 (± 4.09) | 0.8 (± 1.16) | | |
| GSK2487818, Wk 20, Pre-Dose, n=111, 29 | 0.2 (± 0.56) | 0.1 (± 0.31) | | |
| GSK2487818, Wk 20, 1 hour Post-Dose, n=110, 28 | 1.4 (± 3.07) | 1 (± 1.09) | | |
| GSK2487818, Wk 20, 2 hour Post-Dose, n=109, 29 | 2.8 (± 4.28) | 2.7 (± 2.21) | | |
| GSK2487818, Wk 20, 3 hour Post-Dose, n=109, 29 | 3.1 (± 4.07) | 3.1 (± 2.56) | | |
| GSK2506102, Day 1, Pre-Dose, n=128, 35 | 0 (± 0) | 0 (± 0) | | |
| GSK2506102, Wk 4, 6-12 hour Post-Dose, n=116, 31 | 1 (± 1.3) | 1.2 (± 0.65) | | |
| GSK2506102, Wk 4, 7-13 hour Post-Dose, n=117, 31 | 1 (± 1.51) | 1.1 (± 0.61) | | |
| GSK2506102, Wk 4, 8-14 hour Post-Dose, n=116, 31 | 0.9 (± 1.19) | 1 (± 0.61) | | |
| GSK2506102, Wk 4, 9-15 hour Post-Dose, n=116, 31 | 0.9 (± 1.29) | 1.1 (± 0.69) | | |

| | | | | |
|--|--------------|--------------|--|--|
| GSK2506102, Wk 20, Pre-Dose, n=111, 29 | 0.4 (± 0.73) | 0.4 (± 0.42) | | |
| GSK2506102, Wk 20, 1 hour Post-Dose, n=110, 28 | 0.6 (± 0.88) | 0.5 (± 0.4) | | |
| GSK2506102, Wk 20, 2 hour Post-Dose, n=109, 29 | 0.9 (± 1.15) | 1 (± 0.71) | | |
| GSK2506102, Wk 20, 3 hour Post-Dose, n=109, 29 | 1.1 (± 1.25) | 1.2 (± 0.88) | | |
| GSK2531398, Day 1, Pre-Dose, n=128, 35 | 0 (± 0.01) | 0 (± 0) | | |
| GSK2531398, Wk 4, 6-12 hour Post-Dose, n=116, 31 | 1.3 (± 2.06) | 1.4 (± 1.08) | | |
| GSK2531398, Wk 4, 7-13 hour Post-Dose, n=117, 31 | 1.2 (± 2.5) | 1.2 (± 0.99) | | |
| GSK2531398, Wk 4, 8-14 hour Post-Dose, n=116, 31 | 1.1 (± 2.01) | 1.1 (± 0.93) | | |
| GSK2531398, Wk 4, 9-15 hour Post-Dose, n=116, 31 | 1 (± 2.1) | 1.2 (± 1.12) | | |
| GSK2531398, Wk 20, Pre-Dose, n=111, 29 | 0.3 (± 0.87) | 0.3 (± 0.38) | | |
| GSK2531398, Wk 20, 1 hour Post-Dose, n=110, 28 | 0.8 (± 1.53) | 0.6 (± 0.54) | | |
| GSK2531398, Wk 20, 2 hour Post-Dose, n=109, 29 | 1.6 (± 2.31) | 1.5 (± 1.22) | | |
| GSK2531398, Wk 20, 3 hour Post-Dose, n=109, 29 | 2 (± 2.42) | 2 (± 1.57) | | |
| GSK2531401, Day 1, Pre-Dose, n=128, 35 | 0 (± 0) | 0 (± 0) | | |
| GSK2531401, Wk 4, 6-12 hour Post-Dose, n=116, 31 | 2.8 (± 4) | 4.3 (± 2.55) | | |
| GSK2531401, Wk 4, 7-13 hour Post-Dose, n=117, 31 | 2.7 (± 3.58) | 4 (± 2.29) | | |
| GSK2531401, Wk 4, 8-14 hour Post-Dose, n=116, 31 | 2.7 (± 3.74) | 3.8 (± 2.31) | | |
| GSK2531401, Wk 4, 9-15 hour Post-Dose, n=116, 31 | 2.5 (± 3.53) | 3.8 (± 2.29) | | |
| GSK2531401, Wk 20, Pre-Dose, n=111, 29 | 1.3 (± 2.41) | 1.4 (± 1.38) | | |
| GSK2531401, Wk 20, 1 hour Post-Dose, n=110, 28 | 1.6 (± 2.65) | 1.6 (± 1.29) | | |
| GSK2531401, Wk 20, 2 hour Post-Dose, n=109, 29 | 2.3 (± 3.14) | 2.5 (± 1.85) | | |
| GSK2531401, Wk 20, 3 hour Post-Dose, n=109, 29 | 2.8 (± 3.5) | 3.2 (± 2.22) | | |
| GSK2531403, Day 1, Pre-Dose, n=128, 35 | 0 (± 0) | 0 (± 0) | | |
| GSK2531403, Wk 4, 6-12 hour Post-Dose, n=116, 31 | 3.7 (± 5.43) | 4.5 (± 3.14) | | |
| GSK2531403, Wk 4, 7-13 hour Post-Dose, n=117, 31 | 3.5 (± 5.27) | 3.9 (± 2.56) | | |
| GSK2531403, Wk 4, 8-14 hour Post-Dose, n=116, 31 | 3.4 (± 5.68) | 3.7 (± 2.72) | | |
| GSK2531403, Wk 4, 9-15 hour Post-Dose, n=116, 31 | 3.2 (± 5.42) | 3.8 (± 3.01) | | |
| GSK2531403, Wk 20, Pre-Dose, n=111, 29 | 1.4 (± 2.65) | 1.2 (± 1.25) | | |
| GSK2531403, Wk 20, 1 hour Post-Dose, n=110, 28 | 2.3 (± 3.69) | 1.9 (± 1.38) | | |
| GSK2531403, Wk 20, 2 hour Post-Dose, n=109, 29 | 3.9 (± 5.03) | 3.8 (± 2.95) | | |
| GSK2531403, Wk 20, 3 hour Post-Dose, n=109, 29 | 4.7 (± 5.43) | 4.9 (± 3.75) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of dose adjustments up to 24 Weeks

| | |
|-----------------|--|
| End point title | Mean number of dose adjustments up to 24 Weeks ^[11] |
|-----------------|--|

End point description:

After 4 Weeks, the need to adjust the dose of GSK1278863 was evaluated at every scheduled visit, to maintain hemoglobin within the target range. Target range was defined as: Original Hgb Criteria of 9.0 to 10.5 g/dL, and Amended Hgb Criteria of 10.0 to 11.5 g/dL. Sites in the USA used 9.0 to 10.5 g/dL. Dose adjustments were assigned automatically via the interactive voice/web response system. Intent-to-Treat population. Only those participants with at least one dose adjustment of GSK1278863 were analyzed.

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

End point timeframe:

From Week 4 up to 24 Weeks

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Control groups were not measured for this endpoint, so there are not statistics to present.

| End point values | rhEPO-Naive GSK1278863 | rhEPO-User GSK1278863 | | |
|--------------------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 102 | 26 | | |
| Units: number of adjustments | | | | |
| arithmetic mean (standard deviation) | 1.8 (± 0.82) | 1.7 (± 0.72) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with dose adjustments up to 24 Weeks, as a measure of dose adjustment frequency

| | |
|-----------------|--|
| End point title | Number of participants with dose adjustments up to 24 Weeks, as a measure of dose adjustment frequency ^[12] |
|-----------------|--|

End point description:

After 4 Weeks, the need to adjust the dose of GSK1278863 was evaluated at every scheduled visit, to maintain hemoglobin within the target range. Target range was defined as: Original Hgb Criteria of 9.0 to 10.5 g/dL, and Amended Hgb Criteria of 10.0 to 11.5 g/dL. Sites in the USA used 9.0 to 10.5 g/dL. Dose adjustments were assigned automatically via the interactive voice/web response system. Frequency is presented as the number of participants with dose adjustment(s) once, twice, thrice, four times, or five times. Intent-to-Treat population. Only those participants with at least one dose adjustment of GSK1278863 were analyzed.

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

End point timeframe:

From week 4 up to 24 weeks

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Control groups were not measured for this endpoint, so there are not statistics to present.

| End point values | rhEPO-Naive GSK1278863 | rhEPO-User GSK1278863 | | |
|-----------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 102 | 26 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Once | 39 | 11 | | |
| Twice | 50 | 11 | | |
| Thrice | 8 | 4 | | |
| Four times | 4 | 0 | | |
| Five times or more | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Timing of dose adjustments at Weeks 4, 8, 12, 16, and 20

| | |
|-----------------|--|
| End point title | Timing of dose adjustments at Weeks 4, 8, 12, 16, and 20 ^[13] |
|-----------------|--|

End point description:

After 4 Weeks, the need to adjust the dose of GSK1278863 was evaluated at every scheduled visit, to maintain hemoglobin within the target range. Target range was defined as: Original Hgb Criteria of 9.0 to 10.5 g/dL, and Amended Hgb Criteria of 10.0 to 11.5 g/dL. Sites in the USA used 9.0 to 10.5 g/dL. Dose adjustments were assigned automatically via the interactive voice/web response system. The number of participants with an adjustment are presented at the timings at which adjustments were done. ITT population. Only those participants with at least one dose adjustment of GSK1278863 were analyzed.

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

End point timeframe:

From Week 4 up to Week 20

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Control groups were not measured for this endpoint, so there are not statistics to present.

| End point values | rhEPO-Naive GSK1278863 | rhEPO-User GSK1278863 | | |
|-----------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 102 | 26 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Week 4 | 78 | 21 | | |
| Week 8 | 24 | 6 | | |
| Week 12 | 30 | 7 | | |
| Week 16 | 30 | 6 | | |

| | | | | |
|---------|----|---|--|--|
| Week 20 | 22 | 5 | | |
|---------|----|---|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Mean total cumulative dose of GSK1278863 up to 24 Weeks

| | |
|-----------------|---|
| End point title | Mean total cumulative dose of GSK1278863 up to 24 Weeks ^[14] |
|-----------------|---|

End point description:

The starting dose was kept constant for the first 4 Weeks after randomization. Later, the need to adjust the dose of GSK1288863 was evaluated at every scheduled visit according to a pre-specified algorithm, to achieve and maintain hemoglobin within the specified target range. Target range was defined as: Original Hgb Criteria of 9.0 to 10.5 g/dL, and Amended Hgb Criteria of 10.0 to 11.5 g/dL. Sites in the USA used 9.0 to 10.5 g/dL. ITT population

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

End point timeframe:

Up to 24 Weeks

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Control groups were not measured for this endpoint, so there are not statistics to present.

| End point values | rhEPO-Naive GSK1278863 | rhEPO-User GSK1278863 | | |
|--------------------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 33 | | |
| Units: milligrams | | | | |
| arithmetic mean (standard deviation) | 249.75 (± 186.921) | 320.42 (± 214.865) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean final dose of GSK1278863 up to 24 Weeks

| | |
|-----------------|--|
| End point title | Mean final dose of GSK1278863 up to 24 Weeks ^[15] |
|-----------------|--|

End point description:

The starting dose was kept constant for the first 4 Weeks after randomization. Later, the need to adjust the dose of GSK1288863 was evaluated at every scheduled visit according to a pre-specified algorithm, to achieve and maintain hemoglobin within the specified target range. Target range was defined as: Original Hgb Criteria of 9.0 to 10.5 g/dL, and Amended Hgb Criteria of 10.0 to 11.5 g/dL. Sites in the USA used 9.0 to 10.5 g/dL. ITT population.

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

End point timeframe:

Up to 24 Weeks

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Control groups were not measured for this endpoint, so there are not statistics to present.

| End point values | rhEPO-Naive GSK1278863 | rhEPO-User GSK1278863 | | |
|--------------------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 33 | | |
| Units: milligrams per day | | | | |
| arithmetic mean (standard deviation) | 1.75 (± 1.809) | 1.86 (± 1.692) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hemoglobin (Hgb) excursions

| | |
|---|---------------------------------------|
| End point title | Number of hemoglobin (Hgb) excursions |
| End point description: A Hgb excursion is a series of decreasing or increasing Hgb values differing by ≥ 1.5 grams per deciliter. Hgb cycle is calculated as two consecutive Hgb excursions in different directions. Completers Population: ITT participants who fully completed study without prematurely discontinuing study drug. Only participants with Hgb excursions were analyzed. | |
| End point type | Secondary |
| End point timeframe: Up to 24 Weeks. | |

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|-----------------------------|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 10 | 4 | 8 |
| Units: number of excursions | | | | |
| number (not applicable) | 26 | 10 | 4 | 9 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hemoglobin (Hgb) cycles up to 24 Weeks

| | |
|--|--|
| End point title | Number of hemoglobin (Hgb) cycles up to 24 Weeks |
| End point description: A Hgb cycle is calculated as two consecutive Hgb excursions in different directions. A Hgb excursion is a series of decreasing or increasing Hgb values differing by ≥ 1.5 grams per deciliter. Completers population. Only participants with Hgb cycles were analyzed. | |
| End point type | Secondary |

End point timeframe:

Up to 24 Weeks

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|-----------------------------|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 0 ^[16] | 0 ^[17] | 0 ^[18] |
| Units: number of Hgb cycles | | | | |
| number (not applicable) | 3 | | | |

Notes:

[16] - There were no subjects for analysis

[17] - There were no subjects for analysis

[18] - There were no subjects for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Number of dose cycles up to 24 Weeks

| | |
|-----------------|--|
| End point title | Number of dose cycles up to 24 Weeks ^[19] |
|-----------------|--|

End point description:

A dose cycle is a series of three directional dose changes (that is, increase, decrease, increase; or decrease, increase, decrease). Completers population. Only participants with dose cycles were analyzed. Completers population.

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

End point timeframe:

Up to 24 weeks

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Control groups were not measured for this endpoint, so there are not statistics to present.

| End point values | rhEPO-Naive GSK1278863 | rhEPO-User GSK1278863 | | |
|-----------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1 | 0 ^[20] | | |
| Units: number | | | | |
| number (not applicable) | 1 | | | |

Notes:

[20] - There were no subjects for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with at least one hemoglobin (Hgb) excursion up to 24 Weeks.

| | |
|-----------------|---|
| End point title | Number of participants with at least one hemoglobin (Hgb) excursion up to 24 Weeks. |
|-----------------|---|

End point description:

A Hgb excursion is a series of decreasing or increasing Hgb values differing by ≥ 1.5 grams per deciliter. Completers population.

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

End point timeframe:

Up to 24 weeks

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|-----------------------------|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 106 | 36 | 30 | 30 |
| Units: participants | | | | |
| number (not applicable) | 23 | 10 | 4 | 8 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with at least one hemoglobin (Hgb) cycle up to 24 Weeks

| | |
|-----------------|--|
| End point title | Number of participants with at least one hemoglobin (Hgb) cycle up to 24 Weeks |
|-----------------|--|

End point description:

A Hgb excursion is a series of decreasing or increasing Hgb values differing by ≥ 1.5 grams per deciliter. A Hgb cycle is two consecutive Hgb excursions in different directions. Completers population.

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

End point timeframe:

Up to 24 weeks

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|-----------------------------|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 106 | 36 | 30 | 30 |
| Units: participants | | | | |
| number (not applicable) | 3 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with at least one dose cycle up to 24 Weeks

| | |
|-----------------|--|
| End point title | Number of participants with at least one dose cycle up to 24 Weeks ^[21] |
|-----------------|--|

End point description:

A dose cycle is a series of three directional dose changes (that is, increase, decrease, increase; or decrease, increase, decrease). Completers population. Only participants in the GSK1278863 arms were analyzed.

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

End point timeframe:

Up to 24 weeks

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Control groups were not measured for this endpoint, so there are not statistics to present.

| End point values | rhEPO-Naive GSK1278863 | rhEPO-User GSK1278863 | | |
|-----------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106 | 30 | | |
| Units: participants | | | | |
| number (not applicable) | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants receiving additional therapies of blood transfusions, intravenous (IV) iron or rhEPO at any time post-Baseline

| | |
|-----------------|---|
| End point title | Number of participants receiving additional therapies of blood transfusions, intravenous (IV) iron or rhEPO at any time post-Baseline |
|-----------------|---|

End point description:

Participants receiving additional therapies of blood transfusions, intravenous (IV) iron or rhEPO any time Post Baseline were analyzed. RhEPO was not applicable for the control arms since it was a planned therapy in those arms, hence presented as NA. (EudraCT only: A value of 99999 is used where no data is available or NA.) ITT population.

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

End point timeframe:

From Day 1 up to Week 28

| End point values | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 | rhEPO-User Control |
|-----------------------------|---------------------------|------------------------|--------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 123 | 43 | 33 | 36 |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Blood Transfusions | 3 | 1 | 1 | 0 |
| IV Iron | 20 | 3 | 3 | 4 |
| Inadvertent rhEPO use | 4 | 99999 | 9 | 99999 |
| Rescue rhEPO | 1 | 99999 | 0 | 99999 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Weeks dose withheld because hemoglobin (Hgb) exceeded the upper limit

| | |
|-----------------|---|
| End point title | Number of Weeks dose withheld because hemoglobin (Hgb) exceeded the upper limit ^[22] |
|-----------------|---|

End point description:

Number of Weeks dose was withheld because hemoglobin exceed the upper limit is presented as the number of participants with withheld dose during the time periods categorized by Weeks. ITT population.

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

End point timeframe:

From Week 4 up to Week 24

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Control groups were not measured for this endpoint, so there are not statistics to present.

| End point values | rhEPO-Naive GSK1278863 | rhEPO-User GSK1278863 | | |
|-----------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 33 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| 0 Weeks | 102 | 30 | | |
| >0-4 Weeks | 4 | 2 | | |
| >4-8 Weeks | 8 | 0 | | |
| >8-12 Weeks | 8 | 0 | | |
| >12 Weeks | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) and serious adverse events (SAEs) were collected from the start of study treatment until the follow-up contact (up to 28 weeks).

Adverse event reporting additional description:

AEs and SAEs were collected from participants of the safety population, comprised of all participants who received at least one dose of study drug.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | rhEPO-Naive GSK1278863 |
|-----------------------|------------------------|

Reporting group description:

RhEPO-naive participants were randomly assigned to receive GSK1278863 QD for 24 weeks. Participants were blinded to the dose-level they received throughout the study. At Week 24, participants stopped taking GSK1278863, and returned for the follow-up visit at Week 28.

| | |
|-----------------------|---------------------|
| Reporting group title | rhEPO-Naive Control |
|-----------------------|---------------------|

Reporting group description:

RhEPO-naive participants were randomly assigned to receive open-label rhEPO (epoetins or their biosimilars, or darbepoetin) as necessary per standard of care, based on the Investigator's clinical judgment, for 24 weeks. At Week 24, participants stopped taking rhEPO (if applicable) and remained off rhEPO or other Erythropoiesis Stimulating Agents (ESA) until at least the follow-up visit at Week 28.

| | |
|-----------------------|-----------------------|
| Reporting group title | rhEPO-User GSK1278863 |
|-----------------------|-----------------------|

Reporting group description:

RhEPO users were randomly assigned to receive GSK1278863 QD for 24 weeks. Participants were blinded to the dose-level they received throughout the study. At Week 24, participants stopped taking GSK1278863 and did not re-start rhEPO or other ESAs until after the follow-up visit at Week 28 (except in cases where there was a compelling clinical reason [based on Investigator's opinion] to start rhEPO therapy).

| | |
|-----------------------|--------------------|
| Reporting group title | rhEPO-User Control |
|-----------------------|--------------------|

Reporting group description:

RhEPO users were randomly assigned to receive rhEPO (epoetins or their biosimilars, or darbepoetin) as necessary per standard of care, based on the Investigator clinical judgment, for 24 weeks. Participants were allowed to continue rhEPO therapy between Week 24 and 28.

| Serious adverse events | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 |
|---|---------------------------|---------------------|--------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 20 / 134 (14.93%) | 6 / 45 (13.33%) | 6 / 36 (16.67%) |
| number of deaths (all causes) | 2 | 0 | 2 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gallbladder adenocarcinoma | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 134 (0.00%) | 0 / 45 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| HEPATIC CANCER | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 | | | |
| DIABETIC VASCULAR DISORDER | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 0 / 45 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ORTHOSTATIC HYPOTENSION | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| HYPERTENSION | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| General disorders and administration site conditions | | | |
| CHEST PAIN | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 0 / 45 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| Psychiatric disorders | | | |
| CONFUSIONAL STATE | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| MENTAL STATUS CHANGES | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| Investigations | | | |
| FALSE POSITIVE INVESTIGATION RESULT | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| Injury, poisoning and procedural complications | | | |
| Shunt malfunction | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| Cardiac disorders | | | |

| | | | |
|---|-----------------|----------------|----------------|
| ANGINA PECTORIS | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 COMPLETE | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| CARDIAC FAILURE CONGESTIVE | | | |
| subjects affected / exposed | 2 / 134 (1.49%) | 1 / 45 (2.22%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| MYOCARDIAL ISCHAEMIA | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 1 / 45 (2.22%) | 0 / 36 (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 myocardial infarction | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| Nervous system disorders | | | |
| CARPAL TUNNEL SYNDROME | | | |
| alternative dictionary used: MedDRA 16.1 | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| NEURALGIA | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 0 / 45 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CEREBRAL MICROANGIOPATHY | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 0 / 45 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic encephalopathy | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 | | | |
| GASTRIC ULCER | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| SMALL INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 0 / 45 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RECTAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 0 / 45 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 and urinary disorders | | | |

| | | | |
|---|-----------------|----------------|----------------|
| RENAL FAILURE CHRONIC | | | |
| subjects affected / exposed | 2 / 134 (1.49%) | 2 / 45 (4.44%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GLOMERULONEPHRITIS CHRONIC | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 0 / 45 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DIABETIC NEPHROPATHY | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 1 / 45 (2.22%) | 0 / 36 (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 FAILURE | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 0 / 45 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RENAL IMPAIRMENT | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 0 / 45 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| CHONDROCALCINOSIS PYROPHOSPHATE | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| Infections and infestations | | | |
| PNEUMONIA | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 1 / 45 (2.22%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Biliary sepsis | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 134 (0.00%) | 0 / 45 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYELONEPHRITIS CHRONIC | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 1 / 45 (2.22%) | 0 / 36 (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 | 0 / 134 (0.00%) | 0 / 45 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CELLULITIS | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 1 / 45 (2.22%) | 0 / 36 (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 | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| Bronchitis | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 134 (0.00%) | 1 / 45 (2.22%) | 0 / 36 (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 |
| Metabolism and nutrition disorders | | | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| FLUID OVERLOAD | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |
| HYPOGLYCAEMIA | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 1 / 45 (2.22%) | 0 / 36 (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 |
| Gout | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 0 / 36 (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 |

| | | | |
|---|--------------------|--|--|
| Serious adverse events | rhEPO-User Control | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 35 (20.00%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gallbladder adenocarcinoma | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HEPATIC CANCER | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| DIABETIC VASCULAR DISORDER | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ORTHOSTATIC HYPOTENSION | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| CHEST PAIN | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| CONFUSIONAL STATE | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MENTAL STATUS CHANGES | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| FALSE POSITIVE INVESTIGATION RESULT | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Shunt malfunction | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| ANGINA PECTORIS | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ATRIOVENTRICULAR BLOCK COMPLETE | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CARDIAC FAILURE CONGESTIVE | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| MYOCARDIAL ISCHAEMIA | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| CARPAL TUNNEL SYNDROME | | | |
| alternative dictionary used: MedDRA 16.1 | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| NEURALGIA | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CEREBRAL MICROANGIOPATHY | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolic encephalopathy | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| GASTRIC ULCER | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SMALL INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RECTAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| RENAL FAILURE CHRONIC | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|--|--|--|
| <p>GLOMERULONEPHRITIS CHRONIC</p> <p>subjects affected / exposed</p> <p>0 / 35 (0.00%)</p> <p>occurrences causally related to treatment / all</p> <p>0 / 0</p> <p>deaths causally related to treatment / all</p> <p>0 / 0</p> | | | |
| <p>DIABETIC NEPHROPATHY</p> <p>subjects affected / exposed</p> <p>0 / 35 (0.00%)</p> <p>occurrences causally related to treatment / all</p> <p>0 / 0</p> <p>deaths causally related to treatment / all</p> <p>0 / 0</p> | | | |
| <p>RENAL FAILURE</p> <p>subjects affected / exposed</p> <p>1 / 35 (2.86%)</p> <p>occurrences causally related to treatment / all</p> <p>0 / 1</p> <p>deaths causally related to treatment / all</p> <p>0 / 0</p> | | | |
| <p>RENAL IMPAIRMENT</p> <p>subjects affected / exposed</p> <p>1 / 35 (2.86%)</p> <p>occurrences causally related to treatment / all</p> <p>0 / 1</p> <p>deaths causally related to treatment / all</p> <p>0 / 0</p> | | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>CHONDROCALCINOSIS PYROPHOSPHATE</p> <p>subjects affected / exposed</p> <p>1 / 35 (2.86%)</p> <p>occurrences causally related to treatment / all</p> <p>0 / 1</p> <p>deaths causally related to treatment / all</p> <p>0 / 0</p> | | | |
| <p>Infections and infestations</p> <p>PNEUMONIA</p> <p>subjects affected / exposed</p> <p>0 / 35 (0.00%)</p> <p>occurrences causally related to treatment / all</p> <p>0 / 0</p> <p>deaths causally related to treatment / all</p> <p>0 / 0</p> | | | |
| <p>Biliary sepsis</p> <p>subjects affected / exposed</p> <p>0 / 35 (0.00%)</p> <p>occurrences causally related to treatment / all</p> <p>0 / 0</p> <p>deaths causally related to treatment / all</p> <p>0 / 0</p> | | | |
| <p>PYELONEPHRITIS CHRONIC</p> | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| APPENDICITIS | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PNEUMONIA PNEUMOCOCCAL | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CELLULITIS | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| HYPOKALAEMIA | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| FLUID OVERLOAD | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPOGLYCAEMIA | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gout | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | rhEPO-Naive GSK1278863 | rhEPO-Naive Control | rhEPO-User GSK1278863 |
|---|---------------------------|---------------------|--------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 47 / 134 (35.07%) | 14 / 45 (31.11%) | 20 / 36 (55.56%) |
| Investigations | | | |
| BLOOD PRESSURE INCREASED | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 1 / 36 (2.78%) |
| occurrences (all) | 1 | 0 | 2 |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 2 / 134 (1.49%) | 1 / 45 (2.22%) | 4 / 36 (11.11%) |
| occurrences (all) | 3 | 1 | 6 |
| General disorders and administration site conditions | | | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 5 / 134 (3.73%) | 0 / 45 (0.00%) | 2 / 36 (5.56%) |
| occurrences (all) | 3 | 0 | 2 |
| FATIGUE | | | |

| | | | |
|---|------------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 3 / 134 (2.24%) 3 | 1 / 45 (2.22%) 1 | 1 / 36 (2.78%) 1 |
| ASTHENIA subjects affected / exposed occurrences (all) | 1 / 134 (0.75%) 1 | 3 / 45 (6.67%) 3 | 1 / 36 (2.78%) 1 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 0 / 134 (0.00%) 0 | 1 / 45 (2.22%) 1 | 3 / 36 (8.33%) 3 |
| Gastrointestinal disorders DIARRHOEA subjects affected / exposed occurrences (all) | 10 / 134 (7.46%) 10 | 0 / 45 (0.00%) 0 | 0 / 36 (0.00%) 0 |
| NAUSEA subjects affected / exposed occurrences (all) | 8 / 134 (5.97%) 10 | 1 / 45 (2.22%) 1 | 1 / 36 (2.78%) 2 |
| CONSTIPATION subjects affected / exposed occurrences (all) | 5 / 134 (3.73%) 5 | 1 / 45 (2.22%) 1 | 1 / 36 (2.78%) 1 |
| Respiratory, thoracic and mediastinal disorders EPISTAXIS subjects affected / exposed occurrences (all) | 3 / 134 (2.24%) 3 | 0 / 45 (0.00%) 0 | 1 / 36 (2.78%) 1 |
| Skin and subcutaneous tissue disorders PRURITUS subjects affected / exposed occurrences (all) | 0 / 134 (0.00%) 0 | 4 / 45 (8.89%) 4 | 0 / 36 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all) | 2 / 134 (1.49%) 2 | 2 / 45 (4.44%) 2 | 1 / 36 (2.78%) 1 |
| BACK PAIN subjects affected / exposed occurrences (all) | 1 / 134 (0.75%) 1 | 1 / 45 (2.22%) 1 | 1 / 36 (2.78%) 1 |
| Infections and infestations | | | |

| | | | |
|------------------------------------|-------------------|----------------|-----------------|
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 15 / 134 (11.19%) | 2 / 45 (4.44%) | 7 / 36 (19.44%) |
| occurrences (all) | 17 | 2 | 8 |
| CONJUNCTIVITIS | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 2 / 36 (5.56%) |
| occurrences (all) | 1 | 0 | 2 |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 134 (1.49%) | 1 / 45 (2.22%) | 0 / 36 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| HYPERKALAEMIA | | | |
| subjects affected / exposed | 2 / 134 (1.49%) | 0 / 45 (0.00%) | 2 / 36 (5.56%) |
| occurrences (all) | 3 | 0 | 2 |
| GOUT | | | |
| subjects affected / exposed | 2 / 134 (1.49%) | 0 / 45 (0.00%) | 1 / 36 (2.78%) |
| occurrences (all) | 3 | 0 | 1 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 45 (0.00%) | 2 / 36 (5.56%) |
| occurrences (all) | 3 | 0 | 2 |

| | | | |
|---|--------------------|--|--|
| Non-serious adverse events | rhEPO-User Control | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 35 (37.14%) | | |
| Investigations | | | |
| BLOOD PRESSURE INCREASED | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences (all) | 3 | | |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 3 | | |
| FATIGUE | | | |

| | | | |
|---|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |
| ASTHENIA subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | | |
| Gastrointestinal disorders DIARRHOEA subjects affected / exposed occurrences (all) | 6 / 35 (17.14%) 6 | | |
| NAUSEA subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | | |
| CONSTIPATION subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |
| Respiratory, thoracic and mediastinal disorders EPISTAXIS subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |
| Skin and subcutaneous tissue disorders PRURITUS subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all) | 3 / 35 (8.57%) 3 | | |
| BACK PAIN subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |
| Infections and infestations | | | |

| | | | |
|---|---------------------|--|--|
| NASOPHARYNGITIS subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |
| CONJUNCTIVITIS subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | | |
| Bronchitis subjects affected / exposed occurrences (all) | 3 / 35 (8.57%) 3 | | |
| Metabolism and nutrition disorders | | | |
| HYPERKALAEMIA subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| GOUT subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 12 September 2013 | To revise the GSK1278863 Dose Adjustment Algorithm as requested by the United States FDA and to clarify and correct language throughout. |
| 03 October 2013 | Amendment for Japan only. To revise the Time and Events Table (Table 3) to add a HemoCue and Quest Hgb assessment at Week 2 as requested by PMDA. |
| 23 January 2014 | To revise lipid and biomarker assessments, to add reconfirmation of the QTc inclusion criterion at Day 1, to remove requirement for male contraception, to allow an interim cut of data to be taken to facilitate dose modelling, and to make minor clarifications throughout. |
| 04 February 2014 | Document version number change only: Change in document number because an error was found after publishing Amendment 03, but before distribution. The error was corrected and the document republished with a new document number. |
| 08 May 2014 | To change the Hgb entry criteria and target range for countries outside of the United States, to change the TSAT entry criterion, to clarify that subject who are not able to complete quality of life scales without assistance should not complete the scales, to change to the name of the rhEPO group (now called "the Control arm") as well as to clarify how subjects in the Control arm are to be managed; to make minor clarifications to the analysis section and throughout the document. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported