# Clinical trial results:
# A Phase 2 Open-Label Study to Evaluate Etavopivat for the Treatment of Anemia in Patients with Myelodysplastic Syndromes (MDS)

## Summary

| | |
|---|---|
| EudraCT number | 2022-001253-23 |
| Trial protocol | FR |
| Global end of trial date | 15 July 2024 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 31 July 2025 |
| First version publication date | 31 July 2025 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 4202-ONC-203 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05568225 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Novo Nordisk A/S |
| Sponsor organisation address | Novo Allé, Bagsvaerd, Denmark, 2880 |
| Public contact | Novo Nordisk A/S, Clinical Reporting Office (2834), clinicaltrials@novonordisk.com |
| Scientific contact | Novo Nordisk A/S, Clinical Reporting Office (2834), clinicaltrials@novonordisk.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 06 September 2024 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 15 July 2024 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

To assess hematologic improvement based on an erythroid response (HI E) greater than or equal to (≥) 8 weeks duration in subjects with MDS within 24 weeks of etavopivat treatment

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Oct 2013) and International Council for Harmonisation (ICH) Good Clinical Practice, including archiving of essential documents (May 1996) and European Standard (EN) International Standard (ISO) 14155 Part 1 and 2 and Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) 312.120.

Background therapy:

Etavopivat is a selective, orally bioavailable small-molecule activator of the red blood cell pyruvate kinase (PKR) enzyme. By activating PKR, etavopivat aims to increase the production of adenosine triphosphate (ATP) in red blood cells, which is hypothesized to enhance haemoglobin levels and improve erythroid response. This mechanism is particularly relevant for subjects with myelodysplastic syndromes (MDS), where anaemia and reduced red blood cell production are significant concerns.

Subjects in the study were classified into groups based on their risk levels: very low risk, low risk, or intermediate risk MDS. This categorization was important for assessing the therapy's effectiveness and safety in different subject subpopulations, ensuring tailored evaluation of responses to etavopivat and its impact on anaemia management.

Evidence for comparator:

Not applicable

| | |
|---|---|
| Actual start date of recruitment | 15 November 2022 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 5 |
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | France: 2 |
| Worldwide total number of subjects | 17 |
| EEA total number of subjects | 6 |

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) | 3 |
| From 65 to 84 years | 12 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details:

The trial was conducted at 10 sites in 4 countries.

### Pre-assignment

Screening details:

Of the 45 subjects targeted, only 24 were screened, and 17 were enrolled into three groups: Non-transfusion dependent (NTD) N=3, Low transfusion burden (LTB) N=5, and High transfusion burden (HTB) N=9. Each subject received 400 mg of etavopivat daily.

### Period 1

| | |
|---|---|
| Period 1 title | Primary treatment period |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Non-transfusion dependent |

Arm description:

Non transfusion dependent subjects who had received less than equal to (<=) 2 red blood cell (RBC) transfusions for anaemia within the prior 16 weeks, orally received 400 milligram (mg) of etavopivat once daily for up to 48 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Etavopivat |
| Investigational medicinal product code | FT-4202 |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Etavopivat was administrated to subjects as two oral tablets of 200 mg each once daily (daily dosage-400 mg).

| | |
|---|---|
| **Arm title** | Low transfusion burden |

Arm description:

Low transfusion burden subjects who had received 3 to 7 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Etavopivat |
| Investigational medicinal product code | FT-4202 |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Etavopivat was administrated to subjects as two oral tablets of 200 mg each once daily (daily dosage-400 mg).

| | |
|---|---|
| **Arm title** | High transfusion burden |

Arm description:

High transfusion burden subjects who had received >= 8 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Etavopivat |
| Investigational medicinal product code | FT-4202 |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Etavopivat was administrated to subjects as two oral tablets of 200 mg each once daily (daily dosage-400 mg).

| **Number of subjects in period 1** | Non-transfusion dependent | Low transfusion burden | High transfusion burden |
|---|---|---|---|
| Started | 3 | 5 | 9 |
| Efficacy evaluable set (EES) | 1 | 2 | 4 |
| Safety Population | 3 | 5 | 9 |
| Full analysis set (FAS) | 3 | 5 | 9 |
| Pharmacokinetic Population | 3 | 5 | 9 |
| Completed | 1 | 2 | 4 |
| Not completed | 2 | 3 | 5 |
| Physician decision | - | 1 | - |
| Disease progression | - | 1 | - |
| Adverse event, non-fatal | 1 | - | - |
| Termination of the study by the Sponsor | - | - | 1 |
| Withdrawal of conset | 1 | - | 4 |
| Lack of efficacy | - | 1 | - |

## Period 2

| | |
|---|---|
| Period 2 title | Extension treatment period |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Non-transfusion dependent |

Arm description:

Non transfusion dependent subjects who had received <= 2 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Etavopivat |
| Investigational medicinal product code | FT-4202 |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Etavopivat was administrated to subjects as two oral tablets of 200 mg each once daily (daily dosage-400 mg).

| | |
|---|---|
| **Arm title** | Low transfusion burden |

Arm description:

Low transfusion burden subjects who had received 3 to 7 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Etavopivat |
| Investigational medicinal product code | FT-4202 |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Etavopivat was administrated to subjects as two oral tablets of 200 mg each once daily (daily dosage-400 mg).

| | |
|---|---|
| **Arm title** | High transfusion burden |

Arm description:

High transfusion burden subjects who had received >= 8 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Etavopivat |
| Investigational medicinal product code | FT-4202 |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Etavopivat was administrated to subjects as two oral tablets of 200 mg each once daily (daily dosage-400 mg).

| **Number of subjects in period 2** | Non-transfusion dependent | Low transfusion burden | High transfusion burden |
|---|---|---|---|
| Started | 1 | 2 | 4 |
| Completed | 1 | 2 | 1 |
| Not completed | 0 | 0 | 3 |
| Termination of the study by the Sponsor | - | - | 1 |
| Protocol deviation | - | - | 1 |
| Lack of efficacy | - | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Non-transfusion dependent |
| Reporting group description: | |
| Non transfusion dependent subjects who had received less than equal to (<=) 2 red blood cell (RBC) transfusions for anaemia within the prior 16 weeks, orally received 400 milligram (mg) of etavopivat once daily for up to 48 weeks. | |
| Reporting group title | Low transfusion burden |
| Reporting group description: | |
| Low transfusion burden subjects who had received 3 to 7 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks. | |
| Reporting group title | High transfusion burden |
| Reporting group description: | |
| High transfusion burden subjects who had received >= 8 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks. | |

| Reporting group values | Non-transfusion dependent | Low transfusion burden | High transfusion burden |
|---|---|---|---|
| Number of subjects | 3 | 5 | 9 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 3 |
| From 65-84 years | 3 | 4 | 5 |
| 85 years and over | 0 | 1 | 1 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 77.3 | 80.2 | 71.2 |
| standard deviation | ± 5.69 | ± 3.49 | ± 8.11 |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 0 | 1 | 3 |
| Male | 3 | 4 | 6 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 17 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 3 | | |
| From 65-84 years | 12 | | |
| 85 years and over | 2 | | |
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation | <br><br><br>- | | |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 4 | | |
| Male | 13 | | |

## End points

### End points reporting groups

| Reporting group title | Non-transfusion dependent |
|---|---|
| Reporting group description: | |
| Non transfusion dependent subjects who had received less than equal to (<=) 2 red blood cell (RBC) transfusions for anaemia within the prior 16 weeks, orally received 400 milligram (mg) of etavopivat once daily for up to 48 weeks. | |
| Reporting group title | Low transfusion burden |
| Reporting group description: | |
| Low transfusion burden subjects who had received 3 to 7 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks. | |
| Reporting group title | High transfusion burden |
| Reporting group description: | |
| High transfusion burden subjects who had received >= 8 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks. | |
| Reporting group title | Non-transfusion dependent |
| Reporting group description: | |
| Non transfusion dependent subjects who had received <= 2 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks. | |
| Reporting group title | Low transfusion burden |
| Reporting group description: | |
| Low transfusion burden subjects who had received 3 to 7 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks. | |
| Reporting group title | High transfusion burden |
| Reporting group description: | |
| High transfusion burden subjects who had received >= 8 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks. | |

### Primary: Proportion of subjects with Hematologic Improvement– Erythroid (HI-E) response for >=8 weeks within 24 weeks of etavopivat treatment

| End point title | Proportion of subjects with Hematologic Improvement–Erythroid (HI-E) response for >=8 weeks within 24 weeks of etavopivat treatment[1] |
|---|---|
| End point description: | |
| This endpoint reported on the combined incidence of NTD, LTB and HTB in terms of (HI-E) response for >=8 weeks duration in subjects with myelodysplastic syndromes (MDS) within 24 weeks. The subjects were allocated to the following arms which were defined as: 1) NTD: >=1.5 grams per deciliter (g/dL) increase in haemoglobin (Hb) from baseline maintained >=8 consecutive weeks and no transfusion of RBC units for anemia over a continuous 8-week treatment period; 2) LTB: absence of any transfusion for >=8 consecutive weeks; and 3) HTB: reduction by >=50 percent (%) of RBC units for >=8 consecutive weeks. EES: All subjects in the FAS who had completed the week 24 response visit and who had a baseline record of the primary endpoint. | |
| End point type | Primary |
| End point timeframe: | |
| From Baseline to 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: Statistical analyses is not required for this endpoint.

| End point values | Non-transfusion dependent | Low transfusion burden | High transfusion burden | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1 | 2 | 4 | |
| Units: Proportion of subjects | | | | |
| number (not applicable) | 0 | 50 | 25 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects with Hematologic Improvement–Erythroid (HI-E) response for =>8 weeks within 16 and 48 weeks of etavopivat

| End point title | Proportion of subjects with Hematologic Improvement–Erythroid (HI-E) response for =>8 weeks within 16 and 48 weeks of etavopivat |
|---|---|

End point description:

This endpoint focused on the combined incidence of NTD, LTB and HTB subjects, evaluating HI-E lasting =>8 weeks in individuals with MDS within 16 weeks and 48 weeks. Subject's response were defined as follows: 1) NTD: an increase of =>1.5 g/dL in Hb maintained for =>8 consecutive weeks without any RBC transfusions for anemia; 2) LTB: no transfusions over =>8 consecutive weeks; and 3) HTB: a reduction of =>50% in RBC units for =>8 consecutive weeks. FAS: All subjects who signed the informed consent and received at least 1 dose of etavopivat. Data for this endpoint were not evaluable due to low subject enrolment and early termination of study.

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

End point timeframe:

48 weeks

| End point values | Non-transfusion dependent | Low transfusion burden | High transfusion burden | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[2] | 0[3] | 0[4] | |
| Units: Proportion of Subjects | | | | |
| number (not applicable) | | | | |

Notes:

[2] - Data for this endpoint was not analysed due to early termination of study.

[3] - Data for this endpoint was not analysed due to early termination of study.

[4] - Data for this endpoint was not analysed due to early termination of study.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects with Hematologic Improvement– Erythroid (HI-E) response for =>16 weeks within 24 and 48 weeks of etavopivat

| End point title | Proportion of subjects with Hematologic Improvement–Erythroid (HI-E) response for =>16 weeks within 24 and 48 weeks of etavopivat |
|---|---|

End point description:

This endpoint focused on the combined incidence of NDT, LTB and HTB subjects, evaluating HI-E response lasting =>16 weeks in individuals with MDS within 24 weeks and 48 weeks. Subject's response were defined as follows: 1) NTD: an increase of =>1.5 g/dL in Hb maintained for =>16 consecutive weeks without any RBC transfusions for anemia; 2) LTB: no transfusions over =>16 consecutive weeks; and 3) HTB: a reduction of =>50% in RBC units for =>16 consecutive weeks. FAS: All subjects who signed the informed consent and received at least 1 dose of etavopivat. Data for this endpoint were not evaluable due to low subject enrolment and early termination of study.

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

End point timeframe:

48 weeks

| **End point values** | Non-transfusion dependent | Low transfusion burden | High transfusion burden | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[5] | 0[6] | 0[7] | |
| Units: Proportion of Subjects | | | | |
| number (not applicable) | | | | |

Notes:

[5] - Data for this endpoint was not analysed and calculated due to early termination of study.

[6] - Data for this endpoint was not analysed due to early termination of study.

[7] - Data for this endpoint was not analysed due to early termination of study.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of all adverse events (AEs), serious adverse events (SAEs), and AEs related to etavopivat

| End point title | Number of all adverse events (AEs), serious adverse events (SAEs), and AEs related to etavopivat |
|---|---|

End point description:

This endpoint was assessed for total number of AEs and SAEs in subjects, including AEs related to etavopivat. AEs are any unfavorable medical occurrences in subjects taking the medicinal product, regardless of causality. SAEs are severe AEs that result in death, are life-threatening, require hospitalization, lead to significant disability, or involve congenital anomalies. Important medical events posing risks to the subjects are also classified as SAEs. Treatment Emergent Adverse Events (TEAEs) are AEs occurring after treatment initiation, aiding in the safety assessment of etavopivat. TEAEs will be considered drug-related if assessed by the investigator as possibly related or related, or if relationship is missing. Safety population included all subjects who receive at least one dose of etavopivat (including partial dosing).

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

End point timeframe:

From baseline up to 48 weeks

| End point values | Non-transfusion dependent | Low transfusion burden | High transfusion burden | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 5 | 9 | |
| Units: Events | | | | |
| number (not applicable) | | | | |
| AE | 33 | 33 | 54 | |
| SAE | 1 | 0 | 6 | |
| AEs related to etavopivat | 0 | 0 | 1 | |
| AEs possibly related etavopivat | 8 | 3 | 6 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of premature discontinuations, dose interruptions, and dose reductions

| End point title | Number of premature discontinuations, dose interruptions, and dose reductions |
|---|---|

End point description:

The endpoint was assessed for total number of premature discontinuations, dose interruptions and dose reductions. Premature discontinuation was defined as any discontinuation prior to week 48. A dose interruption is a temporary halt in treatment due to an AE, while a dose reduction involves lowering the dosage of the drug when AEs occur. If a subject tolerates a reduced dose for 14 days, a rechallenge with the original dose may occur after a clinic visit, but any new Grade 3 or higher AEs require treatment discontinuation and consultation with the Global Medical Monitor before resuming. Safety population included all subjects who receive at least one dose of etavopivat (including partial dosing).

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

End point timeframe:

Within 48 weeks

| End point values | Non-transfusion dependent | Low transfusion burden | High transfusion burden | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 5 | 9 | |
| Units: Events | | | | |
| number (not applicable) | | | | |
| Premature discontinuations | 1 | 0 | 0 | |
| Dose interruptions | 0 | 0 | 2 | |
| Dose reductions | 0 | 0 | 0 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall response rate

| End point title | Overall response rate |
|---|---|

End point description:

The Overall Response Rate (ORR) is defined as the proportion of subjects who achieve a predefined level of response according to the 2006 International Working Group (IWG) criteria, assessed at each scheduled evaluation. Data for this endpoint were not evaluable due to low subject enrolment and early termination of study.

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

End point timeframe:

Up to 48 weeks

| End point values | Non-transfusion dependent | Low transfusion burden | High transfusion burden | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[8] | 0[9] | 0[10] | |
| Units: Proportion of subjects | | | | |
| number (not applicable) | | | | |

Notes:

[8] - Data for this endpoint was not analysed due to early termination of study.

[9] - Data for this endpoint was not analysed due to early termination of study.

[10] - Data for this endpoint was not analysed due to early termination of study.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of response

| End point title | Duration of response |
|---|---|

End point description:

This endpoint reported duration of response which was defined as duration of response will be summarized with quantiles based on product limit estimates (ie, Kaplan-Meier). Duration of response is defined as the time from date of first known incidence of a 2006 IWG criteria response to the most recent date that the 2006 IWG (International Working Group) criteria is not met following the initial response. If the subject has met IWG criteria throughout the period following the initial response, the subject will be censored at the latest date of end of study, loss to follow-up, or death. Data for this endpoint were not evaluable due to low subject enrolment and early termination of study.

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

End point timeframe:

Up to 48 weeks

| End point values | Non-transfusion dependent | Low transfusion burden | High transfusion burden | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[11] | 0[12] | 0[13] | |
| Units: Days | | | | |
| number (not applicable) | | | | |

Notes:

[11] - Data for this endpoint was not analysed due to early termination of study.

[12] - Data for this endpoint was not analysed due to early termination of study.

[13] - Data for this endpoint was not analysed due to early termination of study.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Reduction in RBC transfusions for >=8 weeks in subjects with LTD or HTB at study entry

| End point title | Reduction in RBC transfusions for >=8 weeks in subjects with LTD or HTB at study entry[14] |
|---|---|

End point description:

This endpoint reports reduction in RBC transfusion by 8-week interval in subjects with LTB and HTB. EES: All subjects in the FAS who have completed the week 24 response visit and who have a baseline record of the primary endpoint. n (number analysed) = subjects with available data for a specified category.

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

End point timeframe:

Up to 48 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: Overall number of subjects analyzed signifies number of subjects evaluable for this outcome measure.

| End point values | Low transfusion burden | High transfusion burden | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 4 | | |
| Units: Total RBS units | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1-8 (n=2,4) | 3.0 (± 2.83) | 5.8 (± 2.63) | | |
| Week 9-16 (n=2,4) | 2.5 (± 2.12) | 6.3 (± 1.71) | | |
| Week 17-24 (n=2,4) | 3.5 (± 2.12) | 7.5 (± 3.00) | | |
| Week 25-32 (n=2,3) | 5.5 (± 0.71) | 7.3 (± 1.15) | | |
| Week 33-40 (n=2,3) | 5.0 (± 4.24) | 6.7 (± 1.15) | | |
| Week 41-48 (n=2,2) | 4.5 (± 2.12) | 7.5 (± 2.12) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change from Baseline in RBC transfusion independence for =>8 weeks in subjects with LTB or HTB at study entry

| End point title | Percent Change from Baseline in RBC transfusion independence for =>8 weeks in subjects with LTB or HTB at study entry[15] |
|---|---|

End point description:

This endpoint is percent change in RBC transfusion by 8-week interval in subjects with LTB and HTB. Percent reduction from baseline in RBC transfusion burden is defined as -100×(Total RBC Units Transfused During Interval)/(Baseline RBC Units Transfused Per 8 Weeks). EES: All subjects in the FAS who have completed the week 24 response visit and who have a baseline record of the primary endpoint. n (number analysed) = subjects with available data for a specified category. 99999 signifies the standard deviation was not evaluable.

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

End point timeframe:

Up to 48 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: Overall number of subjects analyzed signifies number of subjects evaluable for this outcome measure.

| **End point values** | Low transfusion burden | High transfusion burden | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 4 | | |
| Units: Percent change of total RBC units | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1-8 (n=2,4) | -20.83 (± 64.818) | 68.75 (± 156.994) | | |
| Week 9-16 (n=2,4) | -33.33 (± 47.140) | 68.75 (± 98.219) | | |
| Week 17-24 (n=2,4) | -4.17 (± 41.248) | 120.83 (± 191.183) | | |
| Week 25-32 (n=2,3) | 58.33 (± 11.785) | 127.78 (± 149.381) | | |
| Week 33-40 (n=2,3) | 33.33 (± 94.281) | 94.44 (± 91.793) | | |
| Week 41-48 (n=2,2) | 25.00 (± 35.355) | 50.00 (± 99999) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Decrease in ferritin and transferrin saturation (TSAT)

| End point title | Decrease in ferritin and transferrin saturation (TSAT) |
|---|---|

End point description:

This endpoint were to report decrease in ferritin and TSAT from baseline to Week 48. Data for this endpoint were not evaluable due to low subject enrolment and early termination of study.

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

End point timeframe:

Up to 48 weeks

| End point values | Non-transfusion dependent | Low transfusion burden | High transfusion burden | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[16] | 0[17] | 0[18] | |
| Units: ng/mL | | | | |
| number (not applicable) | | | | |

Notes:

[16] - Data for this endpoint was not analysed due to early termination of study.

[17] - Data for this endpoint was not analysed due to early termination of study.

[18] - Data for this endpoint was not analysed due to early termination of study.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in neutrophils and/or platelets counts

| End point title | Change from baseline in neutrophils and/or platelets counts |
|---|---|

End point description:

This endpoint reports the change from baseline in neutrophils and/or platelets counts from baseline to week 48. The safety set includes all subjects who receive at least one dose of etavopivat (including partial dosing).Here, n (number analysed) = subjects with available data for a specified category. 99999 signifies the standard deviation was not evaluable.

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

End point timeframe:

Baseline (week 0), week 48

| End point values | Non-transfusion dependent | Low transfusion burden | High transfusion burden | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 5 | 9 | |
| Units: Giga per liter (10^9/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Neutrophils (n=1,2,1) | -3.200 (± 99999) | -0.950 (± 0.0707) | -0.100 (± 99999) | |
| Platelets counts (n=1,2,1) | 43.0 (± 99999) | -51.0 (± 205.06) | -8.0 (± 99999) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Decrease in iron chelation therapy

| End point title | Decrease in iron chelation therapy |
|---|---|

End point description:

This endpoint was expected to report decrease of Iron chelation therapy recorded throughout the study. Data for this endpoint were not evaluable due to low subject enrolment and early termination of study.

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

End point timeframe:

up to 48 weeks

| End point values | Non-transfusion dependent | Low transfusion burden | High transfusion burden | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[19] | 0[20] | 0[21] | |
| Units: Dose unit | | | | |
| arithmetic mean (standard deviation) | () | () | () | |

Notes:

[19] - Data for this endpoint was not analysed due to early termination of study.

[20] - Data for this endpoint was not analysed due to early termination of study.

[21] - Data for this endpoint was not analysed due to early termination of study.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall survival

| End point title | Overall survival |
|---|---|

End point description:

Overall survival is defined as the time from first dose to date of death. If the subject was alive at last contact, the end date will be censored at the latest of either end of study, loss to follow-up, or study discontinuation. Data for this endpoint were not evaluable due to low subject enrolment and early termination of study.

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

End point timeframe:

Within 48 weeks

| End point values | Non-transfusion dependent | Low transfusion burden | High transfusion burden | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[22] | 0[23] | 0[24] | |
| Units: Months | | | | |
| number (not applicable) | | | | |

Notes:

[22] - Data for this endpoint was not analysed due to early termination of study.

[23] - Data for this endpoint was not analysed due to early termination of study.

[24] - Data for this endpoint was not analysed due to early termination of study.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Etavopivat plasma concentrations

| End point title | Etavopivat plasma concentrations |
|---|---|

End point description:

This endpoint reported Etavopivat plasma concentrations in order to assess the PK properties of etavopivat in subjects with MDS. PK parameters included but not limited to were: Time to maximum observed plasma concentration, area under the plasma concentration-time curve from time zero until the last quantifiable time point (AUC0-last), from time zero to infinity (AUC0-inf), for a dosing interval (AUCtau/AUC0-24).) However due to early termination of the study, all the PK parameters could not be assessed and only the plasma concentrations was assessed. The PK set includes all safety set subjects who have at least one evaluable concentration for etavopivat at a scheduled PK time point after the start of dosing. Here, n (number analysed) = subjects with available data for a specified category. 99999 signifies the arithmetic mean and standard deviation was not evaluable.

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

End point timeframe:

Weeks 1 and 4 pre-dose, post-dose 1, 2, 4, 6 hours.Week 2 and EOT (week 48):pre-dose, post-dose 1, 2 hours

| **End point values** | Non-transfusion dependent | Low transfusion burden | High transfusion burden | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 5 | 9 | |
| Units: Nanograms per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 predose (n=3,4,9) | 0 (± 99999) | 0 (± 99999) | 0 (± 99999) | |
| Week 1 post-dose 1 hour (n=3,5,9) | 379.77 (± 292.748) | 904.80 (± 521.000) | 1016.78 (± 794.503) | |
| Week 1 post-dose 2 hour (n=3,5,9) | 751.67 (± 393.465) | 579.60 (± 403.593) | 519.11 (± 273.776) | |
| Week 1 post-dose 4 hour (n=2,5,9) | 274.50 (± 86.974) | 203.80 (± 134.884) | 165.16 (± 64.895) | |
| Week 1 post-dose 6 hour (n=1,5,7) | 63.50 (± 99999) | 101.02 (± 67.693) | 83.74 (± 40.170) | |
| Week 2 pre-dose (n=3,4,9) | 27.20 (± 17.843) | 19.08 (± 9.037) | 19.20 (± 12.240) | |
| Week 2 post-dose 1 hour (n=3,5,9) | 1156.00 (± 371.198) | 899.40 (± 442.555) | 1076.44 (± 693.907) | |
| Week 2 post-dose 2 hour (n=3,4,9) | 927.00 (± 310.140) | 1024.00 (± 530.102) | 661.78 (± 392.238) | |
| Week 4 predose (n=2,5,9) | 17.04 (± 11.540) | 24.34 (± 23.333) | 20.26 (± 9.289) | |
| Week 4 post-dose 1 hour (n=2,4,9) | 1050.00 (± 28.284) | 386.90 (± 214.249) | 913.20 (± 1013.207) | |
| Week 4 post-dose 2 hour (n=2,5,9) | 526.00 (± 134.350) | 453.40 (± 179.140) | 678.49 (± 379.918) | |
| Week 4 post-dose 4 hour (n=2,4,9) | 151.50 (± 12.021) | 383.73 (± 261.103) | 297.90 (± 282.646) | |
| Week 4 post-dose 6 hour (n=2,3,9) | 60.75 (± 11.526) | 148.13 (± 113.650) | 121.34 (± 115.306) | |
| End of treatment pre-dose (n=0,2,1) | 99999 (± 99999) | 21.60 (± 5.798) | 24.20 (± 99999) | |
| End of treatment post-dose 1 hours (n=0,1,1) | 99999 (± 99999) | 1620.00 (± 99999) | 1680.00 (± 99999) | |
| End of treatment post-dose 2 hours (n=0,1,1) | 99999 (± 99999) | 571.00 (± 99999) | 815.00 (± 99999) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: RBC 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP) levels over time

| End point title | RBC 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP) levels over time |
|---|---|

End point description:

Etavopivat plasma concentrations were collected in order to assess the pharmacodynamic (PD) properties of etavopivat in subjects with MDS. Data for this endpoint were not evaluable due to low subject enrolment and early termination of study.

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

End point timeframe:

Within 48 weeks

| End point values | Non-transfusion dependent | Low transfusion burden | High transfusion burden | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[25] | 0[26] | 0[27] | |
| Units: Micrograms per milliliter | | | | |
| number (not applicable) | | | | |

Notes:

[25] - Data for this endpoint was not analysed due to early termination of study.

[26] - Data for this endpoint was not analysed due to early termination of study.

[27] - Data for this endpoint was not analysed due to early termination of study.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 48 weeks

Adverse event reporting additional description:

All presented AEs are treatment emergent AEs (TEAE). TEAE is defined as any AE that emerges or worsens in the period from first dose of study drug to 28 days after the last dose of study drug. Safety population includes all subjects who receive at least one dose of etavopivat (including partial dosing).

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 25 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Non-transfusion dependent |

Reporting group description:

Non transfusion dependent participants who had received less than equal to <= 2 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks.

| | |
|---|---|
| Reporting group title | High transfusion burden |

Reporting group description:

High transfusion burden participants who had received greater than equal >= 8 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks.

| | |
|---|---|
| Reporting group title | Low transfusion burden |

Reporting group description:

Low transfusion burden participants who had received 3 to 7 RBC transfusions for anaemia within the prior 16 weeks, orally received 400 mg of etavopivat once daily for up to 48 weeks.

| Serious adverse events | Non-transfusion dependent | High transfusion burden | Low transfusion burden |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 3 / 9 (33.33%) | 0 / 5 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (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 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |

| | | | |
|---|---|---|---|
| Arterial rupture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 5 (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 |
| Infections and infestations | | | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (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 |

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

| **Non-serious adverse events** | Non-transfusion dependent | High transfusion burden | Low transfusion burden |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 9 / 9 (100.00%) | 5 / 5 (100.00%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Chills | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Mucosal dryness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 2 | 0 | 1 |
| Depression | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 9 (22.22%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |

| | | | |
|---|---|---|---|
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 0 / 9 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 10 |
| Troponin I increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Transfusion reaction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |

| | | | |
|---|---|---|---|
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 9 (22.22%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 0 / 9 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| External ear inflammation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vertigo | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 9 (22.22%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 9 (22.22%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 3 | 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 9 (22.22%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 2 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Lip infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---|---|---|
| Haemosiderosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Iron overload | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypervolaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 9 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Vitamin B12 deficiency | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 9 (11.11%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 11 April 2022 | Version 1.0: First protocol version |
| 15 June 2022 | Version 2.0: Protocol version 1.0 was not implemented. |
| 31 July 2023 | Version 3.0: 1. Protocol version updated to adjust the treatment period timeframes into a 24-week Primary Treatment period, a 24-week Extension Treatment period, and a Survival Follow-up period. 2. A 'futility assessment' was added. 3. Schedule of Events tables and Appendices were updated as needed to reflect the above changes to the protocol. 4. Safety text has been added throughout the document to reflect the Novo Nordisk Safety Surveillance practice. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The predefined Quality Tolerance Limit (QTL) that required 5 or more subjects to complete 16 weeks of treatment. However, 7 subjects did not fulfill this requirement, leading to the early termination.

Notes: