# Clinical trial results:
# A Phase 2, Randomized, Open Label Study of Bitopertin to Evaluate the Safety, Tolerability, Efficacy, and Protoporphyrin IX (PPIX) Concentrations in Participants with Erythropoietic Protoporphyria (EPP)

## Summary

| | |
|---|---|
| EudraCT number | 2025-000481-28 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 02 May 2024 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 11 June 2026 |
| First version publication date | 11 June 2026 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | DISC-1459-202 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Disc Medicine, Inc. |
| Sponsor organisation address | 321 Arsenal Street, Suite 101, Watertown, MA, United States, 02472 |
| Public contact | Disc Medicine Clinical Trials, Disc Medicine, Inc., +1 617-674-9274, info@discmedicine.com |
| Scientific contact | Disc Medicine Clinical Trials, Disc Medicine, Inc., +1 617-674-9274, medinfo@discmedicine.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA/PE/0004390323 |
| 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 | 16 December 2024 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 02 May 2024 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

• To assess changes in protoporphyrin IX (PPIX) concentration in response to bitopertin treatment

Protection of trial subjects:

This study was designed and monitored in accordance with sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 September 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 | Australia: 26 |
| Worldwide total number of subjects | 26 |
| EEA total number of subjects | 0 |

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) | 4 |
| Adults (18-64 years) | 20 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 2 sites in Australia. Up to 22 participants, aged 12 years and older, were initially planned to be enrolled. Up to 55 participants ≥12 years of age could have been enrolled if additional cohorts were added.

### Pre-assignment

Screening details:

Potential participants were screened for eligibility within 28 days of randomization. During screening, all potential participants underwent a light tolerance assessment that included a diary assessment of historical light tolerance and maximal direct sunlight tolerance time until phototoxic prodrome during 1 day/week over 2-week run-in period.

### Period 1

| | |
|---|---|
| Period 1 title | Treatment phase |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Bitopertin 20 mg |

Arm description:

Adult subjects (N=11) enrolled in Bitopertin 20 mg received two 10-mg tablets of Bitopertin from Day 1. Adolescent subjects (N=3) enrolled in the same treatment arm were started on 50% of the randomized dose (i.e., bitopertin 10 mg), and on Day 15 (±2 days), were dose-escalated to receive the randomized dose of 20 mg.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Bitopertin |
| Investigational medicinal product code | DISC-1459 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received oral bitopertin (20 mg) once daily (QD) for 24 weeks (168 days).

| | |
|---|---|
| **Arm title** | Bitopertin 60 mg |

Arm description:

Adult subjects (N=11) enrolled in Bitopertin 60 mg received two 30-mg tablets of Bitopertin from Day 1. Adolescent subjects (N=1) in the same treatment arm were started on 50% of the randomized dose (i.e., bitopertin 30 mg), and on Day 15 (±2 days), were dose-escalated to receive the randomized dose of 60 mg.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Bitopertin |
| Investigational medicinal product code | DISC-1459 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received oral bitopertin (60 mg) once daily (QD) for 24 weeks (168 days).

| Number of subjects in period 1 | Bitopertin 20 mg | Bitopertin 60 mg |
|---|---|---|
| Started | 14 | 12 |
| Completed | 13 | 12 |
| Not completed | 1 | 0 |
| Adverse event, non-fatal | 1 | - |

## Period 2

| | |
|---|---|
| Period 2 title | Extension phase |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Bitopertin 20 mg |

Arm description:

Subjects enrolled in Bitopertin 20 mg received two 10-mg tablets of Bitopertin

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Bitopertin |
| Investigational medicinal product code | DISC-1459 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received oral bitopertin (20 mg) once daily (QD) for additional 24 weeks, or up to 1 year of total treatment from Day 1.

| | |
|---|---|
| **Arm title** | Bitopertin 60 mg |

Arm description:

Subjects enrolled in Bitopertin 60 mg received two 30-mg tablets of Bitopertin

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Bitopertin |
| Investigational medicinal product code | DISC-1459 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received oral bitopertin (60 mg) once daily (QD) for additional 24 weeks, or up to 1 year of total treatment from Day 1.

| **Number of subjects in period 2[1]** | Bitopertin 20 mg | Bitopertin 60 mg |
|---|---|---|
| Started | 7 | 7 |
| Completed | 0 | 1 |
| Not completed | 7 | 6 |
| Consent withdrawn by subject | 2 | 1 |
| Rolled over to DISC-1459-501 study | 5 | 4 |
| Lost to follow-up | - | 1 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: As per the protocol, after completing the treatment period, the participant could enter the extension period. Based on this, in the extension phase of the study, oral bitopertin was evaluated in 7 adult participants in each of the 20 mg and 60 mg arms.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Bitopertin 20 mg |
| Reporting group description: | |
| Adult subjects (N=11) enrolled in Bitopertin 20 mg received two 10-mg tablets of Bitopertin from Day 1. Adolescent subjects (N=3) enrolled in the same treatment arm were started on 50% of the randomized dose (i.e., bitopertin 10 mg), and on Day 15 (±2 days), were dose-escalated to receive the randomized dose of 20 mg. | |
| Reporting group title | Bitopertin 60 mg |
| Reporting group description: | |
| Adult subjects (N=11) enrolled in Bitopertin 60 mg received two 30-mg tablets of Bitopertin from Day 1. Adolescent subjects (N=1) in the same treatment arm were started on 50% of the randomized dose (i.e., bitopertin 30 mg), and on Day 15 (±2 days), were dose-escalated to receive the randomized dose of 60 mg. | |

| Reporting group values | Bitopertin 20 mg | Bitopertin 60 mg | Total |
|---|---|---|---|
| Number of subjects | 14 | 12 | 26 |
| 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) | 3 | 1 | 4 |
| Adults (18-64 years) | 10 | 10 | 20 |
| From 65-84 years | 1 | 1 | 2 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 37.0 | 42.0 | |
| standard deviation | ± 19.53 | ± 16.25 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 8 | 8 | 16 |
| Male | 6 | 4 | 10 |
| Race<br>Units: Subjects | | | |
| White | 14 | 11 | 25 |
| Asian | 0 | 1 | 1 |
| Ethnicity<br>Units: Subjects | | | |
| Not Hispanic or Latino | 14 | 12 | 26 |
| Time to prodrome<br>Units: Subjects | | | |
| <30 minutes | 7 | 6 | 13 |
| ≥30 minutes | 7 | 6 | 13 |
| Erythropoietic protoporphyria/X-linked | | | |

| | | | |
|---|---|---|---|
| protoporphyria Subgroup<br>Units: Subjects | | | |
| Erythropoietic protoporphyria | 14 | 11 | 25 |
| X-linked protoporphyria | 0 | 1 | 1 |
| Weight<br>Units: Kg | | | |
| arithmetic mean | 78.09 | 79.50 | |
| standard deviation | ± 12.745 | ± 21.017 | - |
| BMI<br>Units: Kg/m^2 | | | |
| arithmetic mean | 27.45 | 27.78 | |
| standard deviation | ± 4.753 | ± 8.414 | - |
| Whole Blood Metal-Free PPIX<br>Units: ng/mL | | | |
| arithmetic mean | 10337.9 | 8143.8 | |
| standard deviation | ± 7303.43 | ± 6505.42 | - |
| Whole Blood Total PPIX<br>Units: ng/mL | | | |
| arithmetic mean | 10947.54 | 9116.00 | |
| standard deviation | ± 7336.749 | ± 6653.471 | - |
| Plasma PPIX | | | |
| Baseline plasma PPIX levels were available for all 14 subjects in the bitopertin 20-mg arm and 11 of 12 subjects in the bitopertin 60-mg arm. | | | |
| Units: ng/mL | | | |
| arithmetic mean | 994.89 | 671.68 | |
| standard deviation | ± 634.764 | ± 454.607 | - |

## End points

### End points reporting groups

| Reporting group title | Bitopertin 20 mg |
|---|---|
| Reporting group description: | |
| Adult subjects (N=11) enrolled in Bitopertin 20 mg received two 10-mg tablets of Bitopertin from Day 1. Adolescent subjects (N=3) enrolled in the same treatment arm were started on 50% of the randomized dose (i.e., bitopertin 10 mg), and on Day 15 (±2 days), were dose-escalated to receive the randomized dose of 20 mg. | |
| Reporting group title | Bitopertin 60 mg |
| Reporting group description: | |
| Adult subjects (N=11) enrolled in Bitopertin 60 mg received two 30-mg tablets of Bitopertin from Day 1. Adolescent subjects (N=1) in the same treatment arm were started on 50% of the randomized dose (i.e., bitopertin 30 mg), and on Day 15 (±2 days), were dose-escalated to receive the randomized dose of 60 mg. | |
| Reporting group title | Bitopertin 20 mg |
| Reporting group description: | |
| Subjects enrolled in Bitopertin 20 mg received two 10-mg tablets of Bitopertin | |
| Reporting group title | Bitopertin 60 mg |
| Reporting group description: | |
| Subjects enrolled in Bitopertin 60 mg received two 30-mg tablets of Bitopertin | |

### Primary: Percent change from baseline in whole blood metal-free PPIX levels

| End point title | Percent change from baseline in whole blood metal-free PPIX levels |
|---|---|
| End point description: | |
| | |
| End point type | Primary |
| End point timeframe: | |
| At Day 169 | |

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 11 | | |
| Units: Percentage | | | | |
| least squares mean (standard error) | -31.7 (± 6.98) | -57.7 (± 7.40) | | |

### Statistical analyses

| Statistical analysis title | Mixed Model Repeated Measures (MMRM) Model |
|---|---|
| Statistical analysis description: | |
| For the MMRM model, the dependent variable was the percentage change from baseline whole blood metal-free PPIX level for all post-baseline assessments for each participant. The model included fixed effects for treatment, randomization stratification factor, baseline whole blood metal-free PPIX level, visit, and visit-by treatment interaction and a random effect for the participant. The model was fit using restricted maximum likelihood estimation with the Kenward-Roger method. | |

| | |
|---|---|
| Comparison groups | Bitopertin 20 mg v Bitopertin 60 mg |
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.018 |
| Method | t-test, 2-sided |
| Parameter estimate | LS Mean Difference |
| Point estimate | -26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -47.16 |
| upper limit | -4.902 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 10.21 |

**Secondary: Total hours of direct sunlight exposure to skin on days with no pain from 1000 to 1800 hours (10:00 AM to 6:00 PM)**

| | |
|---|---|
| End point title | Total hours of direct sunlight exposure to skin on days with no pain from 1000 to 1800 hours (10:00 AM to 6:00 PM) |

End point description:

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

End point timeframe:

At Day 169

| **End point values** | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 12 | | |
| Units: Hours | | | | |
| least squares mean (standard error) | 186.01 (± 33.51) | 209.85 (± 36.20) | | |

**Statistical analyses**

| **Statistical analysis title** | Analysis of variance (ANOVA) Model |
|---|---|

Statistical analysis description:

An ANOVA model was used for the ITT Analysis Set with effects for randomized dose group and the sunlight exposure time to prodromal symptom randomization stratification factor. The model was used to estimate the mean total hours of sunlight exposure on days with no pain from 1000 to 1800 hours (10:00 AM to 6:00 PM) summed over the entire treatment period from randomization to Day 169 for the dose groups.

| | |
|---|---|
| Comparison groups | Bitopertin 20 mg v Bitopertin 60 mg |

| | |
|---|---|
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.633 |
| Method | t-test, 2-sided |
| Parameter estimate | LS Mean Difference |
| Point estimate | 23.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -78.2 |
| upper limit | 125.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 49.33 |

## Secondary: Maximum and average total daily pain intensity scores of phototoxic reactions

| | |
|---|---|
| End point title | Maximum and average total daily pain intensity scores of phototoxic reactions |

End point description:

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

End point timeframe:

Day 1 to Day 169

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Maximum pain | 4.7 (± 3.08) | 4.2 (± 1.33) | | |
| Average daily pain | 11.3 (± 11.96) | 5.0 (± 1.10) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in 2-week average daily exposure time to first prodromal symptom (collected during weekly sunlight exposure challenges)

| | |
|---|---|
| End point title | Change in 2-week average daily exposure time to first prodromal symptom (collected during weekly sunlight exposure challenges) |

End point description:

Two (2)-week averages of daily sunlight exposure time prior to first prodromal symptom (e.g., burning, tingling, itching, or stinging) associated with sunlight exposure between 1 hour post-sunrise and 1 hour

pre-sunset were calculated for the two weeks immediately prior to randomization and for the treatment period from randomization to Day 169 visit, for each participant.

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

End point timeframe:

Day 155 to Day 168

| **End point values** | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 8 | | |
| Units: Hours | | | | |
| least squares mean (standard error) | 75.78 (± 28.35) | 148.23 (± 31.52) | | |

**Statistical analyses**

| **Statistical analysis title** | Mixed-Model Repeated Measures (MMRM) Model |
|---|---|

Statistical analysis description:

The main analysis for this endpoint was based on the mean change from baseline in 2-week average daily exposure time to first prodromal symptom over time, analyzed using a MMRM approach, with 2-week time points being used.

| Comparison groups | Bitopertin 20 mg v Bitopertin 60 mg |
|---|---|
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.095 |
| Method | t-test, 2-sided |
| Parameter estimate | LS Mean Difference |
| Point estimate | 72.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.18 |
| upper limit | 158.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 42.65 |

**Secondary: Percent change from baseline for erythrocyte metal-free PPIX concentrations**

| End point title | Percent change from baseline for erythrocyte metal-free PPIX concentrations |
|---|---|

End point description:

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

End point timeframe:
At Day 169

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 6 | | |
| Units: Percentage | | | | |
| least squares mean (standard error) | -31.1 (± 6.95) | -61.6 (± 7.90) | | |

### Statistical analyses

| Statistical analysis title | Mixed-Model Repeated Measures (MMRM) Model |
|---|---|
| Statistical analysis description: | |
| The PPIX concentrations were converted into percent change from baseline for analysis. | |
| Comparison groups | Bitopertin 20 mg v Bitopertin 60 mg |
| Number of subjects included in analysis | 15 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.008 |
| Method | t-test, 2-sided |
| Parameter estimate | LS Mean Difference |
| Point estimate | -30.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -52.34 |
| upper limit | -8.688 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 10.74 |

## Secondary: Percent change from baseline for total whole blood PPIX concentrations

| End point title | Percent change from baseline for total whole blood PPIX concentrations |
|---|---|
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| At Day 169 | |

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 7 | | |
| Units: Percentage | | | | |
| least squares mean (standard error) | -27.2 (± 5.64) | -56.5 (± 6.05) | | |

## Statistical analyses

| Statistical analysis title | Mixed-Model Repeated Measures (MMRM) Model |
|---|---|

Statistical analysis description:

The PPIX concentrations were converted into percent change from baseline for analysis.

| Comparison groups | Bitopertin 20 mg v Bitopertin 60 mg |
|---|---|
| Number of subjects included in analysis | 16 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.002 |
| Method | t-test, 2-sided |
| Parameter estimate | LS Mean Difference |
| Point estimate | -29.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -46.53 |
| upper limit | -12.11 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 8.3 |

## Secondary: Percent change from baseline for total plasma PPIX concentrations

| End point title | Percent change from baseline for total plasma PPIX concentrations |
|---|---|

End point description:

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

End point timeframe:

At Day 169

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 6 | | |
| Units: Percentage | | | | |
| least squares mean (standard error) | -37.4 (± 10.65) | -47.2 (± 11.82) | | |

### Statistical analyses

| **Statistical analysis title** | Mixed-Model Repeated Measures (MMRM) Model |
|---|---|
| Statistical analysis description:<br>The PPIX concentrations were converted into percent change from baseline for analysis. | |
| Comparison groups | Bitopertin 60 mg v Bitopertin 20 mg |
| Number of subjects included in analysis | 15 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.547 |
| Method | t-test, 2-sided |
| Parameter estimate | LS Mean Difference |
| Point estimate | -9.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -43.42 |
| upper limit | 23.81 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 16 |

## Secondary: Maximum plasma concentration (Cmax) following single oral administrations of bitopertin in adolescents

| End point title | Maximum plasma concentration (Cmax) following single oral administrations of bitopertin in adolescents |
|---|---|

End point description:

Pharmacokinetic (PK) parameters were evaluated on Day 1 when the adolescents were on half the randomized dose (i.e., 10 mg and 30 mg). From Day 15 (±2 days), adolescent participants were dose-escalated to receive the randomized doses of 20 mg and 60 mg. Hence, PK data evaluated for adolescents is after administration of bitopertin at the doses of 10 and 30 mg.

Note: Considering only one subject was evaluable in the bitopertin 60-mg arm, range (min-max) is selected as the precision/dispersion type.

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

End point timeframe:

Day 1

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 1 | | |
| Units: ng/mL | | | | |
| arithmetic mean (full range (min-max)) | 65.2 (52.2 to 81.3) | 145 (145 to 145) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Observed time of the maximum drug concentration (Tmax) following single oral administrations of bitopertin in adolescents

| End point title | Observed time of the maximum drug concentration (Tmax) following single oral administrations of bitopertin in adolescents |
|---|---|

End point description:

Pharmacokinetic (PK) parameters were evaluated on Day 1 when the adolescents were on half the randomized dose (i.e., 10 mg and 30 mg). From Day 15 (±2 days), adolescent participants were dose-escalated to receive the randomized doses of 20 mg and 60 mg. Hence, PK data evaluated for adolescents is after administration of bitopertin at the doses of 10 and 30 mg.

Note: Considering only one subject was evaluable in the bitopertin 60-mg arm, range (min-max) is selected as the precision/dispersion type.

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

End point timeframe:

Day 1

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 1 | | |
| Units: Hours | | | | |
| arithmetic mean (full range (min-max)) | 1.87 (1.75 to 1.97) | 4.08 (4.08 to 4.08) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: AUC from time 0 to 24 hours post-dose on Day 1 (AUC0-24) in adolescents

| End point title | AUC from time 0 to 24 hours post-dose on Day 1 (AUC0-24) in adolescents |
|---|---|

End point description:

Pharmacokinetic (PK) parameters were evaluated on Day 1 when the adolescents were on half the randomized dose (i.e., 10 mg and 30 mg). From Day 15 (±2 days), adolescent participants were dose-escalated to receive the randomized doses of 20 mg and 60 mg. Hence, PK data evaluated for adolescents is after administration of bitopertin at the doses of 10 and 30 mg.

Note: Considering only one subject was evaluable in the bitopertin 60-mg arm, range (min-max) is selected as the precision/dispersion type.

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

End point timeframe:

Day 1

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 1 | | |
| Units: ng*h/mL | | | | |
| arithmetic mean (full range (min-max)) | 693 (530 to 970) | 2570 (2570 to 2570) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma bitopertin concentrations in adolescents at Day 1

| End point title | Plasma bitopertin concentrations in adolescents at Day 1 |
|---|---|

End point description:

Plasma bitopertin concentration was evaluated on Day 1 when the adolescents were on half the randomized dose (i.e., 10 mg and 30 mg). From Day 15 (±2 days), adolescent participants were dose-escalated to receive the randomized doses of 20 mg and 60 mg. Hence, plasma bitopertin concentration on Day 1, for adolescents, is after administration of bitopertin at the doses of 10 and 30 mg.

Note: Considering only one subject was evaluable in the bitopertin 60-mg arm, range (min-max) is selected as the precision/dispersion type.

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

End point timeframe:

Day 1

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 1 | | |
| Units: ng/mL | | | | |
| arithmetic mean (full range (min-max)) | | | | |
| 0 h | 0.00 (0.00 to 0.00) | 0.00 (0.00 to 0.00) | | |
| 2 h | 65.2 (52.2 to 81.3) | 135 (135 to 135) | | |
| 4 h | 41.2 (29.4 to 60.1) | 145 (145 to 145) | | |
| 6 h | 31.9 (23.2 to 47.0) | 121 (121 to 121) | | |

| | | | | |
|---|---|---|---|---|
| 24 h | 16.4 (11.6 to 22.2) | 77.9 (77.9 to 77.9) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma bitopertin concentrations in adolescents at Day 29

| End point title | Plasma bitopertin concentrations in adolescents at Day 29 |
|---|---|

End point description:

Note: Considering only one subject was evaluable in the bitopertin 60-mg arm, range (min-max) is selected as the precision/dispersion type.

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

End point timeframe:

Day 29

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3[1] | 1 | | |
| Units: ng/mL | | | | |
| arithmetic mean (full range (min-max)) | | | | |
| 0 h | 112 (82.2 to 142) | 461 (461 to 461) | | |
| 4 h | 191 (121 to 228) | 640 (640 to 640) | | |

Notes:

[1] - There were 2 subjects evaluated at the 0 h timepoint and 3 subjects evaluated at 4 h timepoint.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum plasma concentration (Cmax) following single oral administrations of bitopertin in adults

| End point title | Maximum plasma concentration (Cmax) following single oral administrations of bitopertin in adults |
|---|---|

End point description:

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

End point timeframe:

Day 1

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 11 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 126 (± 25.6) | 286 (± 88.3) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Observed time of the maximum drug concentration (Tmax) following single oral administrations of bitopertin in adults

| End point title | Observed time of the maximum drug concentration (Tmax) following single oral administrations of bitopertin in adults |
|---|---|

End point description:

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

End point timeframe:

Day 1

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 11 | | |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | 4.15 (± 6.56) | 2.49 (± 1.28) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: AUC from time 0 to 24 hours post-dose on Day 1 (AUC0-24) in adults

| End point title | AUC from time 0 to 24 hours post-dose on Day 1 (AUC0-24) in adults |
|---|---|

End point description:

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

End point timeframe:

Day 1

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 11 | | |
| Units: ng*h/mL | | | | |
| arithmetic mean (standard deviation) | 1570 (± 406) | 3900 (± 1330) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma bitopertin concentrations in adults at Day 1

| End point title | Plasma bitopertin concentrations in adults at Day 1 |
|---|---|

End point description:

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

End point timeframe:

Day 1

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 11 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0 h | 0.00 (± 0.00) | 0.00 (± 0.00) | | |
| 2 h | 123 (± 22.9) | 279 (± 90.8) | | |
| 4 h | 90.1 (± 23.2) | 218 (± 72.0) | | |
| 6 h | 71.5 (± 22.3) | 195 (± 73.3) | | |
| 24 h | 47.3 (± 38.8) | 107 (± 33.6) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma bitopertin concentrations in adults at Day 29

| End point title | Plasma bitopertin concentrations in adults at Day 29 |
|---|---|

End point description:

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

End point timeframe:

Day 29

| End point values | Bitopertin 20 mg | Bitopertin 60 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11[2] | 11[3] | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0 h | 152 (± 63.8) | 531 (± 335) | | |
| 4 h | 249 (± 72.0) | 770 (± 309) | | |

Notes:

[2] - There were 11 subjects evaluated at the 0 h timepoint and 10 subjects evaluated at 4 h timepoint.

[3] - There were 11 subjects evaluated at the 0 h timepoint and 8 subjects evaluated at 4 h timepoint.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment phase (Up to and including Day 169)

Adverse event reporting additional description:

All safety analyses were based on the Safety Analysis Set (SAS), defined as all randomized participants who received at least one dose of study drug. Treatment-emergent AEs that began after the first administration of study drug, or existing AEs that worsened after the first dose of study drug were considered TEAEs and were analyzed.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 25.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Bitopertin 20 mg |

Reporting group description:

Subjects enrolled in Bitopertin 20 mg received two 10-mg tablets of Bitopertin

| | |
|---|---|
| Reporting group title | Bitopertin 60 mg |

Reporting group description:

Subjects enrolled in Bitopertin 60 mg will receive two 30-mg tablets of Bitopertin

| Serious adverse events | Bitopertin 20 mg | Bitopertin 60 mg | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

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

| Non-serious adverse events | Bitopertin 20 mg | Bitopertin 60 mg | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 14 (85.71%) | 12 / 12 (100.00%) | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Non-Cardiac Chest Pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Peripheral Swelling | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Reproductive system and breast disorders | | | |
| Menstruation Irregular | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Ovarian Cyst Ruptured | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Suicidal Ideation | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Gamma-Glutamyltransferase Increased | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Dizziness | | | |
| subjects affected / exposed | 9 / 14 (64.29%) | 8 / 12 (66.67%) | |
| occurrences (all) | 11 | 8 | |
| Headache | | | |
| subjects affected / exposed | 3 / 14 (21.43%) | 1 / 12 (8.33%) | |
| occurrences (all) | 3 | 1 | |
| Cluster Headache | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Disturbance In Attention | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Dizziness Exertional | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Migraine | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Sinus Headache | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye disorders | | | |
| Photophobia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 2 / 12 (16.67%) | |
| occurrences (all) | 1 | 2 | |
| Abdominal Pain Upper | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lip Dry | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Toothache | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus Ulcer | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Myofascial Pain Syndrome | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 0 / 12 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Tooth Infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 0 / 14 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 | |
| Metabolism and nutrition disorders<br>Iron Deficiency<br>subjects affected / exposed<br>occurrences (all) | 1 / 14 (7.14%)<br>1 | 0 / 12 (0.00%)<br>0 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 10 April 2023 | Primary endpoint updated to include whole blood metal free-PPIX levels. Secondary endpoints were updated to Erythrocyte metal-free PPIX concentrations, plasma and whole blood total PPIX concentrations and porphyrins (metal-free whole blood PPIX, metal-free erythrocyte PPIX, whole blood total PPIX, plasma total PPIX). Changes were made regarding porphyrin assessment schedule in alignment with the schedule of assessments (SoA). Information clarified for prohibited iron medications to state that the initiation of iron supplementation (oral or intravenous) during screening or the study was disallowed. Text updated to indicate that RDW, reticulocyte %, and reticulocyte hemoglobin concentration were optional. Remote visits in text and SoA clarified. Additional language added to further describe study rationale and dose-selection rationale in adolescents. Age of adolescents revised to 12 for inclusion in the study. Inclusion criteria revised for the inclusion of adolescent participants and adjusted weight restrictions. Exclusion criteria were revised that new treatment for anemia, including initiation of iron supplementation within the 2 months prior to screening was exclusionary and to exclude any type of active hepatitis and clarify HIV status. Information on dosing schedule for adolescents added. Patient Global Impression of Severity (PGIS) added as one of the exploratory endpoints and protocol updated to include the description of PGIS assessment to the patient reported outcome section. Information updated to include "optional" for blood samples for 3 hematology assessments. Text updated to clarify that clinical laboratory samples were to be analyzed at a local laboratory, and that fasting was only required for blood sample for iron studies. Protocol was updated to include percentage of adolescents and adults to all analysis sets. Additional collection timepoints added for bodyweight/height. Information updated to clarify the dispense of the drug diary. |

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.

| |
|---|
| None reported |

Notes: