



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 Protoporphyrria (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
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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
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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
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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			
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			
Units: years			
arithmetic mean	37.0	42.0	
standard deviation	± 19.53	± 16.25	-
Gender categorical			
Units: Subjects			
Female	8	8	16
Male	6	4	10
Race			
Units: Subjects			
White	14	11	25
Asian	0	1	1
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	14	12	26
Time to prodrome			
Units: Subjects			
<30 minutes	7	6	13
≥ 30 minutes	7	6	13
Erythropoietic protoporphyria/X-linked			

protoporphyria Subgroup			
Units: Subjects			
Erythropoietic protoporphyria	14	11	25
X-linked protoporphyria	0	1	1
Weight			
Units: Kg			
arithmetic mean	78.09	79.50	
standard deviation	± 12.745	± 21.017	-
BMI			
Units: Kg/m ²			
arithmetic mean	27.45	27.78	
standard deviation	± 4.753	± 8.414	-
Whole Blood Metal-Free PPIX			
Units: ng/mL			
arithmetic mean	10337.9	8143.8	
standard deviation	± 7303.43	± 6505.42	-
Whole Blood Total PPIX			
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 (\pm 33.51)	209.85 (\pm 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
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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
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End point description:

End point type	Secondary
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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: 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
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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
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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
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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
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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)		
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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
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	Bitopertin 20 mg
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Reporting group description:

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

Reporting group title	Bitopertin 60 mg
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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 occurrences (all)	0 / 14 (0.00%) 0	1 / 12 (8.33%) 1	
Peripheral Swelling subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 12 (0.00%) 0	
Reproductive system and breast disorders Menstruation Irregular subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 12 (8.33%) 1	
Ovarian Cyst Ruptured subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 12 (8.33%) 1	
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 12 (0.00%) 0	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 12 (0.00%) 0	
Insomnia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 12 (0.00%) 0	
Suicidal Ideation subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 12 (0.00%) 0	
Investigations Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 12 (8.33%) 1	
Gamma-Glutamyltransferase Increased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 12 (8.33%) 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 occurrences (all)	0 / 14 (0.00%) 0	1 / 12 (8.33%) 1	
Metabolism and nutrition disorders Iron Deficiency subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 12 (0.00%) 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: