



Clinical trial results:

Phase III, Multi-Center, Randomized, 12-Week, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate Efficacy and Safety of RO4917838 in Patients With Sub-Optimally Controlled Symptoms of Schizophrenia Treated With Antipsychotics Followed by a 40-Week Double-Blind, Parallel-Group, Placebo-Controlled Treatment Period Summary

EudraCT number	2010-020616-11
Trial protocol	DE ES LT LV SK NL
Global end of trial date	04 July 2014

Results information

Result version number	v1 (current)
This version publication date	19 November 2016
First version publication date	19 November 2016

Trial information

Trial identification

Sponsor protocol code	WN25306
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01235585
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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	04 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 July 2014
Global end of trial reached?	Yes
Global end of trial date	04 July 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This was a phase III, multi-center, randomized, 12-week, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of bitopertin (RO4917838) in participants with sub-optimally controlled symptoms of schizophrenia treated with anti-psychotics, followed by a 44-week double-blind, parallel-group, placebo-controlled treatment period (40-week treatment period followed by a 4-week washout period).

The primary objectives of the study were as follows:

1. To evaluate the efficacy after 12 weeks of treatment with bitopertin versus placebo as adjunct to antipsychotics, in the Positive and Negative Syndrome Scale (PANSS) positive symptom factor score in participants with sub-optimally controlled symptoms of schizophrenia;
2. To evaluate the safety and tolerability after 12 weeks of treatment with bitopertin versus placebo as adjunct to antipsychotics, in participants with sub-optimally controlled symptoms of schizophrenia.

Protection of trial subjects:

The study was conducted in accordance with the principles of "Declaration of Helsinki" and Good Clinical Practice according to the regulations and procedures consistent with the protocol. Approval from Institutional Review Board (IRB) / Ethics Committee (EC) was obtained before study start and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval. An approval from the relevant regulatory authority was also obtained prior to the start of study. All the protocol amendments were submitted to IRB/EC and to the regulatory authorities in accordance with the local regulatory requirements. A written informed consent was obtained from the participants and care givers prior to the participation in the study. All new safety information that resulted in significant changes in the risk/benefit assessment were reviewed and updated in the informed consent form, as necessary. Consent to the expanded pharmacokinetics (PK) assessments and long-term extension period was also obtained from the participants and caregivers, as necessary.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 42
Country: Number of subjects enrolled	Slovakia: 14
Country: Number of subjects enrolled	Spain: 21

Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Latvia: 4
Country: Number of subjects enrolled	Lithuania: 36
Country: Number of subjects enrolled	Turkey: 22
Country: Number of subjects enrolled	Ukraine: 45
Country: Number of subjects enrolled	Canada: 42
Country: Number of subjects enrolled	United States: 177
Country: Number of subjects enrolled	Brazil: 122
Country: Number of subjects enrolled	Chile: 22
Country: Number of subjects enrolled	Taiwan: 17
Worldwide total number of subjects	588
EEA total number of subjects	141

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)	569
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study included 2 treatment periods, Treatment Period 1 (12-Week double blind treatment) and Treatment Period 2 (44-week double blind treatment), and Long Term Extension Period (for 3 years).

Pre-assignment

Screening details:

A total of 597 participants were randomized to receive treatment, 5 participants were randomized to another bitopertin study first and not included in safety population. A further 4 participants were not treated, and therefore, 588 participants were available in safety population. All participants received antipsychotic treatment at baseline.

Period 1

Period 1 title	Treatment Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Bitopertin 5 mg

Arm description:

Participants received bitopertin 5 milligrams (mg) oral tablet once a day (QD) for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bitopertin 5 mg oral tablet QD in the morning, with or without food.

Arm title	Bitopertin 10 mg
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Arm description:

Participants received bitopertin 10 mg oral tablet QD for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bitopertin 10 mg oral tablet QD in the morning, with or without food.

Arm title	Placebo
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Arm description:

Participants received placebo-matched to bitopertin QD for 12 weeks.

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo-matched to bitopertin 5 or 10 mg oral tablet QD in the morning, with or without food.

Number of subjects in period 1	Bitopertin 5 mg	Bitopertin 10 mg	Placebo
Started	195	200	193
Completed	170	175	159
Not completed	25	25	34
Consent withdrawn by subject	3	8	8
Protocol violation	4	1	3
Death	-	-	1
Adverse event	9	9	11
Non-compliance	3	5	2
Administrative/Other	3	-	1
Lost to follow-up	3	2	8

Period 2

Period 2 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Bitoperin 5 mg

Arm description:

Participants received bitopertin 5 mg oral tablet QD from Week 13 to Week 52.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bitopertin 5 mg oral tablet QD in the morning, with or without food.

Arm title	Bitopertin 10 mg
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Arm description:

Participants received bitopertin 10 mg oral tablet QD from Week 13 to Week 52.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bitopertin 10 mg oral tablet QD in the morning, with or without food.

Arm title	Placebo
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Arm description:

Participants received placebo-matched to bitopertin from Week 13 to Week 52.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo-matched to bitopertin 5 or 10 mg oral tablet QD in the morning, with or without food.

Number of subjects in period 2	Bitoperin 5 mg	Bitopertin 10 mg	Placebo
Started	167	173	159
Completed	79	89	84
Not completed	88	84	75
Consent withdrawn by subject	7	10	9
Protocol violation	-	3	3
Adverse event	8	10	9
Non-compliance	3	2	2
Administrative/Other	64	55	51
Lost to follow-up	4	2	1
Lack of efficacy	2	2	-

Period 3

Period 3 title	Washout Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
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Arm title	Bitopertin 5 mg
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Arm description:

Participants received bitopertin 5 mg oral tablet QD during the 4-week washout period (Week 52 to Week 56).

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bitopertin 5 mg oral tablet QD in the morning, with or without food.

Arm title	Bitopertin 5 mg to Placebo
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Arm description:

Participants received matching placebo to bitopertin during the 4-week washout period (Week 52 to Week 56).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo-matched to bitopertin oral tablet QD in the morning, with or without food.

Arm title	Bitopertin 10 mg
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Arm description:

Participants received bitopertin 10 mg oral tablet QD during the 4-week washout period (Week 52 to Week 56).

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bitopertin 10 mg oral tablet QD in the morning, with or without food.

Arm title	Bitopertin 10 mg to Placebo
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Arm description:

Participants received matching placebo to bitopertin during the 4-week washout period (Week 52 to Week 56).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo-matched to bitopertin oral tablet QD in the morning, with or without food.

Arm title	Placebo
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Arm description:

Participants received matching placebo to bitopertin during the 4-week washout period (Week 52 to Week 56).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to bitopertin 5 or 10 mg oral tablet QD in the morning, with or without food.

Number of subjects in period 3	Bitopertin 5 mg	Bitopertin 5 mg to Placebo	Bitopertin 10 mg
Started	39	40	44
Completed	39	34	43
Not completed	0	6	1
Consent withdrawn by subject	-	1	-
Death	-	-	-
Non-compliance	-	2	-
Administrative/Other	-	3	1

Number of subjects in period 3	Bitopertin 10 mg to Placebo	Placebo
Started	43	81
Completed	43	77
Not completed	0	4
Consent withdrawn by subject	-	-
Death	-	1
Non-compliance	-	1
Administrative/Other	-	2

Period 4

Period 4 title	Long-Term Extension
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
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Arm title	Placebo to Bitopertin 10 mg
Arm description: Participants received bitopertin 10 mg oral tablet QD up to 3 years.	
Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Bitopertin 10 mg oral tablet QD up to 3 years, with or without food.	
Arm title	Bitopertin 5 mg to Bitopertin 10 mg
Arm description: Participants received bitopertin 10 mg oral tablet QD up to 3 years.	
Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Bitopertin 10 mg oral tablet QD up to 3 years, with or without food.	
Arm title	Bitopertin 10 mg
Arm description: Participants received bitopertin 10 mg oral tablet QD up to 3 years.	
Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Bitopertin 10 mg oral tablet QD up to 3 years, with or without food.	

Number of subjects in period 4	Placebo to Bitopertin 10 mg	Bitopertin 5 mg to Bitopertin 10 mg	Bitopertin 10 mg
Started	70	62	74
Completed	0	0	0
Not completed	70	62	74
Consent withdrawn by subject	3	1	5
Protocol violation	1	-	1
Adverse event	1	3	5
Administrative/Other	64	57	62
Lost to follow-up	-	-	1
Lack of efficacy	1	1	-

Period 5

Period 5 title	Safety Follow-up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Bitopertin 5 mg

Arm description:

All participants who withdrew early from the study or whose treatment was discontinued during the Long-Term Extension received bitopertin 5 mg QD, for 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bitopertin 5 mg oral tablet QD in the morning, with or without food.

Arm title	Bitopertin 10 mg
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Arm description:

All participants who withdrew early from the study or whose treatment was discontinued during the Long-Term Extension received bitopertin 10 mg QD, for 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bitopertin 10 mg oral tablet QD in the morning, with or without food.

Arm title	Placebo
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Arm description:

All participants who withdrew early from the study or whose treatment was discontinued during the Long-Term Extension received placebo-matched to bitopertin, for 4 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo-matched to bitopertin 5 or 10 mg oral tablet QD in the morning, with or without food.

Number of subjects in period 5	Bitopertin 5 mg	Bitopertin 10 mg	Placebo
Started	133	332	123
Completed	88	281	85
Not completed	45	51	38
Consent withdrawn by subject	16	15	15
Death	-	-	1
Adverse event	1	3	5
Administrative/Other	9	10	2
Lost to follow-up	19	23	15

Baseline characteristics

Reporting groups

Reporting group title	Bitopertin 5 mg
Reporting group description:	
Participants received bitopertin 5 milligrams (mg) oral tablet once a day (QD) for 12 weeks.	
Reporting group title	Bitopertin 10 mg
Reporting group description:	
Participants received bitopertin 10 mg oral tablet QD for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo-matched to bitopertin QD for 12 weeks.	

Reporting group values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo
Number of subjects	195	200	193
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	43.4	40.7	41.9
standard deviation	± 12.2	± 12.6	± 12.3
Gender categorical			
Units: Subjects			
Female	71	55	60
Male	124	145	133

Reporting group values	Total		
Number of subjects	588		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	186		
Male	402		

End points

End points reporting groups

Reporting group title	Bitopertin 5 mg
Reporting group description: Participants received bitopertin 5 milligrams (mg) oral tablet once a day (QD) for 12 weeks.	
Reporting group title	Bitopertin 10 mg
Reporting group description: Participants received bitopertin 10 mg oral tablet QD for 12 weeks.	
Reporting group title	Placebo
Reporting group description: Participants received placebo-matched to bitopertin QD for 12 weeks.	
Reporting group title	Bitopertin 5 mg
Reporting group description: Participants received bitopertin 5 mg oral tablet QD from Week 13 to Week 52.	
Reporting group title	Bitopertin 10 mg
Reporting group description: Participants received bitopertin 10 mg oral tablet QD from Week 13 to Week 52.	
Reporting group title	Placebo
Reporting group description: Participants received placebo-matched to bitopertin from Week 13 to Week 52.	
Reporting group title	Bitopertin 5 mg
Reporting group description: Participants received bitopertin 5 mg oral tablet QD during the 4-week washout period (Week 52 to Week 56).	
Reporting group title	Bitopertin 5 mg to Placebo
Reporting group description: Participants received matching placebo to bitopertin during the 4-week washout period (Week 52 to Week 56).	
Reporting group title	Bitopertin 10 mg
Reporting group description: Participants received bitopertin 10 mg oral tablet QD during the 4-week washout period (Week 52 to Week 56).	
Reporting group title	Bitopertin 10 mg to Placebo
Reporting group description: Participants received matching placebo to bitopertin during the 4-week washout period (Week 52 to Week 56).	
Reporting group title	Placebo
Reporting group description: Participants received matching placebo to bitopertin during the 4-week washout period (Week 52 to Week 56).	
Reporting group title	Placebo to Bitopertin 10 mg
Reporting group description: Participants received bitopertin 10 mg oral tablet QD up to 3 years.	
Reporting group title	Bitopertin 5 mg to Bitopertin 10 mg
Reporting group description: Participants received bitopertin 10 mg oral tablet QD up to 3 years.	
Reporting group title	Bitopertin 10 mg
Reporting group description: Participants received bitopertin 10 mg oral tablet QD up to 3 years.	
Reporting group title	Bitopertin 5 mg

Reporting group description:

All participants who withdrew early from the study or whose treatment was discontinued during the Long-Term Extension received bitopertin 5 mg QD, for 4 weeks.

Reporting group title	Bitopertin 10 mg
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Reporting group description:

All participants who withdrew early from the study or whose treatment was discontinued during the Long-Term Extension received bitopertin 10 mg QD, for 4 weeks.

Reporting group title	Placebo
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Reporting group description:

All participants who withdrew early from the study or whose treatment was discontinued during the Long-Term Extension received placebo-matched to bitopertin, for 4 weeks.

Subject analysis set title	Bitopertin 5 mg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants received bitopertin 5 mg oral tablet QD in the morning with/without food for 12 weeks (Week 0 to Week 12) in Treatment Period 1 and for 40 weeks (Week 13 to Week 52) in Treatment Period 2.

Subject analysis set title	Bitopertin 10 mg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants received bitopertin 10 mg oral tablet QD in the morning with/without food for 12 weeks (Week 0 to Week 12) in Treatment Period 1 and for 40 weeks (Week 13 to Week 52) in Treatment Period 2.

Subject analysis set title	Placebo
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants received placebo-matched to bitopertin taken QD in the morning with/without food for 12 weeks (Week 0 to Week 12) in Treatment Period 1 and for 40 weeks (Week 13 to Week 52) in Treatment Period 2.

Subject analysis set title	ITT Population
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All randomized participants who received at least 1 dose of double-blind study medication and had at least 1 post-baseline assessment of the primary efficacy variable.

Primary: Mean Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Positive Symptoms Factor Score (PSFS) at Week 12

End point title	Mean Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Positive Symptoms Factor Score (PSFS) at Week 12
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End point description:

The PANSS is a 30-item scale designed to capture the degree of severity for many symptoms in schizophrenia. The symptoms are rated on a 7-point scale capturing 1= Absent to 7=Extreme psychopathology. Each item of the PANSS is rated on a 7-point scale, on the basis of the following anchors: 1= Absent; 2= Minimal; 3= Mild; 4= Moderate; 5= Moderately severe; 6= Severe; 7= Extreme. Further assessment of symptoms using a factor analysis of the PANSS was calculated for PSFS which consists of the following items (Delusions [P1], Hallucinatory behavior [P3], Grandiosity [P5], Suspiciousness [P6], Stereotyped thinking [N7], Somatic concern [G1], Unusual thought content [G9] and Lack of judgment and insight [G12]). Scores were transformed to 0 to 6 points with higher scores indicating greater severity of symptoms. If any item score contributing to the factor score is missing, then the factor will be set to missing.

ITT population.

End point type	Primary
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End point timeframe:

Baseline, Week 12

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	186	
Units: units on a scale				
least squares mean (confidence interval 95%)	-4.53 (-5.13 to -3.93)	-4.16 (-4.75 to -3.57)	-4.59 (-5.2 to -3.98)	

Statistical analyses

Statistical analysis title	PANSS PSFS : Placebo versus Bitopertin 5 mg
Statistical analysis description:	
Estimates were from analysis based on Mixed-Effect Model Repeated Measure (MMRM) using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week	
Comparison groups	Bitopertin 5 mg v Placebo
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8823
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	0.92
Variability estimate	Standard error of the mean
Dispersion value	0.434

Statistical analysis title	PANSS PSFS : Placebo versus Bitopertin 10 mg
Statistical analysis description:	
Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week	
Comparison groups	Bitopertin 10 mg v Placebo
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3117
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	1.28
Variability estimate	Standard error of the mean
Dispersion value	0.431

Secondary: Mean Change from Baseline in PANSS Total Score at Week 12

End point title	Mean Change from Baseline in PANSS Total Score at Week 12
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End point description:

The PANSS is a 30-item scale designed to capture the degree of severity for many symptoms in schizophrenia. The symptoms are rated on a 7-point scale capturing 1= Absent to 7= Extreme psychopathology. Each item of the PANSS is rated on a 7-point scale, on the basis of the following anchors: 1= Absent; 2= Minimal; 3= Mild; 4= Moderate; 5= Moderately severe; 6= Severe; 7= Extreme. The total PANSS sum score of all the items ranges from 30 to 210. Higher score indicates greater severity of symptoms. The assessment for each of the 30 items were provided in the electronic case report form to allow calculation of a total score describing overall symptomatology as well as scores for positive, negative, and general psychopathology. If any item score contributing to the factor score is missing, then the factor will be set to missing.
ITT population.

End point type	Secondary
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End point timeframe:

Baseline, Week 12

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	186	
Units: units on a scale				
least squares mean (confidence interval 95%)	-11.41 (-12.99 to -9.83)	-10.5 (-12.06 to -8.95)	-12.1 (-13.7 to -10.49)	

Statistical analyses

Statistical analysis title	PANSS Total Score: Placebo versus Bitopertin 5 mg
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Statistical analysis description:

Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week

Comparison groups	Bitopertin 5 mg v Placebo
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5499
Method	Mixed-Effect Model Repeated Measures
Parameter estimate	Adjusted Mean Difference
Point estimate	0.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	2.94
Variability estimate	Standard error of the mean
Dispersion value	1.147

Statistical analysis title	PANSS Total Score: Placebo versus Bitopertin 10 mg
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Statistical analysis description:

Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment +Treatment * Week

Comparison groups	Bitopertin 10 mg v Placebo
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1625
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	3.83
Variability estimate	Standard error of the mean
Dispersion value	1.139

Secondary: Mean Change from Baseline in PANSS Subscale Score at Week 12

End point title	Mean Change from Baseline in PANSS Subscale Score at Week 12
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End point description:

The PANSS is a 30-item scale designed to capture the degree of severity for many symptoms in schizophrenia. PANSS subscales include positive subscale (PSS), negative subscale (NSS) and general psychopathology subscale (GPSS). Negative and positive subscales includes 7-items each and general psychopathology subscale includes 16 items. Each item is rated on a scale from 1 (symptom not present) to 7 (symptoms extremely severe). Total negative and positive scores= 7 to 49 each, with higher score indicating greater severity and total general psychopathology score= 16 to 112, with higher score indicating greater severity. If any item score contributing to the factor score is missing, then the factor will be set to missing.

ITT population.

End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	186	
Units: units on a scale				
least squares mean (confidence interval 95%)				
PANSS Positive Subscale Score	-4.43 (-5.01 to -3.84)	-4.13 (-4.7 to -3.55)	-4.42 (-5.02 to -3.83)	
PANSS Negative Subscale Score	-1.97 (-2.45 to -1.48)	-1.72 (-2.19 to -1.24)	-2.07 (-2.56 to -1.57)	
PANSS General Psychopathology Subscale Score	-5 (-5.84 to -4.16)	-4.71 (-5.53 to -3.88)	-5.65 (-6.51 to -4.79)	

Statistical analyses

Statistical analysis title	PSS: Placebo versus Bitopertin 5 mg
Statistical analysis description:	
Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.	
Comparison groups	Bitopertin 5 mg v Placebo
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9927 ^[1]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	0.83
Variability estimate	Standard error of the mean
Dispersion value	0.425

Notes:

[1] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	PSS: Placebo versus Bitopertin 10 mg
Statistical analysis description:	
Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.	
Comparison groups	Placebo v Bitopertin 10 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4831 ^[2]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	1.12
Variability estimate	Standard error of the mean
Dispersion value	0.422

Notes:

[2] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	NSS: Placebo versus Biopertin 5 mg
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Statistical analysis description:

Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.

Comparison groups	Bitopertin 5 mg v Placebo
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7797 ^[3]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.1

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.59
upper limit	0.79
Variability estimate	Standard error of the mean
Dispersion value	0.352

Notes:

[3] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	NSS: Placebo versus Bitopertin 10 mg
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Statistical analysis description:

Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.

Comparison groups	Bitopertin 10 mg v Placebo
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3141 ^[4]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.35

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.33
upper limit	1.04
Variability estimate	Standard error of the mean
Dispersion value	0.349

Notes:

[4] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	GPSS: Placebo versus Bitopertin 5 mg
Statistical analysis description:	
Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.	
Comparison groups	Bitopertin 5 mg v Placebo
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2883 ^[5]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	1.85
Variability estimate	Standard error of the mean
Dispersion value	0.61

Notes:

[5] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	GPSS: Placebo versus Bitopertin 10 mg
Statistical analysis description:	
Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.	
Comparison groups	Bitopertin 10 mg v Placebo
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1197 ^[6]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	2.13
Variability estimate	Standard error of the mean
Dispersion value	0.606

Notes:

[6] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Secondary: Mean Change from Baseline in PANSS Symptom Factor Score at Week 12

End point title	Mean Change from Baseline in PANSS Symptom Factor Score at Week 12
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End point description:

The PANSS is a 30-item scale designed to capture the degree of severity for many symptoms in schizophrenia. PANSS factor score included negative symptoms factor (NSF) score (7-items), disorganized thought/cognition factor (DT/CF) score (7-items), anxiety/depression factor (A/DF) score (4-items), and uncontrolled hostility/excitement factor (UH/EF) score (4-items). Each item is rated on a scale from 1 (symptom not present) to 7 (symptoms extremely severe). Total negative symptoms and disorganized thought/cognition factor scores = 1 to 7 each, with higher score indicating greater severity and total anxiety/depression factor score and uncontrolled hostility/excitement scores = 1 to 4 each, with higher score indicating greater severity. If any item score contributing to the factor score is missing, then the factor will be set to missing.

ITT population.

End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	186	
Units: units on a scale				
least squares mean (confidence interval 95%)				
PANSS Negative Symptom Factor Score	-2.04 (-2.55 to -1.53)	-1.91 (-2.41 to -1.41)	-2.11 (-2.63 to -1.59)	
PANSS Disorganized Thoughts/Cognition Factor Score	-2.01 (-2.43 to -1.59)	-1.95 (-2.37 to -1.53)	-2.38 (-2.81 to -1.95)	
PANSS Anxiety/Depression Factor Score	-1.46 (-1.81 to -1.11)	-1.63 (-1.97 to -1.28)	-1.77 (-2.13 to -1.41)	
PANSS Hostility/Excitement Factor Score	-1.38 (-1.71 to -1.05)	-0.97 (-1.29 to -0.65)	-1.34 (-1.67 to -1)	

Statistical analyses

Statistical analysis title	NSF: Placebo versus Bitopertin 5 mg
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Statistical analysis description:

Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.

Comparison groups	Bitopertin 5 mg v Placebo
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8568 ^[7]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	0.79

Variability estimate	Standard error of the mean
Dispersion value	0.37

Notes:

[7] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	NSF: Placebo versus Bitopertin 10 mg
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Statistical analysis description:

Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.

Comparison groups	Bitopertin 10 mg v Placebo
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5899 [8]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	0.92
Variability estimate	Standard error of the mean
Dispersion value	0.367

Notes:

[8] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	DT/CF: Placebo versus Bitopertin 5 mg
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Statistical analysis description:

Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week

Comparison groups	Placebo v Bitopertin 5 mg
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2311 [9]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.97
Variability estimate	Standard error of the mean
Dispersion value	0.307

Notes:

[9] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	DT/CF: Placebo versus Bitopertin 10 mg
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Statistical analysis description:

Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.

Comparison groups	Bitopertin 10 mg v Placebo
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.1616
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	1.03
Variability estimate	Standard error of the mean
Dispersion value	0.305

Notes:

[10] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	A/DF: Placebo versus Bitopertin 5 mg
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Statistical analysis description:

Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.

Comparison groups	Bitopertin 5 mg v Placebo
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2215 ^[11]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.81
Variability estimate	Standard error of the mean
Dispersion value	0.255

Notes:

[11] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	A/DF: Placebo versus Bitopertin 10 mg
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Statistical analysis description:

Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.

Comparison groups	Bitopertin 10 mg v Placebo
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Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5816 ^[12]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.64
Variability estimate	Standard error of the mean
Dispersion value	0.253

Notes:

[12] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	UH/EF: Placebo versus Bitopertin 5 mg
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Statistical analysis description:

Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.

Comparison groups	Bitopertin 5 mg v Placebo
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8515 ^[13]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.42
Variability estimate	Standard error of the mean
Dispersion value	0.238

Notes:

[13] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	UH/EF: Placebo versus Bitopertin 10 mg
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Statistical analysis description:

Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.

Comparison groups	Placebo v Bitopertin 10 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1192 ^[14]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.83
Variability estimate	Standard error of the mean
Dispersion value	0.237

Notes:

[14] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Secondary: Percentage of Participants with a 20% or Greater Improvement in PANSS PSFS at Week 12

End point title	Percentage of Participants with a 20% or Greater Improvement in PANSS PSFS at Week 12
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End point description:

PANSS: 30-item scale designed to capture degree of severity for many symptoms in schizophrenia. Symptoms are rated on 7-point scale capturing 1= Absent to 7= Extreme psychopathology. Each item rated on 7-point scale on basis of following anchors: 1= Absent; 2= Minimal; 3= Mild; 4= Moderate; 5= Moderately severe; 6= Severe; 7= Extreme. Further assessment of symptoms using factor analysis of PANSS was calculated for PSFS which consists of following items (Delusions [P1], Hallucinatory behavior [P3], Grandiosity [P5], Suspiciousness [P6], Stereotyped thinking [N7], Somatic concern [G1], Unusual thought content [G9] and Lack of judgment and insight [G12]). Scores were transformed to 0 to 6 points with higher scores indicating greater severity of symptoms. If any item score contributing to factor score is missing, then factor will be set to missing. A PANSS 20% responder was defined as participant who had reduction from baseline of at least 20% in PANSS PSFS at Week 12.

ITT population.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	186	
Units: percentage of participants				
number (not applicable)	55.6	51.3	53.8	

Statistical analyses

Statistical analysis title	Placebo versus Bitopertin 5 mg
Comparison groups	Bitopertin 5 mg v Placebo
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7571 ^[15]
Method	Cochran-Mantel-Haenszel

Notes:

[15] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline as stratification variables.

Statistical analysis title	Placebo versus Bitopertin 10 mg
Comparison groups	Bitopertin 10 mg v Placebo
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.623 ^[16]
Method	Cochran-Mantel-Haenszel

Notes:

[16] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline as stratification variables.

Secondary: Percentage of Participants with a 20% or Greater Improvement in PANSS PSFS At Least at Two Out of the Three Last Post-Baseline Assessments

End point title	Percentage of Participants with a 20% or Greater Improvement in PANSS PSFS At Least at Two Out of the Three Last Post-Baseline Assessments
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End point description:

PANSS: 30-item scale designed to capture degree of severity for many symptoms in schizophrenia. The symptoms are rated on 7-point scale capturing 1= absent to 7=extreme psychopathology. Each item of PANSS rated on 7-point scale on basis of following anchors: 1= Absent; 2= Minimal; 3= Mild; 4= Moderate; 5= Moderately severe; 6= Severe; 7= Extreme. Further assessment of symptoms using factor analysis of PANSS was calculated for PSFS which consists of following items (Delusions [P1], Hallucinatory behavior [P3], Grandiosity [P5], Suspiciousness [P6], Stereotyped thinking [N7], Somatic concern [G1], Unusual thought content [G9] and Lack of judgment and insight [G12]). Scores were transformed to 0 to 6 points with higher scores indicating greater severity of symptoms. A PANSS 20% responder was defined as a participant who had a reduction from baseline of at least 20% in the PANSS PSFS at least at two of three last post-baseline assessments during the initial 12 weeks.

ITT population.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	186	
Units: percentage of participants				
number (not applicable)	39	37.7	39.2	

Statistical analyses

Statistical analysis title	Placebo versus Bitopertin 5 mg
Comparison groups	Placebo v Bitopertin 5 mg
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9606 ^[17]
Method	Cochran-Mantel-Haenszel

Notes:

[17] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline as stratification variables.

Statistical analysis title	Placebo versus Bitopertin 10 mg
Comparison groups	Placebo v Bitopertin 10 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8088 [18]
Method	Cochran-Mantel-Haenszel

Notes:

[18] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline as stratification variables.

Secondary: Percentage of Participants with a Rating of Either 'Much' or 'Very Much' Improvement in Clinical Global Impression-Improvement (CGI-I) Overall Rating Score at Week 12

End point title	Percentage of Participants with a Rating of Either 'Much' or 'Very Much' Improvement in Clinical Global Impression-Improvement (CGI-I) Overall Rating Score at Week 12
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End point description:

The CGI-I is used to assess the clinical change as compared to symptoms at baseline using a 7-point scale that requires the clinician to assess how much the participant's illness has improved or worsened relative to a baseline state at the beginning of the intervention. The CGI-I score ranges from 1-7, where 1= very much improved; 2= much improved; 3= minimally improved; 4= no change; 5= minimally worse; 6= much worse; or 7= very much worse. Percentage of participants with a rating of either 'Much' or 'Very Much' improvement in CGI-I overall rating score at Week 12 is reported.

ITT population. Here, Number of subjects analyzed = number of participants analyzed for this endpoint.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	185	
Units: percentage of participants				
number (not applicable)	15.5	15.7	16.8	

Statistical analyses

Statistical analysis title	Placebo versus Bitopertin 5 mg
Comparison groups	Bitopertin 5 mg v Placebo

Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7275 ^[19]
Method	Cochran-Mantel-Haenszel

Notes:

[19] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline as stratification variables.

Statistical analysis title	Placebo versus Bitopertin 10 mg
Comparison groups	Bitopertin 10 mg v Placebo
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7534 ^[20]
Method	Cochran-Mantel-Haenszel

Notes:

[20] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline as stratification variables.

Secondary: Percentage of Participants with a Rating of Either 'Much' or 'Very Much' Improvement in CGI-I Overall Rating Score At Least at Two of the Three Last Post-Baseline Assessments

End point title	Percentage of Participants with a Rating of Either 'Much' or 'Very Much' Improvement in CGI-I Overall Rating Score At Least at Two of the Three Last Post-Baseline Assessments
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End point description:

The CGI-I is used to assess the clinical change as compared to symptoms at baseline using a 7-point scale that requires the clinician to assess how much the participant's illness has improved or worsened relative to a baseline state at the beginning of the intervention. The CGI-I score ranges from 1-7, where 1= very much improved; 2= much improved; 3= minimally improved; 4= no change; 5= minimally worse; 6= much worse; or 7= very much worse. Percentage of participants with a rating of either 'Much' or 'Very Much' improvement in CGI-I overall rating score at least at two out of the three last post-baseline assessments during the initial 12 weeks is reported.

ITT population. Here, Number of subjects analyzed = number of participants analyzed for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	185	
Units: percentage of participants				
number (not applicable)	10.7	10.5	10.8	

Statistical analyses

Statistical analysis title	Placebo versus Bitopertin 5 mg
Comparison groups	Bitopertin 5 mg v Placebo

Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9503 ^[21]
Method	Cochran-Mantel-Haenszel

Notes:

[21] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline as stratification variables.

Statistical analysis title	Placebo versus Bitopertin 10 mg
Comparison groups	Placebo v Bitopertin 10 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8778 ^[22]
Method	Cochran-Mantel-Haenszel

Notes:

[22] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline as stratification variables.

Secondary: Percentage of Participants with a Rating of Either 'Much' or 'Very Much' Improvement in CGI-I Positive Symptom Rating Score at Week 12

End point title	Percentage of Participants with a Rating of Either 'Much' or 'Very Much' Improvement in CGI-I Positive Symptom Rating Score at Week 12
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End point description:

The CGI-I is used to assess the clinical change as compared to symptoms at baseline using a 7-point scale that requires the clinician to assess how much the participant's illness has improved or worsened relative to a baseline state at the beginning of the intervention. The CGI-I score ranges from 1-7, where 1= very much improved; 2= much improved; 3= minimally improved; 4= no change; 5= minimally worse; 6= much worse; or 7= very much worse. Percentage of participants with a rating of either 'Much' or 'Very Much' improvement in CGI-I positive symptom rating score at Week 12 is reported. ITT population. Here, Number of subjects analyzed = number of participants analyzed for this endpoint.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	185	
Units: percentage of participants				
number (not applicable)	18.7	19.4	18.9	

Statistical analyses

Statistical analysis title	Placebo versus Bitopertin 5 mg
Comparison groups	Placebo v Bitopertin 5 mg

Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9331 ^[23]
Method	Cochran-Mantel-Haenszel

Notes:

[23] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline as stratification variables.

Statistical analysis title	Placebo versus Bitopertin 10 mg
Comparison groups	Placebo v Bitopertin 10 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9727 ^[24]
Method	Cochran-Mantel-Haenszel

Notes:

[24] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline as stratification variables.

Secondary: Percentage of Participants with a Rating of Either 'Much' or 'Very Much' Improvement in CGI-I Positive Symptom Rating Score At Least at Two of the Three Last Post-Baseline Assessments

End point title	Percentage of Participants with a Rating of Either 'Much' or 'Very Much' Improvement in CGI-I Positive Symptom Rating Score At Least at Two of the Three Last Post-Baseline Assessments
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End point description:

The CGI-I is used to assess the clinical change as compared to symptoms at baseline using a 7-point scale that requires the clinician to assess how much the participant's illness has improved or worsened relative to a baseline state at the beginning of the intervention. The CGI-I score ranges from 1-7, where 1= very much improved; 2= much improved; 3= minimally improved; 4= no change; 5= minimally worse; 6= much worse; or 7= very much worse. Percentage of participants with a rating of either 'Much' or 'Very Much' improvement in CGI-I positive symptom rating score at least at two out of the three last post-baseline assessments during the initial 12 weeks is reported.

ITT population. Here, Number (No.) of subjects analyzed = number of participants (pts) analyzed for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	185	
Units: percentage of participants				
number (not applicable)	12.8	14.7	13	

Statistical analyses

Statistical analysis title	Placebo versus Bitopertin 5 mg
Comparison groups	Bitopertin 5 mg v Placebo
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9501 ^[25]
Method	Cochran-Mantel-Haenszel

Notes:

[25] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline as stratification variables.

Statistical analysis title	Placebo versus Bitopertin 10 mg
Comparison groups	Bitopertin 10 mg v Placebo
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6807 ^[26]
Method	Cochran-Mantel-Haenszel

Notes:

[26] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline as stratification variables.

Secondary: Percentage of Participants With at Least 20% Improvement From Baseline in the PANSS PSFS and With a CGI-I Positive Symptoms Rating of Either 'Much' or 'Very Much' Improved at Week 12

End point title	Percentage of Participants With at Least 20% Improvement From Baseline in the PANSS PSFS and With a CGI-I Positive Symptoms Rating of Either 'Much' or 'Very Much' Improved at Week 12
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End point description:

PANSS: 30-item scale designed to capture degree of severity for many symptoms in schizophrenia. Symptoms are rated on 7-point scale capturing 1= Absent to 7= Extreme psychopathology. Each item rated on 7-point scale on basis of following anchors: 1= Absent; 2= Minimal; 3= Mild; 4= Moderate; 5= Moderately severe; 6= Severe; 7= Extreme. Assessment of symptoms using factor analysis of PANSS was calculated for PSFS which consists of items (Delusions [P1], Hallucinatory behavior [P3], Grandiosity [P5], Suspiciousness [P6], Stereotyped thinking [N7], Somatic concern [G1], Unusual thought content [G9] and Lack of judgment and insight [G12]). Scores were transformed to 0 to 6 points with higher scores indicating greater severity of symptoms. CGI-I is used to assess the clinical change as compared to symptoms at baseline using 7-point scale, score ranges from 1-7, where 1= very much improved to 7= very much worse.

ITT population. No. of subjects analyzed= no. of pts analyzed for the endpoint.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	185	
Units: percentage of participants				
number (not applicable)	18.2	17.8	17.3	

Statistical analyses

Statistical analysis title	Placebo versus Bitopertin 5 mg
Comparison groups	Bitopertin 5 mg v Placebo
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8342 [27]
Method	Cochran-Mantel-Haenszel

Notes:

[27] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline was used as stratification variable.

Statistical analysis title	Placebo versus Bitopertin 10 mg
Comparison groups	Placebo v Bitopertin 10 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9463 [28]
Method	Cochran-Mantel-Haenszel

Notes:

[28] - Unadjusted p-value with region and type of primary antipsychotic background medication at baseline was used as stratification variable.

Secondary: Mean Change from Baseline in Clinical Global Impression – Severity (CGI-S) Overall Symptoms Rating Score at Week 12

End point title	Mean Change from Baseline in Clinical Global Impression – Severity (CGI-S) Overall Symptoms Rating Score at Week 12
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End point description:

The CGI-S reflects the severity of illness on a 7-point scale that requires the clinician to rate the severity of the participant's illness at the time of assessment. Participant was assessed on severity of mental illness at the time of rating 1= normal, not at all ill; 2= borderline mentally ill; 3= mildly ill; 4= moderately ill; 5= markedly ill; 6= severely ill; or 7= extremely ill. The improvement in symptoms is represented by negative values.

ITT population.

End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	186	
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.51 (-0.62 to -0.41)	-0.46 (-0.56 to -0.36)	-0.57 (-0.68 to -0.46)	

Statistical analyses

Statistical analysis title	Placebo versus Bitopertin 5 mg
Statistical analysis description:	
Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.	
Comparison groups	Bitopertin 5 mg v Placebo
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4353 ^[29]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.21
Variability estimate	Standard error of the mean
Dispersion value	0.076

Notes:

[29] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	Placebo versus Bitopertin 10 mg
Statistical analysis description:	
Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.	
Comparison groups	Placebo v Bitopertin 10 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1404 ^[30]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.26

Variability estimate	Standard error of the mean
Dispersion value	0.075

Notes:

[30] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Secondary: Mean Change from Baseline in CGI-S Positive Symptoms Rating Score at Week 12

End point title	Mean Change from Baseline in CGI-S Positive Symptoms Rating Score at Week 12
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End point description:

The CGI-S reflects the severity of illness on a 7-point scale that requires the clinician to rate the severity of the participant's illness at the time of assessment. Participant was assessed on severity of mental illness at the time of rating 1= normal, not at all ill; 2= borderline mentally ill; 3= mildly ill; 4= moderately ill; 5= markedly ill; 6= severely ill; 7= extremely ill. The improvement in symptoms is represented by negative values.

ITT population.

End point type	Secondary
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End point timeframe:

Baseline, Week 12

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	186	
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.61 (-0.72 to -0.5)	-0.56 (-0.66 to -0.45)	-0.6 (-0.71 to -0.49)	

Statistical analyses

Statistical analysis title	Placebo versus Bitopertin 5 mg
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Statistical analysis description:

Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.

Comparison groups	Placebo v Bitopertin 5 mg
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8853 ^[31]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.078

Notes:

[31] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	Placebo versus Bitopertin 10 mg
Statistical analysis description: Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.	
Comparison groups	Bitopertin 10 mg v Placebo
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5668 ^[32]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.078

Notes:

[32] - Unadjusted p-values for pairwise comparisons with placebo were presented.

Secondary: Mean Change from Baseline in Personal and Social Performance (PSP) Total Score at Week 12

End point title	Mean Change from Baseline in Personal and Social Performance (PSP) Total Score at Week 12
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End point description:

The PSP scale assesses degree of a participant's dysfunction within 4 domains of behavior: socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behavior. Score ranges from 1 to 100, divided into 10 equal intervals to rate degree of difficulty ('1= absent' to '6= very severe') in each of the 4 domains. Based on 4 domains there will be one total score. Participants with score of 71 to 100 have mild degree of difficulty; from 31 to 70 have varying degrees of disability; less than or equal to 30 have functioning so poorly as to require intensive supervision. ITT population.

End point type	Secondary
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End point timeframe:

Baseline, Week 12

End point values	Bitopertin 5 mg	Bitopertin 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	191	186	
Units: units on a scale				
least squares mean (confidence interval 95%)	6.04 (4.86 to 7.22)	5.42 (4.26 to 6.59)	5.53 (4.33 to 6.74)	

Statistical analyses

Statistical analysis title	Placebo versus Bitopertin 5 mg
Statistical analysis description: Estimates were from analysis based on MMRM using unstructured covariance matrix. Change = Baseline + Week + Treatment + Treatment * Week.	
Comparison groups	Bitopertin 5 mg v Placebo
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5583 ^[33]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	2.19
Variability estimate	Standard error of the mean
Dispersion value	0.858

Notes:

[33] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Statistical analysis title	Placebo versus Bitopertin 10 mg
Comparison groups	Bitopertin 10 mg v Placebo
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8955 ^[34]
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Adjusted Mean Difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.78
upper limit	1.56
Variability estimate	Standard error of the mean
Dispersion value	0.851

Notes:

[34] - Unadjusted p-value for pairwise comparisons with placebo was presented.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Safety follow-up period (approximately 4 years)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	Bitopertin 5 mg – Treatment Period
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Reporting group description:

Participants received bitopertin 5 mg oral tablet QD in the morning with/without food for 12 weeks (Week 0 to Week 12) in Treatment Period 1 and for 40 weeks (Week 13 to Week 52) in Treatment Period 2.

Reporting group title	Bitopertin 10 mg – Treatment Period
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Reporting group description:

Participants received bitopertin 10 mg oral tablet QD in the morning with/without food for 12 weeks (Week 0 to Week 12) in Treatment Period 1 and for 40 weeks (Week 13 to Week 52) in Treatment Period 2.

Reporting group title	Placebo – Treatment Period
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Reporting group description:

Participants received placebo-matched to bitopertin taken QD in the morning with/without food for 12 weeks (Week 0 to Week 12) in Treatment Period 1 and for 40 weeks (Week 13 to Week 52) in Treatment Period 2.

Reporting group title	Bitopertin 5 mg – Washout Period
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Reporting group description:

Participants received bitopertin 5 mg oral tablet QD during the 4-week washout period (Week 52 to Week 56).

Reporting group title	Bitopertin 5 mg to Placebo - Washout Period
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Reporting group description:

Participants received matching placebo to bitopertin during the 4-week washout period (Week 52 to Week 56).

Reporting group title	Bitopertin 10 mg - Washout Period
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Reporting group description:

Participants received bitopertin 10 mg oral tablet QD during the 4-week washout period (Week 52 to Week 56).

Reporting group title	Bitopertin 10 mg to Placebo – Washout Period
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Reporting group description:

Participants received matching placebo to bitopertin during the 4-week washout period (Week 52 to Week 56).

Reporting group title	Placebo – Washout Period
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Reporting group description:

Participants received matching placebo to bitopertin during the 4-week washout period (Week 52 to Week 56).

Reporting group title	Placebo to Bitopertin 10 mg – Long-Term Extension
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Reporting group description:

Participants received bitopertin 10 mg oral tablet QD, up to 3 years.

Reporting group title	Bitopertin 5 mg to Bitopertin 10 mg - Long-Term Extension
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Reporting group description:

Participants received bitopertin 10 mg oral tablet QD up to 3 years.

Reporting group title	Bitopertin 10 mg - Long-Term Extension
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Reporting group description:

Participants received bitopertin 10 mg oral tablet QD up to 3 years.

Reporting group title	Bitopertin 5 mg - Safety Follow-up Period
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Reporting group description:

All participants who withdrew early from the study or whose treatment was discontinued during the Long-Term Extension received bitopertin 5 mg QD, for 4 weeks.

Reporting group title	Bitopertin 10 mg - Safety Follow-up Period
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Reporting group description:

All participants who withdrew early from the study or whose treatment was discontinued during the Long-Term Extension received bitopertin 10 mg QD, for 4 weeks.

Reporting group title	Placebo - Safety Follow-up Period
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Reporting group description:

All participants who withdrew early from the study or whose treatment was discontinued during the Long-Term Extension received placebo-matched to bitopertin, for 4 weeks.

Serious adverse events	Bitopertin 5 mg - Treatment Period	Bitopertin 10 mg - Treatment Period	Placebo - Treatment Period
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 195 (3.59%)	7 / 200 (3.50%)	15 / 193 (7.77%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	1 / 193 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	0 / 195 (0.00%)	1 / 200 (0.50%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 195 (0.51%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mood altered			
subjects affected / exposed	0 / 195 (0.00%)	1 / 200 (0.50%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 195 (0.00%)	1 / 200 (0.50%)	5 / 193 (2.59%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	2 / 195 (1.03%)	1 / 200 (0.50%)	3 / 193 (1.55%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 195 (0.51%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 195 (0.51%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal behaviour			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			

subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	1 / 193 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	1 / 193 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	2 / 193 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Parkinsonism			
subjects affected / exposed	1 / 195 (0.51%)	0 / 200 (0.00%)	0 / 193 (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
Ischaemic Stroke			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	1 / 193 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 195 (0.51%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 195 (0.00%)	1 / 200 (0.50%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 200 (0.50%)	2 / 193 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal abscess			

subjects affected / exposed	0 / 195 (0.00%)	1 / 200 (0.50%)	0 / 193 (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
Mastitis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	1 / 193 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess sweat gland			
subjects affected / exposed	0 / 195 (0.00%)	0 / 200 (0.00%)	0 / 193 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Bitopertin 5 mg – Washout Period	Bitopertin 5 mg to Placebo – Washout Period	Bitopertin 10 mg – Washout Period
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mood altered			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal behaviour			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			

subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Parkinsonism			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal abscess			

subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastitis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess sweat gland			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Bitopertin 10 mg to Placebo – Washout Period	Placebo – Washout Period	Placebo to Bitopertin 10 mg – Long-Term Extension
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	1 / 81 (1.23%)	4 / 70 (5.71%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mood altered			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	2 / 70 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal behaviour			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			

subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 43 (0.00%)	1 / 81 (1.23%)	0 / 70 (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
Nervous system disorders			
Parkinsonism			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal abscess			

subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess sweat gland			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Bitopertin 5 mg to Bitopertin 10 mg - Long-Term Extension	Bitopertin 10 mg - Long-Term Extension	Bitopertin 5 mg - Safety Follow-up Period
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 62 (4.84%)	6 / 74 (8.11%)	1 / 133 (0.75%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mood altered			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 62 (1.61%)	2 / 74 (2.70%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	1 / 62 (1.61%)	2 / 74 (2.70%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 62 (0.00%)	2 / 74 (2.70%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal behaviour			
subjects affected / exposed	1 / 62 (1.61%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Agitation			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Parkinsonism			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			

subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 62 (0.00%)	1 / 74 (1.35%)	0 / 133 (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
Scrotal abscess			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess sweat gland			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Bitopertin 10 mg – Safety Follow-up Period	Placebo – Safety Follow-up Period	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 332 (1.20%)	5 / 123 (4.07%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	0 / 332 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mood altered			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 332 (0.30%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	3 / 332 (0.90%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 332 (0.30%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abnormal behaviour			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	0 / 332 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Parkinsonism			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			

subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 332 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 332 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 332 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			

subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess sweat gland			
subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Bitopertin 5 mg – Treatment Period	Bitopertin 10 mg – Treatment Period	Placebo – Treatment Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 195 (27.18%)	50 / 200 (25.00%)	45 / 193 (23.32%)
Investigations			
Weight increased			
subjects affected / exposed	5 / 195 (2.56%)	7 / 200 (3.50%)	11 / 193 (5.70%)
occurrences (all)	5	7	11
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 195 (9.74%)	11 / 200 (5.50%)	6 / 193 (3.11%)
occurrences (all)	25	13	6
Somnolence			

subjects affected / exposed occurrences (all)	9 / 195 (4.62%) 10	10 / 200 (5.00%) 10	7 / 193 (3.63%) 9
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0	0 / 200 (0.00%) 0	0 / 193 (0.00%) 0
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	9 / 195 (4.62%) 10	13 / 200 (6.50%) 15	10 / 193 (5.18%) 10
Insomnia subjects affected / exposed occurrences (all)	11 / 195 (5.64%) 11	11 / 200 (5.50%) 13	10 / 193 (5.18%) 11
Schizophrenia subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0	0 / 200 (0.00%) 0	0 / 193 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	13 / 195 (6.67%) 14	11 / 200 (5.50%) 11	11 / 193 (5.70%) 13

Non-serious adverse events	Bitopertin 5 mg – Washout Period	Bitopertin 5 mg to Placebo - Washout Period	Bitopertin 10 mg - Washout Period
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 39 (0.00%)	2 / 40 (5.00%)	0 / 44 (0.00%)
Investigations Weight increased subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 40 (0.00%) 0	0 / 44 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 40 (0.00%) 0	0 / 44 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 40 (0.00%) 0	0 / 44 (0.00%) 0
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 40 (0.00%) 0	0 / 44 (0.00%) 0
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 40 (0.00%) 0	0 / 44 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 40 (0.00%) 0	0 / 44 (0.00%) 0
Schizophrenia subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 40 (0.00%) 0	0 / 44 (0.00%) 0
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 40 (5.00%) 2	0 / 44 (0.00%) 0

Non-serious adverse events	Bitopertin 10 mg to Placebo – Washout Period	Placebo – Washout Period	Placebo to Bitopertin 10 mg – Long-Term Extension
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 43 (0.00%)	1 / 81 (1.23%)	7 / 70 (10.00%)
Investigations			
Weight increased subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 81 (0.00%) 0	0 / 70 (0.00%) 0
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 81 (0.00%) 0	0 / 70 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 81 (0.00%) 0	0 / 70 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 81 (0.00%) 0	1 / 70 (1.43%) 1
Psychiatric disorders			

Anxiety			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Schizophrenia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 81 (0.00%)	2 / 70 (2.86%)
occurrences (all)	0	0	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 81 (1.23%)	4 / 70 (5.71%)
occurrences (all)	0	1	4

Non-serious adverse events	Bitopertin 5 mg to Bitopertin 10 mg - Long-Term Extension	Bitopertin 10 mg - Long-Term Extension	Bitopertin 5 mg - Safety Follow-up Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 62 (9.68%)	10 / 74 (13.51%)	0 / 133 (0.00%)
Investigations			
Weight increased			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 62 (0.00%)	4 / 74 (5.41%)	0 / 133 (0.00%)
occurrences (all)	0	4	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 62 (0.00%)	0 / 74 (0.00%)	0 / 133 (0.00%)
occurrences (all)	0	0	0
Insomnia			

subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	0 / 74 (0.00%) 0	0 / 133 (0.00%) 0
Schizophrenia subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 3	5 / 74 (6.76%) 5	0 / 133 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 5	2 / 74 (2.70%) 2	0 / 133 (0.00%) 0

Non-serious adverse events	Bitopertin 10 mg – Safety Follow-up Period	Placebo – Safety Follow-up Period	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 332 (0.00%)	0 / 123 (0.00%)	
Investigations Weight increased subjects affected / exposed occurrences (all)	0 / 332 (0.00%) 0	0 / 123 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 332 (0.00%) 0	0 / 123 (0.00%) 0	
Somnolence subjects affected / exposed occurrences (all)	0 / 332 (0.00%) 0	0 / 123 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 332 (0.00%) 0	0 / 123 (0.00%) 0	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 332 (0.00%) 0	0 / 123 (0.00%) 0	
Insomnia subjects affected / exposed occurrences (all)	0 / 332 (0.00%) 0	0 / 123 (0.00%) 0	
Schizophrenia			

subjects affected / exposed occurrences (all)	0 / 332 (0.00%) 0	0 / 123 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 332 (0.00%) 0	0 / 123 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 September 2010	Version B: <ul style="list-style-type: none"> - Addition of Liver enzymes (aspartate aminotransferase or alanine aminotransferase at or above 3x upper limit of normal (ULN), or bilirubin at above 2x ULN to the exclusion criteria. - Editorial clarification for secondary objective time point for safety and tolerability. - Addition of text to clarify processes around participant randomization. - Minor changes to schedule of assessments for physical examination, Clinical Global Impression - Improvement, and electrocardiogram. - A new table was created to clarify visits in long-term extension.
21 April 2011	Version C: <ul style="list-style-type: none"> - More details on the long-term extension were provided following the request from Health Authorities. - Exploratory objectives, safety, efficacy and pharmacoeconomic endpoints were updated for the long-term extension period. - Inclusion of Food and Drug Administration requirements for analysis of iron inclusion bodies. - Entry criteria for treatment period 2 and long-term extension were updated. - Local urine pregnancy testing was amended to be performed at randomization. - For participants requiring psycho-social and/or rehabilitative therapies during treatment period, the protocol was amended to include this after treatment period 1 was complete. - Video Enhancement of Rater Interviewing for Independent Evaluation of Data was included in the description of system for PANSS. - Inclusion and exclusion criteria were updated. Reporting of Adverse Events were amended. Overall risk and benefit assessment added. - Clarified on restricted and prohibited concomitant medication. Administrative changes were updated.
20 February 2012	Version D: <ul style="list-style-type: none"> - Addition of biomarker defined subpopulations as a secondary objective. - Clarification of timing of screening and prospective stabilization period. - Clarification of exclusionary hemoglobin criterion in males from 13 to 12 grams per deciliter, body mass index of less than 18.5 or greater than 40 kilograms per square meter, wash out times for depot and long acting antipsychotics, and updated the requirements for past use of clozapine. - Updated dosing of concomitant antipsychotics for inclusion criteria. - The definition of caregiver in the inclusion criteria was revised. - Added eszopiclone (Lunesta) to the list of restricted medications. - Additional follow-up for treatment withdrawal and at Week-52 initiation of washout, and clarification of withdrawal process. - Included description of an exploratory electrophysiological biomarker substudy to evaluate the effects of adjunctive RO4917838 treatment on neurocognitive deficits and assess candidate electrophysiological biomarkers in participants with schizophrenia. - New guidance was added regarding withdrawal for hepatic abnormalities. - Administrative changes were reported.
30 May 2012	Version D-1 (Country Specific): <ul style="list-style-type: none"> - Modification of the Caregiver Burden Assessment/Questionnaire. - The Schizophrenia Caregiver Questionnaire added the caregiver global impression scale to evaluate participant's severity of illness and change in severity of illness over time from a caregiver's perspective.

01 November 2012	Version E: - This version E combined the approach for Modification of the Caregiver Burden Assessment/Questionnaire in Version D and D-1. - Inclusion of fertility analysis. - Addition of biomarker defined subpopulation: complement factor H-related protein 1 high subgroup to the objectives. - Change in data safety monitoring board to independent data monitoring committee. - Modification to exclusion criteria relevant to body mass index. - Addition of 12-lead electrocardiogram assessment in long-term extension. - Changes in serious adverse event reporting, definition of safety population, and length of study. - Removal of per protocol population. - Administrative changes were reported.
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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.

Results of many secondary endpoints were not reported as the study was terminated early due to failure in demonstration of adjunctive therapy with bitopertin in primary endpoint.
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Notes: