Clinical trial results:
A Phase III, Multi-Center, Randomized, 24 Week, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate Efficacy and Safety of Bitopertin in Stable Patients With Persistent, Predominant Negative Symptoms of Schizophrenia Treated With Antipsychotics Followed by a 28 Week, Double-Blind Treatment Period

Summary

EudraCT number	2010-020470-42
Trial protocol	CZ IT BG
Global end of trial date	08 July 2014

Results information

Result version number	v1 (current)
This version publication date	18 June 2016
First version publication date	18 June 2016

Trial information

Trial identification

Sponsor protocol code	WN25308

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01192880
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	21 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 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, 24 week, double-blind, parallel-group, placebo-controlled study to evaluate efficacy and safety of bitopertin (RO4917838) in stable participants with persistent, predominant negative symptoms of schizophrenia treated with anti-psychotics followed by a 28-week, double-blind placebo-controlled treatment period.

Protection of trial subjects:

The investigator ensured that this study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study fully adhered to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it afforded greater protection to the participant. For studies conducted in the European Union/European Economic Area (EU/EEA) countries, the investigator ensured compliance with the EU Clinical Trial Directive [2001/20/EC].For studies conducted in the United States of America (USA) or under US Investigational New Drug (IND), the investigator additionally ensured adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of21 Code of Federal Regulations (CFR), subchapter D, part 312, "Responsibilities of sponsors and Investigators",part 50, "Protection of Human Patients", and part 56, "Institutional Review Boards".

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 92
Country: Number of subjects enrolled	Czech Republic: 91
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	China: 229
Country: Number of subjects enrolled	Russian Federation: 18
Country: Number of subjects enrolled	United States: 86
Country: Number of subjects enrolled	Japan: 80
Worldwide total number of subjects	620
EEA total number of subjects	207

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)	615
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening period was up to 30 days before the first dose of study drug.

Period 1

Period 1 title	Overall Study (overall period)
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	Placebo-Treatment Period 1

Arm description:

Matching oral placebo doses (10 milligrams [mg] or 20 mg) in the morning with/without food adjunct to stable antipsychotic treatment for 24 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:

Oral dose of placebo tablet in the morning with/without food.

Arm title	Bitopertin 10 mg-Treatment Period 1

Arm description:

Oral doses of 10 mg bitopertin tablet in the morning with/without food adjunct to stable antipsychotic treatment for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral dose of bitopertin tablet in the morning with/without food.

Arm title	Bitopertin 20 mg-Treatment Period 1

Arm description:

Oral doses of 20 mg bitopertin tablet in the morning with/without food during adjunct to stable antipsychotic treatment for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral dose of bitopertin tablet in the morning with/without food.

Arm title	Placebo-Treatment Period 2

Arm description:

Matching oral placebo doses (10 mg or 20 mg) in the morning with/without food adjunct to stable antipsychotic treatment for 28 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:

Oral dose of placebo tablet in the morning with/without food.

Arm title	Bitopertin 10 mg-Treatment Period 2

Arm description:

Oral doses of 10 mg bitopertin tablet in the morning with/without food adjunct to stable antipsychotic treatment for 28 weeks.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral dose of bitopertin tablet in the morning with/without food.

Arm title	Bitopertin 20 mg-Treatment Period 2

Arm description:

Oral doses of 20 mg bitopertin tablet in the morning with/without food during adjunct to stable antipsychotic treatment for 28 weeks.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral dose of bitopertin tablet in the morning with/without food.

Arm title	Placebo-Washout Period

Arm description:

Matching oral placebo doses (10 mg or 20 mg) in the morning with/without food adjunct to stable antipsychotic treatment 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:

Oral dose of placebo tablet in the morning with/without food.

Arm title	Bitopertin 10 mg-Washout Period

Arm description:

Oral doses of 10 mg bitopertin tablet in the morning with/without food adjunct to stable antipsychotic treatment for 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral dose of bitopertin tablet in the morning with/without food.

Arm title	Bitopertin 10 mg to Placebo-Washout Period

Arm description:

Bitopertin 10 mg switched to placebo for duration of washout period; adjunct to stable antipsychotic treatment 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:

Oral dose of placebo tablet in the morning with/without food.

Arm title	Bitopertin 20 mg-Washout Period

Arm description:

Oral doses of 20 mg bitopertin tablet in the morning with/without food during adjunct to stable antipsychotic treatment for 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral dose of bitopertin tablet in the morning with/without food.

Arm title	Bitopertin 20 mg to Placebo-Washout Period

Arm description:

Bitopertin 20 mg switched to placebo for duration of washout period; adjunct to stableantipsychotic treatment 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:

Oral dose of placebo tablet in the morning with/without food.

Arm title	Placebo to Bitopertin 10 mg-LTE Period

Arm description:

Placebo during previous periods: switched to bitopertin 10 mg adjunct to stableantipsychotic treatment up to 3 years.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral dose of bitopertin tablet in the morning with/without food.

Arm title	Bitopertin 10 mg-LTE Period

Arm description:

Bitopertin 10 mg adjunct to stable antipsychotic treatment for up to 3 years.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral dose of bitopertin tablet in the morning with/without food.

Arm title	Bitopertin 20 mg-LTE Period

Arm description:

Bitopertin 20 mg adjunct to stable antipsychotic treatment for up to 3 years.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral dose of bitopertin tablet in the morning with/without food.

Arm title	Placebo – Safety Follow-up Period

Arm description:

Participants who were on placebo treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Bitopertin 10 mg – Safety Follow-up Period

Arm description:

Participants who were on bitopertin 10 mg treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Bitopertin 20 mg – Safety Follow-up Period

Arm description:

Participants who were on bitopertin 20 mg treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Placebo-Treatment Period 1	Bitopertin 10 mg-Treatment Period 1	Bitopertin 20 mg-Treatment Period 1
Started	206	206	208
Completed	170	166	163
Not completed	36	40	45
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	7	6	7
Adverse event, non-fatal	12	9	6
Protocol violation	-	1	2
Administrative/other	5	9	13
Non-compliance	5	9	5
Unspecified	-	-	-
Lost to follow-up	3	5	8
Lack of efficacy	4	1	3

Number of subjects in period 1	Placebo-Treatment Period 2	Bitopertin 10 mg-Treatment Period 2	Bitopertin 20 mg-Treatment Period 2
Started	162	160	157
Completed	114	117	114
Not completed	48	43	43
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	3	4	3
Adverse event, non-fatal	6	1	5
Protocol violation	-	-	-
Administrative/other	34	34	31
Non-compliance	2	4	2
Unspecified	-	-	-
Lost to follow-up	3	-	-
Lack of efficacy	-	-	1

Number of subjects in period 1	Placebo-Washout Period	Bitopertin 10 mg-Washout Period	Bitopertin 10 mg to Placebo-Washout Period
Started	113	57	58

Completed	110	54	56
Not completed	3	3	2
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	-	-
Protocol violation	-	-	-
Administrative/other	2	1	2
Non-compliance	1	1	-
Unspecified	-	-	-
Lost to follow-up	-	-	-
Lack of efficacy	-	-	-

Number of subjects in period 1	Bitopertin 20 mg-Washout Period	Bitopertin 20 mg to Placebo-Washout Period	Placebo to Bitopertin 10 mg-LTE Period
Started	56	57	94
Completed	55	57	0
Not completed	1	0	94
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	-	5
Adverse event, non-fatal	-	-	6
Protocol violation	-	-	-
Administrative/other	1	-	76
Non-compliance	-	-	4
Unspecified	-	-	1
Lost to follow-up	-	-	-
Lack of efficacy	-	-	2

Number of subjects in period 1	Bitopertin 10 mg-LTE Period	Bitopertin 20 mg-LTE Period	Placebo – Safety Follow-up Period
Started	102	98	113
Completed	0	0	74
Not completed	102	98	39
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	7	4	11
Adverse event, non-fatal	6	4	1
Protocol violation	-	-	-
Administrative/other	87	83	11
Non-compliance	2	4	-
Unspecified	-	-	-
Lost to follow-up	-	1	16
Lack of efficacy	-	2	-

Number of subjects in period 1	Bitopertin 10 mg – Safety Follow-up Period	Bitopertin 20 mg – Safety Follow-up Period
Started	299	208
Completed	251	158
Not completed	48	50
Adverse event, serious fatal	-	2
Consent withdrawn by subject	18	19
Adverse event, non-fatal	4	2
Protocol violation	-	-
Administrative/other	8	8
Non-compliance	-	-
Unspecified	-	-
Lost to follow-up	18	19
Lack of efficacy	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	620	620	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	38		
standard deviation	± 12.4	-	
Gender categorical Units: Subjects			
Female	230	230	
Male	390	390	

End points

End points reporting groups

Reporting group title	Placebo-Treatment Period 1
Reporting group description:	
Matching oral placebo doses (10 milligrams [mg] or 20 mg) in the morning with/without food adjunct to stable antipsychotic treatment for 24 weeks.	
Reporting group title	Bitopertin 10 mg-Treatment Period 1
Reporting group description:	
Oral doses of 10 mg bitopertin tablet in the morning with/without food adjunct to stable antipsychotic treatment for 24 weeks.	
Reporting group title	Bitopertin 20 mg-Treatment Period 1
Reporting group description:	
Oral doses of 20 mg bitopertin tablet in the morning with/without food during adjunct to stable antipsychotic treatment for 24 weeks.	
Reporting group title	Placebo-Treatment Period 2
Reporting group description:	
Matching oral placebo doses (10 mg or 20 mg) in the morning with/without food adjunct to stable antipsychotic treatment for 28 weeks.	
Reporting group title	Bitopertin 10 mg-Treatment Period 2
Reporting group description:	
Oral doses of 10 mg bitopertin tablet in the morning with/without food adjunct to stable antipsychotic treatment for 28 weeks.	
Reporting group title	Bitopertin 20 mg-Treatment Period 2
Reporting group description:	
Oral doses of 20 mg bitopertin tablet in the morning with/without food during adjunct to stable antipsychotic treatment for 28 weeks.	
Reporting group title	Placebo-Washout Period
Reporting group description:	
Matching oral placebo doses (10 mg or 20 mg) in the morning with/without food adjunct to stable antipsychotic treatment for 4 weeks.	
Reporting group title	Bitopertin 10 mg-Washout Period
Reporting group description:	
Oral doses of 10 mg bitopertin tablet in the morning with/without food adjunct to stable antipsychotic treatment for 4 weeks.	
Reporting group title	Bitopertin 10 mg to Placebo-Washout Period
Reporting group description:	
Bitopertin 10 mg switched to placebo for duration of washout period; adjunct to stable antipsychotic treatment for 4 weeks.	
Reporting group title	Bitopertin 20 mg-Washout Period
Reporting group description:	
Oral doses of 20 mg bitopertin tablet in the morning with/without food during adjunct to stable antipsychotic treatment for 4 weeks.	
Reporting group title	Bitopertin 20 mg to Placebo-Washout Period
Reporting group description:	
Bitopertin 20 mg switched to placebo for duration of washout period; adjunct to stableantipsychotic treatment for 4 weeks.	
Reporting group title	Placebo to Bitopertin 10 mg-LTE Period
Reporting group description:	
Placebo during previous periods: switched to bitopertin 10 mg adjunct to stableantipsychotic treatment up to 3 years.	
Reporting group title	Bitopertin 10 mg-LTE Period
Reporting group description:	
Bitopertin 10 mg adjunct to stable antipsychotic treatment for up to 3 years.	

Reporting group title	Bitopertin 20 mg-LTE Period

Reporting group description:

Bitopertin 20 mg adjunct to stable antipsychotic treatment for up to 3 years.

Reporting group title	Placebo – Safety Follow-up Period

Reporting group description:

Participants who were on placebo treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment.

Reporting group title	Bitopertin 10 mg – Safety Follow-up Period

Reporting group description:

Participants who were on bitopertin 10 mg treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment.

Reporting group title	Bitopertin 20 mg – Safety Follow-up Period

Reporting group description:

Participants who were on bitopertin 20 mg treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment.

Primary: Mean Change From Baseline in Positive and Negative Symptom Scales (PANSS) Negative Symptom Factor Score (NSFS) at Week 24

End point title	Mean Change From Baseline in Positive and Negative Symptom Scales (PANSS) Negative Symptom Factor Score (NSFS) at Week 24[1]

End point description:

The PANSS is a 30-item medical scale used for measuring symptom severity of participants with schizophrenia. The NSFS assesses negative symptoms associated with schizophrenia. The 7 items make up the NSFS are blunted affect, emotional withdrawal, poor rapport,passive/apathetic social withdrawal, lack of spontaneity, flow of conversation, motor retardation and active social avoidance. Each item was rated on a scale from 1 (absent) to 7 (extreme). Total NSFS score ranged from 7 to 49; higher score indicating greater severity of negative symptom psychopathology. Intent to Treat (ITT) Population: Included all randomized participants who received at least 1 dose of double-blind study drug and had at least 1 post-baseline assessment for primary efficacy variable was considered for this analysis. For all analyses of PANSS data the scores were transformed to 0-6 points to express "absent" as 0. Change from baseline in NSFS at Week 24 is reported .

End point type	Primary

End point timeframe:

Baseline, Week 24

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The baseline period arms include treatment period 1 arms (placebo-treatment period 1, bitopertin 10 mg-treatment period 1, and bitopertin 20 mg-treatment period 1) and statistics for these arms is reported.

End point values	Placebo-Treatment Period 1	Bitopertin 10 mg-Treatment Period 1	Bitopertin 20 mg-Treatment Period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201	198	199	
Units: units on a scale				
least squares mean (standard error)	-5.52 (± 0.341)	-5.46 (± 0.344)	-5.32 (± 0.346)	

Statistical analyses

Statistical analysis title	Statistical analysis I

Statistical analysis description:

Primary analysis population was ITT population. For all analyses of PANSS data, scores were transformed into 0-6 points to express “absent” as 0. Mean change from baseline in PANSS NSFS at Week 24 was analyzed using an MMRM incorporating data collected up to 24 weeks of treatment to assess all data collected over time with consideration of the variance−covariance matrix of repeated measures. No imputations for missing data were used in primary analyses.

Comparison groups	Placebo-Treatment Period 1 v Bitopertin 10 mg-Treatment Period 1
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9008
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	1.01

Statistical analysis title	Statistical analysis II

Statistical analysis description:

Primary analysis population was ITT population. For all analyses of PANSS data, scores were transformed into 0-6 points to express “absent” as 0. Mean change from baseline in PANSS NSFS at Week 24 was analyzed using an MMRM incorporating data collected up to 24 weeks of treatment to assess all data collected over time with consideration of the variance−covariance matrix of repeated measures. No imputations for missing data were used in primary analyses.

Comparison groups	Placebo-Treatment Period 1 v Bitopertin 20 mg-Treatment Period 1
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6844
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	1.15

Secondary: Mean Change From Baseline in Personal and Social Performance (PSP) Total Score at Week 24

End point title	Mean Change From Baseline in Personal and Social Performance (PSP) Total Score at Week 24[2]

End point description:

The PSP scale was designed to assess the degree of dysfunction a participant exhibits within 4 domains of behavior: a) socially useful activities, b) personal and social relationships, c) self-care, and d) disturbing and aggressive behavior, each rated on 6-point scale (1=absent to 6=very severe). Total transformed score from 1 to 100 is generated from raw score based on clinical interpretation of scores generated in 4 areas of functioning. A score lying between 71 and 100 indicated a good functioning; one between 31 and 70 indicated varying degrees of difficulty, and a score of <=30 indicated functioning so poor that participant required intensive supervision. ITT population was considered for the analysis. Here, number of participants analyzed signifies participants with baseline and at least one post baseline assessment for this endpoint. Change from baseline in NSFS at Week 24 is reported.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The baseline period arms include treatment period 1 arms (placebo-treatment period 1, bitopertin 10 mg-treatment period 1, and bitopertin 20 mg-treatment period 1) and statistics for these arms is reported.

End point values	Placebo-Treatment Period 1	Bitopertin 10 mg-Treatment Period 1	Bitopertin 20 mg-Treatment Period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201	197	199	
Units: units on a scale				
least squares mean (standard error)	8.04 (± 0.761)	9 (± 0.769)	7.83 (± 0.77)	

Statistical analyses

Statistical analysis title	Statistical analysis I

Statistical analysis description:

Primary analysis population was ITT population. Mean change from baseline in PSP total score at Week 24 was analyzed using an MMRM incorporating data collected up to 24 weeks of treatment to assess all data collected over time with consideration of the variance−covariance matrix of repeated measures. No imputations for missing data were used in primary analyses.

Comparison groups	Placebo-Treatment Period 1 v Bitopertin 10 mg-Treatment Period 1
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3763
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.96

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	3.08

Statistical analysis title	Statistical analysis II

Statistical analysis description:

Primary analysis population was ITT population. Mean change from baseline in PSP total score at Week 24 was analyzed using an MMRM incorporating data collected up to 24 weeks of treatment to assess all data collected over time with consideration of the variance−covariance matrix of repeated measures. No imputations for missing data were used in primary analyses.

Comparison groups	Placebo-Treatment Period 1 v Bitopertin 20 mg-Treatment Period 1
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8476
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.34
upper limit	1.92

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening to 4 weeks after the last dose of the study medication(up to 4 years)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo – Treatment Periods 1 and 2

Reporting group description:

Matching oral placebo doses (10 mg or 20 mg) in the morning with/without food adjunct to stable antipsychotic treatment for 52 weeks. Adverse event data reported are for treatment periods 1 and 2.

Reporting group title	Bitopertin 10 mg – Treatment Periods 1 and 2

Reporting group description:

Oral doses of 10 mg bitopertin tablet in the morning with/without food adjunct to stable antipsychotic treatment for 52 weeks. Adverse event data reported are for treatment periods 1 and 2.

Reporting group title	Bitopertin 20 mg – Treatment Periods 1 and 2

Reporting group description:

Oral doses of 20 mg bitopertin tablet in the morning with/without food during adjunct to stable antipsychotic treatment for 52 weeks. Adverse event data reported are for treatment periods 1 and 2.

Reporting group title	Placebo – Washout Period

Reporting group description:

Matching oral placebo doses (10 mg or 20 mg) in the morning with/without food adjunct to stable antipsychotic treatment for 4 weeks. Adverse event data reported are for washout period.

Reporting group title	Bitopertin 10 mg – Washout Period

Reporting group description:

Oral doses of 10 mg bitopertin tablet in the morning with/without food adjunct to stable antipsychotic treatment for 4 weeks. Adverse event data reported are for washout period.

Reporting group title	Bitopertin 10 mg to Placebo – Washout Period

Reporting group description:

Bitopertin 10 mg switched to placebo for duration of washout period; adjunct to stable antipsychotic treatment for 4 weeks. Adverse event data reported are for washout period.

Reporting group title	Bitopertin 20 mg – Washout Period

Reporting group description:

Oral doses of 20 mg bitopertin tablet in the morning with/without food during adjunct to stable antipsychotic treatment for 4 weeks. Adverse event data reported are for washout period.

Reporting group title	Bitopertin 20 mg to Placebo – Washout Period

Reporting group description:

Bitopertin 20 mg switched to placebo for duration of washout period; adjunct to stable antipsychotic treatment for 4 weeks. Adverse event data reported are for washout period.

Reporting group title	Placebo to Bitopertin 10 mg – LTE period

Reporting group description:

Placebo during previous periods: switched to bitopertin 10 mg adjunct to stableantipsychotic treatment up to 3 years. Adverse event data reported are for LTE period.

Reporting group title	Bitopertin 10 mg – LTE Period

Reporting group description:

Bitopertin 10 mg adjunct to stable antipsychotic treatment for up to 3 years.Adverse event data reported are for LTE period.

Reporting group title	Bitopertin 20 mg – LTE Period

Reporting group description:

Bitopertin 20 mg adjunct to stable antipsychotic treatment for up to 3 years. Adverse event data reported are for LTE period.

Reporting group title	Placebo – Safety Follow-up Period

Reporting group description:

Participants who were on placebo treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included.No intervention during this period; adjunct to stable antipsychotic treatment. Adverse event data reported are for safety follow-up period.

Reporting group title	Bitopertin 10 mg – Safety Follow-up Period

Reporting group description:

Participants who were on bitopertin 10 mg treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment. Adverse event data reported are for safety follow-up period.

Reporting group title	Bitopertin 20 mg – Safety Follow-up Period

Reporting group description:

Participants who were on bitopertin 20 mg treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment. Adverse event data reported are for safety follow-up period.

Serious adverse events	Placebo – Treatment Periods 1 and 2	Bitopertin 10 mg – Treatment Periods 1 and 2	Bitopertin 20 mg – Treatment Periods 1 and 2
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 206 (2.91%)	4 / 206 (1.94%)	6 / 208 (2.88%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chemical poisoning			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 208 (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			
Atrioventricular block first degree			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			

subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 208 (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
Myocarditis			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 208 (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			
Encephalopathy			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 208 (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			
Gastritis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 208 (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
Pancreatitis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 208 (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
Respiratory, thoracic and mediastinal disorders			
Completed suicide			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
Pneumonia aspiration			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 208 (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			
Hepatic function abnormal			

subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 208 (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
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 208 (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			
Schizophrenia			
subjects affected / exposed	2 / 206 (0.97%)	0 / 206 (0.00%)	3 / 208 (1.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 208 (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	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 208 (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
Persecutory delusion			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 208 (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
Tension			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 208 (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 / 206 (0.00%)	0 / 206 (0.00%)	0 / 208 (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			
Bronchopneumonia			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo – Washout Period	Bitopertin 10 mg – Washout Period	Bitopertin 10 mg to Placebo – Washout Period
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Chemical poisoning			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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			
Atrioventricular block first degree			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Atrioventricular block second degree			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Myocarditis			

subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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			
Encephalopathy			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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			
Gastritis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Pancreatitis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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			
Completed suicide			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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 aspiration			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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			
Hepatic function abnormal			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Hepatitis			

subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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			
Schizophrenia			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Mental disorder			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Persecutory delusion			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Tension			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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			
Bronchopneumonia			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (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 20 mg – Washout Period	Bitopertin 20 mg to Placebo – Washout Period	Placebo to Bitopertin 10 mg – LTE period
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 56 (1.79%)	0 / 57 (0.00%)	3 / 94 (3.19%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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
Chemical poisoning			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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			
Atrioventricular block first degree			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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
Atrioventricular block second degree			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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
Myocarditis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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			

Encephalopathy			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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			
Gastritis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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
Pancreatitis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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			
Completed suicide			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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 aspiration			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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			
Hepatic function abnormal			
subjects affected / exposed	1 / 56 (1.79%)	0 / 57 (0.00%)	0 / 94 (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
Hepatitis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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
Skin and subcutaneous tissue disorders			
Psoriasis			

subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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			
Schizophrenia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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 / 56 (0.00%)	0 / 57 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Persecutory delusion			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tension			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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			
Bronchopneumonia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	0 / 94 (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 – LTE Period	Bitopertin 20 mg – LTE Period	Placebo – Safety Follow-up Period
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 102 (2.94%)	1 / 98 (1.02%)	2 / 113 (1.77%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	0 / 102 (0.00%)	0 / 98 (0.00%)	0 / 113 (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
Chemical poisoning			
subjects affected / exposed	1 / 102 (0.98%)	0 / 98 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 102 (0.00%)	0 / 98 (0.00%)	0 / 113 (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
Atrioventricular block second degree			
subjects affected / exposed	0 / 102 (0.00%)	0 / 98 (0.00%)	0 / 113 (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
Myocarditis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 98 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 102 (0.98%)	0 / 98 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			

subjects affected / exposed	0 / 102 (0.00%)	0 / 98 (0.00%)	0 / 113 (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
Pancreatitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 98 (0.00%)	0 / 113 (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			
Completed suicide			
subjects affected / exposed	0 / 102 (0.00%)	0 / 98 (0.00%)	0 / 113 (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 aspiration			
subjects affected / exposed	1 / 102 (0.98%)	0 / 98 (0.00%)	0 / 113 (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
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 102 (0.00%)	1 / 98 (1.02%)	0 / 113 (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
Hepatitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 98 (0.00%)	0 / 113 (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
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 98 (0.00%)	0 / 113 (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			
Schizophrenia			

subjects affected / exposed	1 / 102 (0.98%)	0 / 98 (0.00%)	2 / 113 (1.77%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder			
subjects affected / exposed	0 / 102 (0.00%)	0 / 98 (0.00%)	0 / 113 (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 / 102 (0.00%)	0 / 98 (0.00%)	0 / 113 (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
Persecutory delusion			
subjects affected / exposed	0 / 102 (0.00%)	0 / 98 (0.00%)	0 / 113 (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
Tension			
subjects affected / exposed	1 / 102 (0.98%)	0 / 98 (0.00%)	0 / 113 (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
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 102 (0.98%)	0 / 98 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 98 (0.00%)	0 / 113 (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	Bitopertin 20 mg – Safety Follow-up Period	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 299 (0.67%)	4 / 208 (1.92%)	
number of deaths (all causes)	0	0	

number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical poisoning			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (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			
Completed suicide			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 299 (0.00%)	1 / 208 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	1 / 299 (0.33%)	3 / 208 (1.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			

subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (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	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Persecutory delusion			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (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 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (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	Placebo – Treatment Periods 1 and 2	Bitopertin 10 mg – Treatment Periods 1 and 2	Bitopertin 20 mg – Treatment Periods 1 and 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 206 (14.56%)	34 / 206 (16.50%)	26 / 208 (12.50%)
Nervous system disorders			
Headache			

subjects affected / exposed	9 / 206 (4.37%)	16 / 206 (7.77%)	3 / 208 (1.44%)
occurrences (all)	16	21	8
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	23 / 206 (11.17%)	24 / 206 (11.65%)	23 / 208 (11.06%)
occurrences (all)	32	38	28
Upper respiratory tract infection			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	0 / 208 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo – Washout Period	Bitopertin 10 mg – Washout Period	Bitopertin 10 mg to Placebo – Washout Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (0.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 113 (0.00%)	0 / 57 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Bitopertin 20 mg – Washout Period	Bitopertin 20 mg to Placebo – Washout Period	Placebo to Bitopertin 10 mg – LTE period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	14 / 94 (14.89%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	1 / 94 (1.06%)
occurrences (all)	0	0	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	11 / 94 (11.70%)
occurrences (all)	0	0	15
Upper respiratory tract infection			

subjects affected / exposed	0 / 56 (0.00%)	0 / 57 (0.00%)	3 / 94 (3.19%)
occurrences (all)	0	0	5

Non-serious adverse events	Bitopertin 10 mg – LTE Period	Bitopertin 20 mg – LTE Period	Placebo – Safety Follow-up Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 102 (18.63%)	13 / 98 (13.27%)	0 / 113 (0.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 102 (6.86%)	3 / 98 (3.06%)	0 / 113 (0.00%)
occurrences (all)	9	3	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 102 (12.75%)	8 / 98 (8.16%)	0 / 113 (0.00%)
occurrences (all)	18	10	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 102 (2.94%)	5 / 98 (5.10%)	0 / 113 (0.00%)
occurrences (all)	4	8	0

Non-serious adverse events	Bitopertin 10 mg – Safety Follow-up Period	Bitopertin 20 mg – Safety Follow-up Period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 299 (0.00%)	0 / 208 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2010	Addition of creatine phosphokinase for laboratory testing; Clarification on procedures for exploratory objective; Rewording and changing the order and number of the items of Work readiness questionnaire (WoRQ); Updates in schedule of assessments and procedures; Clarification on data collection; Spelling/formatting corrections; and Clarification on urinalysis and liver enzymes.
21 April 2011	Based on the request of the Health Authorities, the protocol was amended to include additional information related to the Long-term extension period of the study pertaining to withdrawal effects, safety and tolerability of long-term use (beyond 56 weeks) of study drug in combination with anti-psychotics, and long-term effects on the symptoms, functioning and quality of life and caregivers burden. A questionnaire was added to collect data related to past psychiatry history of the participant at the screening visit. The protocol was amended to harmonize with Roche safety reporting requirements with respect to the length of time female participants of reproductive status were being asked to comply with approved contraception methods.
20 February 2012	The protocol was amended to include the secondary objective related to evaluation of efficacy for the subgroups of participants defined by complement factor H-related protein 1 (CFHR1) biomarker. Amendment combined the screening and the prospective stabilization periods to shorten the time from the screening to the baseline visit. The study period was defined that it was approximately 4 years in total or until 31st December 2014, whichever came first after a participant completed 56 weeks in the study.
30 October 2012	Efficacy and Pharmacoeconomics endpoints section was amended with "SCQ: mean change from baseline at each assessment time" and "Caregiver Global Impression Scales: mean change from baseline at each assessment time"end points. The protocol was amended to include the interim futility analysis based on the primary efficacy endpoint, to be performed by an independent statistician supporting the Independent Data Monitoring Committee (iDMC).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 July 2014	Study was prematurely terminated as pre-specified interim futility analysis predicted a low probability of success.	-

Notes:

Limitations and caveats

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

Study was prematurely terminated as pre-specified interim futility analysis predicted a low probability of success. Consequently the study was terminated with last participant's last visit on 08 Jul 2014.

Notes: