Clinical trial results:
A Phase III, multi-center, randomized, 12-week, double-blind, parallel-group, placebo-controlled study to evaluate the 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	2010-020718-26
Trial protocol	CZ IT BG
Global end of trial date	12 December 2014

Results information

Result version number	v1 (current)
This version publication date	24 June 2016
First version publication date	24 June 2016

Trial information

Trial identification

Sponsor protocol code	WN25305

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01235559
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	F. Hoffmann-La Roche AG, Roche Trial Information Hotline, 41 61 6878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, Roche Trial Information Hotline, 41 61 6878333, 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	23 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 December 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 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, and 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 the 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 the 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	29 October 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: 80
Country: Number of subjects enrolled	Czech Republic: 69
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	China: 182
Country: Number of subjects enrolled	Japan: 71
Country: Number of subjects enrolled	United States: 170
Country: Number of subjects enrolled	Russian Federation: 3

Worldwide total number of subjects	596
EEA total number of subjects	170

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)	587
From 65 to 84 years	9
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:

Out of 602 randomized participants, 2 were randomized to another bitopertin study first and not included in the safety population. A further 3 participants were randomized twice and only first randomization were analysed. One participant was randomized but not treated, and therefore, 596 participants were available in the safety population.

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?	Yes
Arm title	Bitopertin 10 mg – Treatment Period 1

Arm description:

Participants received bitopertin 10 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 10 mg oral tablet QD in the morning, with or without food for 12 weeks.

Arm title	Bitopertin 20 mg – Treatment Period 1

Arm description:

Participants received bitopertin 20 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 20 mg oral tablet QD in the morning, with or without food for 12 weeks.

Arm title	Placebo – Treatment Period 1

Arm description:

Participants received placebo-matched to bitopertin QD for 12 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 Biopterin oral tablet QD in the morning, with or without food for 12 weeks.

Number of subjects in period 1	Bitopertin 10 mg – Treatment Period 1	Bitopertin 20 mg – Treatment Period 1	Placebo – Treatment Period 1
Started	198	199	199
Completed	165	173	177
Not completed	33	26	22
Consent withdrawn by subject	9	7	1
Death	2	-	-
Administrative/other	2	4	3
Adverse event	4	2	7
Non−compliance	7	4	2
Lost to follow-up	6	6	6
Lack of efficacy	2	-	-
Protocol deviation	1	3	3

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	Bitopertin 10 mg – Treatment Period 2

Arm description:

Participants received bitopertin 10 mg oral tablet QD for 40 weeks (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 for 40 weeks (from Week 13 to Week 52).

Arm title	Bitopertin 20 mg – Treatment Period 2
Arm description:	
Participants received bitopertin 20 mg oral tablet QD for 40 weeks (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 20 mg oral tablet QD in the morning, with or without food for 40 weeks.	

Arm title	Placebo – Treatment Period 2
Arm description:	
Participants received placebo-matched to bitopertin QD for 40 weeks (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 Biopterin oral tablet QD in the morning, with or without food for 40 weeks.	

Number of subjects in period 2	Bitopertin 10 mg – Treatment Period 2	Bitopertin 20 mg – Treatment Period 2	Placebo – Treatment Period 2
Started	165	173	177
Completed	110	105	111
Not completed	55	68	66
Consent withdrawn by subject	15	10	9
Did not continue in Treatment Period 2	2	2	3
Death	1	-	-
Administrative/other	22	31	25
Adverse event	7	10	9
Non−compliance	2	3	7
Lost to follow-up	4	8	6
Lack of efficacy	2	2	5
Protocol deviation	-	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?	Yes
Arm title	Bitopertin 10 mg – Washout Period

Arm description:

Participants received bitopertin 10 mg oral tablet QD for 4 weeks (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 for 4 weeks (Week 52 to Week 56).

Arm title	Bitopertin 10 mg to Placebo – Washout Period

Arm description:

Participants who received bitopertin 10 mg oral tablet QD during the treatment period 1 and 2 were switched to placebo for 4 weeks (Week 52 to Week 56).

Arm type	Experimental
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 10 mg oral tablet QD in the morning, with or without food for 4 weeks.

Arm title	Bitopertin 20 mg – Washout Period

Arm description:

Participants received bitopertin 20 mg oral tablet QD for 4 weeks (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 20 mg oral tablet QD in the morning, with or without food for 4 weeks (Week 52 to Week 56).

Arm title	Bitopertin 20 mg to Placebo – Washout Period

Arm description:

Participants who received bitopertin 20 mg oral tablet QD during the treatment period 1 and 2 were switched to placebo for 4 weeks (Week 52 to Week 56).

Arm type	Experimental

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 for 4 weeks (Week 52 to Week 56).

Arm title	Placebo – Washout Period

Arm description:

Participants received placebo-matched to bitopertin QD for 4 weeks (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 Biopterin oral tablet QD in the morning, with or without food for 4 weeks.

Number of subjects in period 3	Bitopertin 10 mg – Washout Period	Bitopertin 10 mg to Placebo – Washout Period	Bitopertin 20 mg – Washout Period
Started	56	54	53
Completed	54	53	49
Not completed	2	1	4
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	1
Administrative/other	1	1	1
Lost to follow-up	1	-	2

Number of subjects in period 3	Bitopertin 20 mg to Placebo – Washout Period	Placebo – Washout Period
Started	52	110
Completed	51	107
Not completed	1	3
Consent withdrawn by subject	-	2
Adverse event, non-fatal	1	-
Administrative/other	-	1
Lost to follow-up	-	-

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
Arm title	Bitopertin 10 mg – Long-Term Extension

Arm description:

Participants received bitopertin 10 mg oral tablet once a day (QD) for 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 in the morning, with or without food for 3 years.

Arm title	Bitopertin 20 mg – Long-Term Extension

Arm description:

Participants received bitopertin 20 mg oral tablet QD for 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 20 mg oral tablet QD in the morning, with or without food for 3 years.

Arm title	Placebo to Biopterin 10 mg – Long-Term Extension

Arm description:

Participants received placebo-matched to bitopertin QD for 3 years.

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 Biopterin oral tablet QD in the morning, with or without food for 3 years.

Number of subjects in period 4	Bitopertin 10 mg – Long-Term Extension	Bitopertin 20 mg – Long-Term Extension	Placebo to Biopterin 10 mg – Long-Term Extension
Started	95	90	94
Completed	0	0	0
Not completed	95	90	94
Consent withdrawn by subject	11	5	6
Death	-	-	1
Administrative/other	75	77	73
Adverse event	3	2	4
Non−compliance	3	1	4
Lost to follow-up	1	3	2
Protocol deviation	1	1	1
Lack of efficacy	1	1	3

Period 5	
Period 5 title	Safety Follow-up
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 10 mg – Safety Follow-up

Arm description:

Participants received bitopertin 10 mg oral tablet 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 for 4 weeks.

Arm title	Bitopertin 20 mg – Safety Follow-up

Arm description:

Participants received bitopertin 20 mg oral tablet 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 20 mg oral tablet QD in the morning, with or without food for 4 weeks.

Arm title	Placebo – Safety Follow-up

Arm description:

Participants received placebo-matched to bitopertin QD 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 Biopterin 10 or 20 mg oral tablet QD in the morning, with or without food for 4 weeks.

Number of subjects in period 5	Bitopertin 10 mg – Safety Follow-up	Bitopertin 20 mg – Safety Follow-up	Placebo – Safety Follow-up
Started	292	199	105
Completed	218	137	63
Not completed	74	62	42
Consent withdrawn by subject	29	17	13
Death	4	-	-
Administrative/other	9	12	3
Adverse event	5	4	2
Lost to follow-up	27	29	24

Baseline characteristics

Reporting groups	
Reporting group title	Bitopertin 10 mg – Treatment Period 1
Reporting group description:	
Participants received bitopertin 10 milligrams (mg) oral tablet once a day (QD) for 12 weeks.	
Reporting group title	Bitopertin 20 mg – Treatment Period 1
Reporting group description:	
Participants received bitopertin 20 mg oral tablet QD for 12 weeks.	
Reporting group title	Placebo – Treatment Period 1
Reporting group description:	
Participants received placebo-matched to bitopertin QD for 12 weeks.	

Reporting group values	Bitopertin 10 mg – Treatment Period 1	Bitopertin 20 mg – Treatment Period 1	Placebo – Treatment Period 1
Number of subjects	198	199	199
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 40.2 ± 12.4	 39.1 ± 12.2	 39.7 ± 12.7
Gender categorical Units: Subjects			
Female	85	85	65
Male	113	114	134

Reporting group values	Total		
Number of subjects	596		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female	235		
Male	361		

End points

End points reporting groups

Reporting group title	Bitopertin 10 mg – Treatment Period 1
Reporting group description:	
Participants received bitopertin 10 milligrams (mg) oral tablet once a day (QD) for 12 weeks.	
Reporting group title	Bitopertin 20 mg – Treatment Period 1
Reporting group description:	
Participants received bitopertin 20 mg oral tablet QD for 12 weeks.	
Reporting group title	Placebo – Treatment Period 1
Reporting group description:	
Participants received placebo-matched to bitopertin QD for 12 weeks.	
Reporting group title	Bitopertin 10 mg – Treatment Period 2
Reporting group description:	
Participants received bitopertin 10 mg oral tablet QD for 40 weeks (from Week 13 to Week 52).	
Reporting group title	Bitopertin 20 mg – Treatment Period 2
Reporting group description:	
Participants received bitopertin 20 mg oral tablet QD for 40 weeks (from Week 13 to Week 52).	
Reporting group title	Placebo – Treatment Period 2
Reporting group description:	
Participants received placebo-matched to bitopertin QD for 40 weeks (from Week 13 to Week 52).	
Reporting group title	Bitopertin 10 mg – Washout Period
Reporting group description:	
Participants received bitopertin 10 mg oral tablet QD for 4 weeks (Week 52 to Week 56).	
Reporting group title	Bitopertin 10 mg to Placebo – Washout Period
Reporting group description:	
Participants who received bitopertin 10 mg oral tablet QD during the treatment period 1 and 2 were switched to placebo for 4 weeks (Week 52 to Week 56).	
Reporting group title	Bitopertin 20 mg – Washout Period
Reporting group description:	
Participants received bitopertin 20 mg oral tablet QD for 4 weeks (Week 52 to Week 56).	
Reporting group title	Bitopertin 20 mg to Placebo – Washout Period
Reporting group description:	
Participants who received bitopertin 20 mg oral tablet QD during the treatment period 1 and 2 were switched to placebo for 4 weeks (Week 52 to Week 56).	
Reporting group title	Placebo – Washout Period
Reporting group description:	
Participants received placebo-matched to bitopertin QD for 4 weeks (Week 52 to Week 56).	
Reporting group title	Bitopertin 10 mg – Long-Term Extension
Reporting group description:	
Participants received bitopertin 10 mg oral tablet once a day (QD) for 3 years.	
Reporting group title	Bitopertin 20 mg – Long-Term Extension
Reporting group description:	
Participants received bitopertin 20 mg oral tablet QD for 3 years.	
Reporting group title	Placebo to Biopterin 10 mg – Long-Term Extension
Reporting group description:	
Participants received placebo-matched to bitopertin QD for 3 years.	
Reporting group title	Bitopertin 10 mg – Safety Follow-up
Reporting group description:	
Participants received bitopertin 10 mg oral tablet QD for 4 weeks.	
Reporting group title	Bitopertin 20 mg – Safety Follow-up

Reporting group description:	
Participants received bitopertin 20 mg oral tablet QD for 4 weeks.	
Reporting group title	Placebo – Safety Follow-up
Reporting group description:	
Participants received placebo-matched to bitopertin QD for 4 weeks.	

Primary: Change From Baseline in the PANSS Positive Symptom Factor Score (PSFS) at Week 12

End point title	Change From Baseline in the PANSS Positive Symptom Factor Score (PSFS) at Week 12
End point description:	
PANSS was a 30-item scale designed to capture degree of severity for many symptoms in schizophrenia. Symptoms and each item of the PANSS was rated on a 7-point scale: 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 were calculated for PSFS which consisted of the following items: Delusions [P1], Hallucinatory behaviour[P3], Grandiosity [P5], Suspiciousness [P6], Stereotyped thinking [N7], Somatic concern [G1], Unusual thought content [G9], Lack of judgment and insight [G12]. Scores were transformed to 0-6 points with higher scores indicating greater severity of symptoms and 0 as absent. If any item score contributing to the factor score was missing then the factor was set to missing. Intent-to-Treat (ITT) population: 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.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	Bitopertin 10 mg – Treatment Period 1	Bitopertin 20 mg – Treatment Period 1	Placebo – Treatment Period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	190	189	
Units: units on a scale				
least squares mean (confidence interval 95%)	-5.14 (-5.78 to -4.5)	-4.22 (-4.85 to -3.6)	-3.77 (-4.4 to -3.14)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bitopertin 10 mg – Treatment Period 1 v Placebo – Treatment Period 1
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0028
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	-1.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.27
upper limit	-0.47
Variability estimate	Standard error of the mean
Dispersion value	0.457

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo – Treatment Period 1 v Bitopertin 20 mg – Treatment Period 1
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3142
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	0.452

Primary: Change From Baseline in the PANSS-PSFS at Week 12 - Complement factor H-related protein 1 (CFHR1)-High Subgroup

End point title	Change From Baseline in the PANSS-PSFS at Week 12 - Complement factor H-related protein 1 (CFHR1)-High Subgroup

End point description:

PANSS was a 30-item scale designed to capture degree of severity for many symptoms in schizophrenia. Symptoms and each item of the PANSS was rated on a 7-point scale: 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 were calculated for PSFS which consisted of the following items: Delusions [P1], Hallucinatory behaviour[P3], Grandiosity [P5], Suspiciousness [P6], Stereotyped thinking [N7], Somatic concern [G1], Unusual thought content [G9], Lack of judgment and insight [G12]. Scores were transformed to 0-6 points with higher scores indicating greater severity of symptoms and 0 as absent. If any item score contributing to the factor score was missing then the factor was set to missing.
ITT population(CFHR1-High Subgroup):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.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	Bitopertin 10 mg – Treatment Period 1	Bitopertin 20 mg – Treatment Period 1	Placebo – Treatment Period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	127	129	
Units: units on a scale				
least squares mean (confidence interval 95%)	-5.16 (-6 to -4.31)	-3.64 (-4.42 to -2.86)	-3.58 (-4.35 to -2.81)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bitopertin 10 mg – Treatment Period 1 v Placebo – Treatment Period 1
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0069
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	-1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.72
upper limit	-0.44
Variability estimate	Standard error of the mean
Dispersion value	0.581

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo – Treatment Period 1 v Bitopertin 20 mg – Treatment Period 1
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9099
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	1.03
Variability estimate	Standard error of the mean
Dispersion value	0.558

Secondary: Change From Baseline in the PANSS Total Score at Week 12

End point title	Change From Baseline in the PANSS Total Score at Week 12

End point description:

PANSS total score (sum of 30 items) assessed the positive symptoms (delusions, hallucination, grandiosity, suspiciousness, stereotyped thinking, somatic concern, unusual thought content, lack of judgment and insight), negative symptoms (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation, motor retardation, active social avoidance), general psychopathology (somatic concern, anxiety, guilt feelings, tension, mannerisms/posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment/insight, disturbance of volition, poor impulse control, preoccupation, active social avoidance). Each item was rated on a 7 point scale (1=Absent; 2=Minimal; 3=Mild; 4=Moderate; 5=Moderately severe; 6=Severe; 7=Extreme). Total score ranged from 30 to 210; higher score indicated greater severity.
ITT population were used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Bitopertin 10 mg – Treatment Period 1	Bitopertin 20 mg – Treatment Period 1	Placebo – Treatment Period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	190	189	
Units: units on a scale				
least squares mean (confidence interval 95%)	-14.44 (-16.14 to -12.74)	-11.81 (-13.48 to -10.14)	-11.65 (-13.32 to -9.98)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bitopertin 10 mg – Treatment Period 1 v Placebo – Treatment Period 1
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0217
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	-2.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.17
upper limit	-0.41

Variability estimate	Standard error of the mean
Dispersion value	1.213

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo – Treatment Period 1 v Bitopertin 20 mg – Treatment Period 1
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8954
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.52
upper limit	2.2
Variability estimate	Standard error of the mean
Dispersion value	1.202

Secondary: Change From Baseline in the PANSS Negative, Positive, and Psychopathology Subscale Score at Week 12

End point title	Change From Baseline in the PANSS Negative, Positive, and Psychopathology Subscale Score at Week 12

End point description:

The PANSS was a 30-item scale designed to capture the degree of severity for many symptoms in schizophrenia. PANSS subscales include (Negative subscale, positive subscale and generalized psychopathology). Negative and positive subscale score included 7-items each and generalized psychopathology included 16 items. Each item was rated on a scale from 1 (symptom not present) to 7 (symptoms extremely severe). Total negative and positive scores = 1 to 7 each, with higher score indicating greater severity and total generalized psychopathology score = 1 to 16, higher score indicating greater severity.
The study program was terminated early, after the primary endpoint since the primary endpoint was not reached at higher doses of bitopertin. Analysis of the incomplete data set was not performed because it could potentially produce skewed or statistically irrelevant data.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Bitopertin 10 mg – Treatment Period 1	Bitopertin 20 mg – Treatment Period 1	Placebo – Treatment Period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[1]	0[2]	0[3]	
Units: units on a scale				
least squares mean (confidence interval	(to)	(to)	(to)	

95%)

Notes:

[1] - Due to early termination of study, insufficient data were available to perform all planned analyses.

[2] - Due to early termination of study, insufficient data were available to perform all planned analyses.

[3] - Due to early termination of study, insufficient data were available to perform all planned analyses.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the PANSS Negative Symptom Factor Score at Week 12

End point title	Change From Baseline in the PANSS Negative Symptom Factor Score at Week 12

End point description:

The PANSS was a 30-item scale designed to capture the degree of severity for many symptoms in schizophrenia. PANSS factor score included negative symptoms factor score (7-items), disorganized thought/cognition factor score (7-items), uncontrolled hostility/excitement factor score (4-items), and anxiety/depression factor score (4-items). Each item was 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 uncontrolled hostility/excitement and anxiety/depression factor score = 1 to 4 each, with higher score indicating greater severity.
The study program was terminated early, after the primary endpoint since the primary endpoint was not reached at higher doses of bitopertin. Analysis of the incomplete data set was not performed because it could potentially produce skewed or statistically irrelevant data.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Bitopertin 10 mg – Treatment Period 1	Bitopertin 20 mg – Treatment Period 1	Placebo – Treatment Period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[4]	0[5]	0[6]	
Units: units on a scale				
least squares mean (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[4] - Due to early termination of study, insufficient data were available to perform all planned analyses.

[5] - Due to early termination of study, insufficient data were available to perform all planned analyses.

[6] - Due to early termination of study, insufficient data were available to perform all planned analyses.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With PANSS-PSFS

End point title	Percentage of Participants With PANSS-PSFS

End point description:

Percentage of responders: Participants who have at least 20 percent (%) improvement from baseline in the PANSS PSFS (percentage decrease from baseline greater than or equal to [>=] 20%). Percentage of

responders = Positive symptoms factor score at Week 12 minus Positive symptoms factor score at baseline divided by Positive symptoms factor score at baseline multiplied by 100.
The study program was terminated early, after the primary endpoint since the primary endpoint was not reached at higher doses of bitopertin. Analysis of the incomplete data set was not performed because it could potentially produce skewed or statistically irrelevant data.

End point type	Secondary

End point timeframe:

Week 12

End point values	Bitopertin 10 mg – Treatment Period 1	Bitopertin 20 mg – Treatment Period 1	Placebo – Treatment Period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[7]	0[8]	0[9]	
Units: units on a scale				
least squares mean (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[7] - Due to early termination of study, insufficient data were available to perform all planned analyses.

[8] - Due to early termination of study, insufficient data were available to perform all planned analyses.

[9] - Due to early termination of study, insufficient data were available to perform all planned analyses.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Global Impression - Improvement (CGI-I) Symptoms Scale Score

End point title	Percentage of Participants With Clinical Global Impression - Improvement (CGI-I) Symptoms Scale Score

End point description:

Percentage of responders: Participants with "much" or "very much" improvement in the CGI-I overall and positive symptoms from baseline. Participants with a rating of either "much" or "very much" improvement in at least two of the three last post-baseline assessments (separated by at least 2 weeks) during the initial 12 weeks. Each of the CGI-I scales were rated on a 7-point scale. Ratings were based on degree of improvement from baseline. A CGI-I score of 1 refers to "very much improved" and a score of 7 refers to "very much worse." Higher score = more affected.
The study program was terminated early, after the primary endpoint since the primary endpoint was not reached at higher doses of Bitopertin. Analysis of the incomplete data set was not performed because it could potentially produce skewed or statistically irrelevant data.

End point type	Secondary

End point timeframe:

Week 12

End point values	Bitopertin 10 mg – Treatment Period 1	Bitopertin 20 mg – Treatment Period 1	Placebo – Treatment Period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[10]	0[11]	0[12]	
Units: units on a scale				
least squares mean (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[10] - Due to early termination of study, insufficient data were available to perform all planned analyses.
[11] - Due to early termination of study, insufficient data were available to perform all planned analyses.
[12] - Due to early termination of study, insufficient data were available to perform all planned analyses.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression - Improvement (CGI-I) Symptoms Scale Score at Week 12

End point title	Change From Baseline in Clinical Global Impression - Improvement (CGI-I) Symptoms Scale Score at Week 12

End point description:

CGI-I: 7-point clinician rated scale ranging from 1 (very much improved) to 7 (very much worse). Improvement was defined as a score of 1 (very much improved), 2 (much improved), or 3 (minimally improved) on the scale. Higher score = more affected.
The study program was terminated early, after the primary endpoint since the primary endpoint was not reached at higher doses of Bitopertin. Analysis of the incomplete data set was not performed because it could potentially produce skewed or statistically irrelevant data.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Bitopertin 10 mg – Treatment Period 1	Bitopertin 20 mg – Treatment Period 1	Placebo – Treatment Period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[13]	0[14]	0[15]	
Units: units on a scale				
least squares mean (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[13] - Due to early termination of study, insufficient data were available to perform all planned analyses.
[14] - Due to early termination of study, insufficient data were available to perform all planned analyses.
[15] - Due to early termination of study, insufficient data were available to perform all planned analyses.

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Personal and Social Performance (PSP) Total Score at Week 12

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. The study program was terminated early, after the primary endpoint since the primary endpoint was not reached at higher doses of Bitopertin. Analysis of the incomplete data set was not performed because it could potentially produce skewed or statistically irrelevant data.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Bitopertin 10 mg – Treatment Period 1	Bitopertin 20 mg – Treatment Period 1	Placebo – Treatment Period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[16]	0[17]	0[18]	
Units: units on a scale				
least squares mean (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[16] - Due to early termination of study, insufficient data were available to perform all planned analyses.

[17] - Due to early termination of study, insufficient data were available to perform all planned analyses.

[18] - Due to early termination of study, insufficient data were available to perform all planned analyses.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Bitopertin 10 mg – Treatment Period

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	Bitopertin 20mg – Treatment Period

Reporting group description:

Participants received bitopertin 20 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

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 10 mg – Washout Period

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

Reporting group description:

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

Reporting group title	Bitopertin 20mg – Washout Period

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 20mg to Placebo – Washout Period

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

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 10mg – Long-Term Extension

Reporting group description:

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

Reporting group title	Bitopertin 10mg – Long-Term Extension

Reporting group description:

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

Reporting group title	Bitopertin 20mg – Long-Term Extension

Reporting group description:

Participants received bitopertin 20 mg oral tablet QD up to 3 years.

Reporting group title	Bitopertin 10 mg - Safety Follow-up

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	Bitopertin 20 mg - Safety Follow-up

Reporting group description:

All participants who withdrew early from the study or whose treatment was discontinued during the Long-Term Extension received bitopertin 20 mg QD, for 4 weeks.

Reporting group title	Placebo - Safety Follow-up

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 10 mg – Treatment Period	Bitopertin 20mg – Treatment Period	Placebo – Treatment Period
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 198 (4.04%)	7 / 199 (3.52%)	6 / 199 (3.02%)
number of deaths (all causes)	4	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal cancer metastatic			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 198 (0.00%)	0 / 199 (0.00%)	1 / 199 (0.50%)
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			
Coronary artery disease			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	0 / 199 (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

Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 198 (0.00%)	0 / 199 (0.00%)	0 / 199 (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
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	0 / 198 (0.00%)	0 / 199 (0.00%)	0 / 199 (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			
Ileus			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	0 / 199 (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
Large intestine polyp			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	0 / 199 (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
Pancreatitis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	0 / 199 (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
Duodenal ulcer			
subjects affected / exposed	0 / 198 (0.00%)	0 / 199 (0.00%)	0 / 199 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 198 (0.00%)	0 / 199 (0.00%)	0 / 199 (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			
Pneumonia aspiration			

subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	0 / 199 (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
Psychiatric disorders			
Psychiatric Symptom			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	0 / 199 (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	2 / 198 (1.01%)	1 / 199 (0.50%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	2 / 199 (1.01%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	0 / 199 (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
Completed suicide			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Depressed mood			
subjects affected / exposed	0 / 198 (0.00%)	0 / 199 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	0 / 199 (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
Anger			

subjects affected / exposed	0 / 198 (0.00%)	0 / 199 (0.00%)	0 / 199 (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
Paranoia			
subjects affected / exposed	0 / 198 (0.00%)	0 / 199 (0.00%)	0 / 199 (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
Schizoaffective disorder bipolar type			
subjects affected / exposed	0 / 198 (0.00%)	0 / 199 (0.00%)	0 / 199 (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			
Localised infection			
subjects affected / exposed	0 / 198 (0.00%)	0 / 199 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 198 (0.00%)	0 / 199 (0.00%)	0 / 199 (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
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	0 / 199 (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
Hyperglycaemia			
subjects affected / exposed	0 / 198 (0.00%)	0 / 199 (0.00%)	1 / 199 (0.50%)
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 – Washout Period	Bitopertin 10 mg to Placebo – Washout Period	Bitopertin 20mg – Washout Period
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal cancer metastatic			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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			
Alcohol poisoning			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Hip fracture			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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			
Coronary artery disease			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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			
Ileus			

subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Large intestine polyp			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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 / 54 (0.00%)	0 / 53 (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
Duodenal ulcer			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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			
Pneumonia aspiration			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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			
Psychiatric Symptom			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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 / 54 (0.00%)	0 / 53 (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 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Completed suicide			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Depressed mood			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Hallucination			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Anger			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Paranoia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Schizoaffective disorder bipolar type			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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			

Localised infection			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Bronchopneumonia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Hyperglycaemia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (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 20mg to Placebo – Washout Period	Placebo – Washout Period	Placebo to Bitopertin 10mg – Long-Term Extension
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (0.00%)	6 / 94 (6.38%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal cancer metastatic			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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
Hip fracture			

subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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			
Coronary artery disease			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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			
Ileus			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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
Large intestine polyp			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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 / 52 (0.00%)	0 / 110 (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
Duodenal ulcer			

subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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			
Pneumonia aspiration			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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			
Psychiatric Symptom			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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 / 52 (0.00%)	0 / 110 (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
Schizophrenia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (0.00%)	3 / 94 (3.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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
Completed suicide			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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

Depressed mood			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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
Hallucination			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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
Anger			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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
Paranoia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (0.00%)	2 / 94 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizoaffective disorder bipolar type			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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
Infections and infestations			
Localised infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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
Bronchopneumonia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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 / 1
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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

Hyperglycaemia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (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 10mg – Long-Term Extension	Bitopertin 20mg – Long-Term Extension	Bitopertin 10 mg - Safety Follow-up
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (0.00%)	4 / 292 (1.37%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal cancer metastatic			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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			
Alcohol poisoning			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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
Hip fracture			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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			
Coronary artery disease			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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

Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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
Large intestine polyp			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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
Duodenal ulcer			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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			
Psychiatric Symptom			

subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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 / 95 (0.00%)	0 / 90 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (0.00%)	0 / 292 (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	0 / 95 (0.00%)	0 / 90 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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
Depressed mood			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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
Hallucination			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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
Anger			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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
Paranoia			

subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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
Schizoaffective disorder bipolar type			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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			
Localised infection			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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
Bronchopneumonia			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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
Hyperglycaemia			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 292 (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 - Safety Follow-up	Placebo - Safety Follow-up	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 199 (3.02%)	1 / 105 (0.95%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal cancer metastatic			

subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 199 (0.50%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	1 / 199 (0.50%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			

subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (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 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (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			
Pneumonia aspiration			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric Symptom			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (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 / 199 (0.50%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	2 / 199 (1.01%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Suicidal ideation			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed mood			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anger			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizoaffective disorder bipolar type			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (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			
Localised infection			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 199 (0.50%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (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 10 mg – Treatment Period	Bitopertin 20mg – Treatment Period	Placebo – Treatment Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 198 (16.16%)	37 / 199 (18.59%)	32 / 199 (16.08%)
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 198 (5.56%)	6 / 199 (3.02%)	4 / 199 (2.01%)
occurrences (all)	18	8	5
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 198 (8.08%)	18 / 199 (9.05%)	22 / 199 (11.06%)
occurrences (all)	25	27	35
Upper respiratory tract infection			
subjects affected / exposed	8 / 198 (4.04%)	15 / 199 (7.54%)	9 / 199 (4.52%)
occurrences (all)	9	17	10

Non-serious adverse events	Bitopertin 10 mg – Washout Period	Bitopertin 10 mg to Placebo – Washout Period	Bitopertin 20mg – Washout Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 56 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Bitopertin 20mg to Placebo – Washout Period	Placebo – Washout Period	Placebo to Bitopertin 10mg – Long-Term Extension
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (0.00%)	12 / 94 (12.77%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (0.00%)	5 / 94 (5.32%)
occurrences (all)	0	0	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (0.00%)	8 / 94 (8.51%)
occurrences (all)	0	0	11
Upper respiratory tract infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 110 (0.00%)	0 / 94 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Bitopertin 10mg – Long-Term Extension	Bitopertin 20mg – Long-Term Extension	Bitopertin 10 mg - Safety Follow-up
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 95 (11.58%)	15 / 90 (16.67%)	0 / 292 (0.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 95 (3.16%)	6 / 90 (6.67%)	0 / 292 (0.00%)
occurrences (all)	3	8	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 95 (10.53%)	11 / 90 (12.22%)	0 / 292 (0.00%)
occurrences (all)	16	16	0

Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 95 (0.00%) 0	0 / 90 (0.00%) 0	0 / 292 (0.00%) 0

Non-serious adverse events	Bitopertin 20 mg - Safety Follow-up	Placebo - Safety Follow-up	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 199 (0.00%)	0 / 105 (0.00%)	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 199 (0.00%) 0	0 / 105 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 199 (0.00%) 0 0 / 199 (0.00%) 0	0 / 105 (0.00%) 0 0 / 105 (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: Protocol was amended to clarify the exclusion criteria of hepatic dysfunction, secondary objective time point for safety and tolerability.
21 April 2011	Version C: Protocol was amended to clarify on the long term extension period, female contraception method and pregnancy testing, initiation of psychotherapy/rehabilitative, non-serious adverse events of special interest and reporting process, restricted and prohibited concomitant medication.
20 February 2012	Version D: Protocol was amended to clarify on addition of biomarker defined subpopulations as a secondary objective, timing of screening and prospective stabilization period, exclusion criteria (haemoglobin criterion, body mass index, requirement for past use of clonazepam), inclusion criteria (dosing of concomitant antipsychotics, definition of caregivers and burden assessment/questionnaire), updated list of restricted medications, updated definition of postmenopausal, and duration of the study. Added new guideline regarding withdrawal for hepatic laboratory abnormalities.
30 May 2012	Version D-1: Protocol was amended to include a revised version of the Zarit Burden Interview (ZBI) questionnaire, the Schizophrenia Caregiver Questionnaire (SCQ) to optimize assessment of caregiver burden for caregivers of patients with schizophrenia. Additionally, the Caregiver Global Impression scale was added.
30 October 2012	Version E: Protocol was amended to clarify on inclusion of futility analysis and addition of biomarker defined subpopulation analysis to the objectives, exclusion criteria (body mass index, patients with prior history of clozapine treatment), addition of 12-lead electrocardiogram (ECG) assessment in long term extension period, changes in serious adverse event (SAE) reporting, definition of safety population, and definition of length of the study.

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.

Notes: