Clinical trial results:
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	2010-020696-23
Trial protocol	GB HU FI SE
Global end of trial date	08 July 2014

Results information

Result version number	v1 (current)
This version publication date	22 April 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	NN25307

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01235520
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	To Be Added In By Sponsor, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline , F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline , F. Hoffmann-La Roche AG, 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	08 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 July 2014
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:

The primary objectives in this study were as follows:
- To evaluate the efficacy after 12 weeks of treatment with bitopertin vs. placebo, as adjunct to antipsychotics, in the Positive and Negative Syndrome Scale (PANSS) Positive Symptom Factor Score (PSFS) in patients with sub-optimally controlled symptoms of schizophrenia;
- To evaluate the safety and tolerability after 12 weeks of treatment with bitopertin vs. placebo, as adjunct to antipsychotics, in patients with sub-optimally controlled symptoms of schizophrenia.

The key secondary objective in this study was:
- To evaluate the efficacy after 12 weeks of treatment with bitopertin vs. placebo, as adjunct to antipsychotics, in the PANSS PSFS in the complement factor H-related protein 1 (CFHR1)-high subgroup of patients with sub-optimally controlled symptoms of schizophrenia.

Protection of trial subjects:

Signed written informed consent after the scope and nature of the investigation had been explained to them before screening evaluations and willingness to comply with the study restrictions.

Background therapy:

There was former psychiatric care given to a number of patients being treated. This previous psychiatric care was given prior to the study.

Evidence for comparator: -

Actual start date of recruitment	19 November 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Hungary: 33
Country: Number of subjects enrolled	Romania: 26
Country: Number of subjects enrolled	Russian Federation: 102
Country: Number of subjects enrolled	United States: 149
Country: Number of subjects enrolled	Argentina: 42
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Colombia: 22
Country: Number of subjects enrolled	India: 80

Country: Number of subjects enrolled	Korea, Republic of: 36
Country: Number of subjects enrolled	Mexico: 44
Worldwide total number of subjects	588
EEA total number of subjects	99

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)	578
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screened for a period of up to 37 days.

Period 1

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

Blinding implementation details:

Blinding for Arms with the following designation in the name of the arm: Treatment Period 1, Treatment Period 2, and Washout Period. During the Long-Term Extension period, all patients received active treatment but remained blinded to their treatment during the double-blind treatment phase. Patients were blinded but did not receive treatment during follow-up period.

Arms

Are arms mutually exclusive?	No
Arm title	Placebo, 12 weeks - Treatment Period 1

Arm description:

Patients randomized to placebo (10 or 20 mg) taken orally, once daily for 12 weeks in double-blind treatment

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:

10 or 20 mg tablet taken once daily for 12 weeks

Arm title	Bitopertin 10 mg, 12 weeks - Treatment Period 1

Arm description:

Patients randomized to bitopertin 10 mg taken orally, once daily for 12 weeks in double-blind treatment

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

Dosage and administration details:

10 mg tablet taken orally once daily for 12 weeks

Arm title	Bitopertin 20 mg, 12 weeks - Treatment Period 1

Arm description:

Patients randomized to bitopertin 20 mg taken orally, once daily for 12 weeks in double-blind treatment

Arm type	Experimental

Investigational medicinal product name	RO4917838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

20 mg tablet taken orally once daily for 12 weeks

Arm title	Placebo, weeks 13-52 - Treatment Period 2

Arm description:

Patients randomized to placebo taken orally, once daily from week 13 through week 52 in double-blind treatment

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:

10 or 20 mg tablet taken once daily from week 13-52

Arm title	Bitopertin 10 mg, weeks 13-52 - Treatment Period 2

Arm description:

Patients randomized to bitopertin (10 mg) taken orally, once daily from week 13 through week 52 in double-blind treatment

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

Dosage and administration details:

10 mg tablet taken once daily, weeks 13-52

Arm title	Bitopertin 20 mg, weeks 13-52 - Treatment Period 2

Arm description:

Patients randomized to bitopertin (20 mg) taken orally, once daily from week 13 through week 52 in double-blind treatment

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

Dosage and administration details:

20 mg tablet taken orally once daily, weeks 13-52

Arm title	Placebo - Washout Period

Arm description: -

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: 10 or 20 mg tablet taken once daily

Arm title	Bitopertin 10 mg - Washout Period
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	RO4917838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 10 mg tablet taken orally once daily	
Arm title	Bitopertin 10 mg to Placebo - Washout Period
Arm description: -	
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: 10 tablet taken once daily	
Arm title	Bitopertin 20 mg - Washout Period
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	RO4917838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 20 mg tablet taken orally once daily	
Arm title	Bitopertin 20 mg to Placebo - Washout Period
Arm description: -	
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: 20 mg tablet taken once daily	
Arm title	Placebo to Bitopertin 10 mg - Long-Term Extension Period
Arm description: Randomized - controlled, not blinded	
Arm type	Experimental

Investigational medicinal product name	RO4917838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 10 mg tablet taken orally once daily	
Arm title	Bitopertin 10 mg - Long-Term Extension Period
Arm description: Randomized - controlled, not blinded	
Arm type	Experimental
Investigational medicinal product name	RO4917838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 10 mg tablet taken orally once daily	
Arm title	Bitopertin 20 mg - Long-Term Extension Period
Arm description: Randomized - controlled, not blinded	
Arm type	Experimental
Investigational medicinal product name	RO4917838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 20 mg tablet taken orally once daily	
Arm title	Placebo - Follow-up Period
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Bitopertin 10 mg - Follow-up Period
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Bitopertin 20 mg - Follow-up Period
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Placebo, 12 weeks - Treatment Period 1	Bitopertin 10 mg, 12 weeks - Treatment Period 1	Bitopertin 20 mg, 12 weeks - Treatment Period 1
Started	196	198	194
Completed	161	171	171
Not completed	35	27	23
Ongoing in follow-up period	-	-	-
Protocol violation	1	2	3
Adverse event, non-fatal	10	7	7
Death	-	-	-
Administrative/other	6	2	5
Non-compliance	4	2	4
Lost to follow-up	3	3	1
Withdrawal by subject	11	10	3
Lack of efficacy	-	1	-

Number of subjects in period 1	Placebo, weeks 13-52 - Treatment Period 2	Bitopertin 10 mg, weeks 13-52 - Treatment Period 2	Bitopertin 20 mg, weeks 13-52 - Treatment Period 2
Started	157	170	168
Completed	75	86	88
Not completed	82	84	80
Ongoing in follow-up period	-	-	-
Protocol violation	1	1	2
Adverse event, non-fatal	9	10	15
Death	-	-	-
Administrative/other	47	51	42
Non-compliance	6	4	3
Lost to follow-up	5	6	5
Withdrawal by subject	12	12	7
Lack of efficacy	2	-	6

Number of subjects in period 1	Placebo - Washout Period	Bitopertin 10 mg - Washout Period	Bitopertin 10 mg to Placebo - Washout Period
Started	75	44	42
Completed	70	42	39
Not completed	5	2	3
Ongoing in follow-up period	-	-	-
Protocol violation	-	-	-
Adverse event, non-fatal	1	-	-
Death	-	-	-
Administrative/other	4	2	2
Non-compliance	-	-	-

Lost to follow-up	-	-	-
Withdrawal by subject	-	-	1
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 - Long-Term Extension Period
Started	45	43	58
Completed	44	39	2
Not completed	1	4	56
Ongoing in follow-up period	-	-	-
Protocol violation	-	-	1
Adverse event, non-fatal	-	1	-
Death	-	-	-
Administrative/other	1	3	51
Non-compliance	-	-	1
Lost to follow-up	-	-	-
Withdrawal by subject	-	-	2
Lack of efficacy	-	-	1

Number of subjects in period 1	Bitopertin 10 mg - Long-Term Extension Period	Bitopertin 20 mg - Long-Term Extension Period	Placebo - Follow-up Period
Started	66	67	138
Completed	3	2	67
Not completed	63	65	71
Ongoing in follow-up period	-	-	12
Protocol violation	-	-	-
Adverse event, non-fatal	-	1	3
Death	-	-	-
Administrative/other	59	58	13
Non-compliance	-	-	-
Lost to follow-up	1	2	27
Withdrawal by subject	2	4	16
Lack of efficacy	1	-	-

Number of subjects in period 1	Bitopertin 10 mg - Follow-up Period	Bitopertin 20 mg - Follow-up Period
Started	251	192
Completed	119	116
Not completed	132	76
Ongoing in follow-up period	11	10
Protocol violation	-	-
Adverse event, non-fatal	6	4
Death	1	-

Administrative/other	22	16
Non-compliance	-	-
Lost to follow-up	77	35
Withdrawal by subject	15	11
Lack of efficacy	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall period (overall period)

Reporting group description: -

Reporting group values	Overall period (overall period)	Total	
Number of subjects	588	588	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 40.7 ± 11.8	 -	
Gender categorical Units: Subjects			
Female	215	215	
Male	373	373	

End points

End points reporting groups

Reporting group title	Placebo, 12 weeks - Treatment Period 1
Reporting group description:	
Patients randomized to placebo (10 or 20 mg) taken orally, once daily for 12 weeks in double-blind treatment	
Reporting group title	Bitopertin 10 mg, 12 weeks - Treatment Period 1
Reporting group description:	
Patients randomized to bitopertin 10 mg taken orally, once daily for 12 weeks in double-blind treatment	
Reporting group title	Bitopertin 20 mg, 12 weeks - Treatment Period 1
Reporting group description:	
Patients randomized to bitopertin 20 mg taken orally, once daily for 12 weeks in double-blind treatment	
Reporting group title	Placebo, weeks 13-52 - Treatment Period 2
Reporting group description:	
Patients randomized to placebo taken orally, once daily from week 13 through week 52 in double-blind treatment	
Reporting group title	Bitopertin 10 mg, weeks 13-52 - Treatment Period 2
Reporting group description:	
Patients randomized to bitopertin (10 mg) taken orally, once daily from week 13 through week 52 in double-blind treatment	
Reporting group title	Bitopertin 20 mg, weeks 13-52 - Treatment Period 2
Reporting group description:	
Patients randomized to bitopertin (20 mg) taken orally, once daily from week 13 through week 52 in double-blind treatment	
Reporting group title	Placebo - Washout Period
Reporting group description: -	
Reporting group title	Bitopertin 10 mg - Washout Period
Reporting group description: -	
Reporting group title	Bitopertin 10 mg to Placebo - Washout Period
Reporting group description: -	
Reporting group title	Bitopertin 20 mg - Washout Period
Reporting group description: -	
Reporting group title	Bitopertin 20 mg to Placebo - Washout Period
Reporting group description: -	
Reporting group title	Placebo to Bitopertin 10 mg - Long-Term Extension Period
Reporting group description:	
Randomized - controlled, not blinded	
Reporting group title	Bitopertin 10 mg - Long-Term Extension Period
Reporting group description:	
Randomized - controlled, not blinded	
Reporting group title	Bitopertin 20 mg - Long-Term Extension Period
Reporting group description:	
Randomized - controlled, not blinded	
Reporting group title	Placebo - Follow-up Period
Reporting group description: -	
Reporting group title	Bitopertin 10 mg - Follow-up Period
Reporting group description: -	
Reporting group title	Bitopertin 20 mg - Follow-up Period
Reporting group description: -	

Primary: Mean change from baseline in the Positive and Negative Syndrome Scale (PANSS) Positive Symptom Factor Score (PSFS) at Week 12

End point title	Mean change from baseline in the Positive and Negative Syndrome Scale (PANSS) Positive Symptom Factor Score (PSFS) at Week 12[1]

End point description:

End point type	Primary

End point timeframe:

Timeframe is week 12

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: This final abbreviated Clinical Study Report (CSR) presents the data at Week 12 for the primary endpoint, PANSS PSFS, and one of the secondary endpoints, PANSS Total Score. The study did not meet its primary endpoint.

End point values	Placebo, 12 weeks - Treatment Period 1	Bitopertin 10 mg, 12 weeks - Treatment Period 1	Bitopertin 20 mg, 12 weeks - Treatment Period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	186	188	186	
Units: Scores on a scale				
arithmetic mean (standard error)	-4.88 (± 0.357)	-4.46 (± 0.327)	-4.67 (± 0.297)	

Statistical analyses

Statistical analysis title	Difference from placebo: 10 mg RO4917838

Statistical analysis description:

Difference of treatment with 10 mg RO4917838 from placebo based on mixed-effect model of repeated measures (MMRM) using unstructured covariance matrix

Comparison groups	Bitopertin 10 mg, 12 weeks - Treatment Period 1 v Placebo, 12 weeks - Treatment Period 1
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2169
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (net)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	1.5

Statistical analysis title	Difference from placebo: 20 mg RO4917838 MMRM

Statistical analysis description:

Difference of treatment with 20 mg RO4917838 from placebo based on mixed-effect model of repeated measures (MMRM) using unstructured covariance matrix

Comparison groups	Placebo, 12 weeks - Treatment Period 1 v Bitopertin 20 mg, 12 weeks - Treatment Period 1
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3572
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (net)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	1.36

Secondary: Mean Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score at Week 12

End point title	Mean Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score at Week 12[2]

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 12

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: This final abbreviated Clinical Study Report (CSR) presents the data at Week 12 for the primary endpoint, PANSS PSFS, and one of the secondary endpoints, PANSS Total Score. The study did not meet its primary endpoint.

End point values	Placebo, 12 weeks - Treatment Period 1	Bitopertin 10 mg, 12 weeks - Treatment Period 1	Bitopertin 20 mg, 12 weeks - Treatment Period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	186	188	186	
Units: Scores on a scale				
arithmetic mean (standard error)	-13.36 (± 0.88)	-12.24 (± 0.804)	-13.05 (± 0.823)	

Statistical analyses

Statistical analysis title	Difference from placebo: 10 mg RO4917838
Comparison groups	Placebo, 12 weeks - Treatment Period 1 v Bitopertin 10 mg, 12 weeks - Treatment Period 1

Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2789
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (net)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	3.64

Statistical analysis title	Difference from placebo: 20 mg RO4917838
Comparison groups	Placebo, 12 weeks - Treatment Period 1 v Bitopertin 20 mg, 12 weeks - Treatment Period 1
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.647
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (net)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	2.9

Adverse events

Adverse events information

Timeframe for reporting adverse events:

This abbreviated study report presents the final analysis of safety and includes all available safety data up to the time of the primary analysis and all available AE and laboratory assessment data for all study periods up to the LPLV.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Placebo - Treatment Periods 1 & 2
Reporting group description: -	
Reporting group title	Bitopertin 10 mg - Treatment Periods 1 & 2
Reporting group description: -	
Reporting group title	Bitopertin 20 mg - Treatment Periods 1 & 2
Reporting group description: -	
Reporting group title	Placebo during washout period
Reporting group description: -	
Reporting group title	Bitopertin 10 mg during washout period
Reporting group description: -	
Reporting group title	Bitopertin 10 mg to placebo during washout period
Reporting group description: -	
Reporting group title	Bitopertin 20 mg during washout period
Reporting group description: -	
Reporting group title	Bitopertin 20 mg to placebo during washout period
Reporting group description: -	
Reporting group title	Placebo to Bitopertin 10 mg during long-term extension
Reporting group description: -	
Reporting group title	Bitopertin 10 mg during long-term extension
Reporting group description: -	
Reporting group title	Bitopertin 20 mg during long-term extension
Reporting group description: -	
Reporting group title	Placebo - follow-up period
Reporting group description: -	
Reporting group title	Bitopertin 10 mg - follow-up period
Reporting group description: -	
Reporting group title	Bitopertin 20 mg - follow-up period

Reporting group description: -

Serious adverse events	Placebo - Treatment Periods 1 & 2	Bitopertin 10 mg - Treatment Periods 1 & 2	Bitopertin 20 mg - Treatment Periods 1 & 2
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 196 (5.10%)	13 / 198 (6.57%)	9 / 194 (4.64%)
number of deaths (all causes)	0	0	0
number of deaths resulting from			

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 196 (0.51%)	0 / 198 (0.00%)	0 / 194 (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
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 196 (0.00%)	1 / 198 (0.51%)	0 / 194 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	0 / 194 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 196 (0.00%)	1 / 198 (0.51%)	0 / 194 (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
Respiratory, thoracic and mediastinal disorders			
Sinus polyp			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	0 / 194 (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	2 / 196 (1.02%)	2 / 198 (1.01%)	3 / 194 (1.55%)
occurrences causally related to treatment / all	2 / 2	1 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major Depression			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychotic Disorder			
subjects affected / exposed	2 / 196 (1.02%)	0 / 198 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood altered			
subjects affected / exposed	1 / 196 (0.51%)	0 / 198 (0.00%)	0 / 194 (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
Schizophrenia, paranoid type			
subjects affected / exposed	0 / 196 (0.00%)	1 / 198 (0.51%)	0 / 194 (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
Suicidal ideation			
subjects affected / exposed	1 / 196 (0.51%)	0 / 198 (0.00%)	0 / 194 (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
Anxiety			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	0 / 194 (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
Insomnia			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	0 / 194 (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			
Limb injury			
subjects affected / exposed	0 / 196 (0.00%)	1 / 198 (0.51%)	0 / 194 (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
Overdose			
subjects affected / exposed	0 / 196 (0.00%)	1 / 198 (0.51%)	0 / 194 (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

Post-traumatic pain			
subjects affected / exposed	0 / 196 (0.00%)	1 / 198 (0.51%)	0 / 194 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 196 (0.00%)	1 / 198 (0.51%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 196 (0.51%)	0 / 198 (0.00%)	0 / 194 (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			
Syncope			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 196 (0.51%)	0 / 198 (0.00%)	0 / 194 (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
Dizziness			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	0 / 194 (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			
Hepatitis			

subjects affected / exposed	1 / 196 (0.51%)	0 / 198 (0.00%)	0 / 194 (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
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 196 (0.00%)	1 / 198 (0.51%)	0 / 194 (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
Musculoskeletal and connective tissue disorders			
Jaw cyst			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	0 / 194 (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 / 196 (0.00%)	0 / 198 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 196 (0.00%)	2 / 198 (1.01%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 196 (0.00%)	1 / 198 (0.51%)	0 / 194 (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
Cellulitis			
subjects affected / exposed	1 / 196 (0.51%)	0 / 198 (0.00%)	0 / 194 (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
Otitis media chronic			
subjects affected / exposed	0 / 196 (0.00%)	1 / 198 (0.51%)	0 / 194 (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

Tonsillitis			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	0 / 194 (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
Tooth abscess			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	0 / 194 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	0 / 194 (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			
Hyperglycaemia			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	0 / 194 (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	Placebo during washout period	Bitopertin 10 mg during washout period	Bitopertin 10 mg to placebo during washout period
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 76 (1.32%)	1 / 44 (2.27%)	0 / 42 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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 spontaneous			

subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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			
Sinus polyp			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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 / 76 (1.32%)	0 / 44 (0.00%)	0 / 42 (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
Major Depression			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Mood altered			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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, paranoid type			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Insomnia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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			
Limb injury			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Overdose			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Post-traumatic pain			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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			
Acute myocardial infarction			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Atrial flutter			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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			
Syncope			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Dizziness			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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			
Hepatitis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Jaw cyst			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Bronchitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 44 (2.27%)	0 / 42 (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
Cellulitis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Otitis media chronic			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Tonsillitis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Tooth abscess			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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			
Hyperglycaemia			

subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (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 during washout period	Bitopertin 20 mg to placebo during washout period	Placebo to Bitopertin 10 mg during long-term extension
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (0.00%)	2 / 58 (3.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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			
Sinus polyp			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			

Schizophrenia			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Major Depression			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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 / 45 (0.00%)	0 / 43 (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
Mood altered			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Schizophrenia, paranoid type			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Suicidal ideation			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Anxiety			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Insomnia			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Injury, poisoning and procedural complications			

Limb injury			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Overdose			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Post-traumatic pain			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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			
Acute myocardial infarction			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Atrial flutter			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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			
Syncope			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Dizziness			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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

Ischaemic stroke			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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			
Hepatitis			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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 / 45 (0.00%)	0 / 43 (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
Musculoskeletal and connective tissue disorders			
Jaw cyst			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (0.00%)	1 / 58 (1.72%)
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 / 45 (0.00%)	0 / 43 (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			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Bronchitis			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Cellulitis			

subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Otitis media chronic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Tonsillitis			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Tooth abscess			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (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 10 mg during long-term extension	Bitopertin 20 mg during long-term extension	Placebo - follow-up period
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 66 (7.58%)	1 / 67 (1.49%)	2 / 138 (1.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			

subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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 spontaneous			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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			
Sinus polyp			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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	3 / 66 (4.55%)	0 / 67 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major Depression			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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 / 66 (0.00%)	0 / 67 (0.00%)	2 / 138 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood altered			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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, paranoid type			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 138 (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
Insomnia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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			
Limb injury			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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
Overdose			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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
Post-traumatic pain			

subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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			
Acute myocardial infarction			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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
Atrial flutter			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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			
Syncope			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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
Dizziness			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 138 (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
Ischaemic stroke			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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			
Hepatitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Jaw cyst			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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
Bronchitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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
Cellulitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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
Otitis media chronic			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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
Tonsillitis			

subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 138 (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
Tooth abscess			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 138 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (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			
Hyperglycaemia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 138 (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

Serious adverse events	Bitopertin 10 mg - follow-up period	Bitopertin 20 mg - follow-up period	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 251 (1.99%)	6 / 192 (3.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			

subjects affected / exposed	0 / 251 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (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			
Sinus polyp			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (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 / 251 (0.40%)	4 / 192 (2.08%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major Depression			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (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 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood altered			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia, paranoid type			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Suicidal ideation			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 251 (0.40%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic pain			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 251 (0.40%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (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 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Jaw cyst			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (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	1 / 251 (0.40%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (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			
Hyperglycaemia			

subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (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 & 2	Bitopertin 10 mg - Treatment Periods 1 & 2	Bitopertin 20 mg - Treatment Periods 1 & 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 196 (12.24%)	36 / 198 (18.18%)	33 / 194 (17.01%)
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 196 (4.08%)	12 / 198 (6.06%)	11 / 194 (5.67%)
occurrences (all)	13	19	14
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	0 / 194 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 196 (4.59%)	7 / 198 (3.54%)	10 / 194 (5.15%)
occurrences (all)	9	7	11
Influenza			
subjects affected / exposed	0 / 196 (0.00%)	0 / 198 (0.00%)	0 / 194 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo during washout period	Bitopertin 10 mg during washout period	Bitopertin 10 mg to placebo during washout period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 76 (6.58%)	6 / 44 (13.64%)	0 / 42 (0.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0

Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 76 (0.00%)	0 / 44 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Bitopertin 20 mg during washout period	Bitopertin 20 mg to placebo during washout period	Placebo to Bitopertin 10 mg during long-term extension
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (0.00%)	11 / 58 (18.97%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 45 (0.00%)	0 / 43 (0.00%)	4 / 58 (6.90%)
occurrences (all)	0	0	4

Non-serious adverse events	Bitopertin 10 mg during long-term extension	Bitopertin 20 mg during long-term extension	Placebo - follow-up period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 66 (37.88%)	19 / 67 (28.36%)	11 / 138 (7.97%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Depression			

subjects affected / exposed	4 / 66 (6.06%)	3 / 67 (4.48%)	0 / 138 (0.00%)
occurrences (all)	4	3	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 138 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	2 / 66 (3.03%)	2 / 67 (2.99%)	0 / 138 (0.00%)
occurrences (all)	3	2	0

Non-serious adverse events	Bitopertin 10 mg - follow-up period	Bitopertin 20 mg - follow-up period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 251 (10.76%)	25 / 192 (13.02%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	0 / 251 (0.00%)	0 / 192 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2010	Amendment A: Clarified study duration; Clarification on procedures collecting data for the Roche Clinical Repository (RCR) for exploratory objective; Changes to Work Readiness Questionnaire (WoRQ); Addition of inclusion criteria; Clarification of data collection: no details required on non-psychotropic medication; Change to the process to collect data in the eCRF for screened patient; Addition of Pharmacogenomic assessments to Other Endpoints; Clarification in Laboratory Assessments section to spell out "mean corpuscular volume" (MCV), and "mean corpuscular hemoglobin" (MCH); Clarification of urinalysis: to be performed at central laboratory; Addition of creatine phosphokinase for laboratory testing.
22 September 2010	Amendment B: Clarification on exclusion: to exclude patients who may have pre-existing potentially clinically significant hepatic dysfunction; Clarification of the secondary objective time point for safety and tolerability: 52 weeks randomized study treatment; Clarification of processes around patient randomization; Clarification of study duration; Clarification of Laboratory Assessments: guidelines added around fasting prior to blood sampling; Changes to schedule of assessment and procedure: Physical Examination changed from Week 16 to Week 12, ECG at Week 4 added, Clinical Global Impression – Improvement (CGI-I) assessment were assigned to the Baseline/Randomization visit-Day 1 was removed, Examination of Vital signs were added at Week 68, Week 80 and to be assessed every 12 weeks, Physical Examination, Smoking status, ESRS-A, and Eye Examination will be assessed in addition at Week 80, and Assessment of C-SSRS was added at Week 58.
21 April 2011	Amendment C: Further information on Long Term Extension regarding withdrawal effect based on the data collected during washout, safety and tolerability of long term use (beyond 56 weeks) of RO4917838 in combination with anti-psychotics and long-term treatment effects (beyond 56 weeks) on symptoms, functioning, quality of life and caregivers' burden; Change in requirements for female contraception methods; Change in method for pregnancy testing; Initiation of psychotherapy and/or rehabilitative therapy permitted from Treatment Period 2 (TP2) onwards; Adding of exclusion criterion 21: Both cannabis and barbiturates can be retested if positive at screening; Adding of exclusion criterion 22: as glycine supplementation and other products may have an effect on Nmethyl-D aspartate (NMDA)-type glutamate receptors these substances will be prohibited during study participation to avoid confounding study results; Extension of visit window of prospective stabilization period; Clarification of repeating screening assessments and rescreening; Changes to Schedule of Assessments section: Addition of questionnaire and Patient Assessment Form (PAF) for screening visit, removal of abbreviated inclusion/exclusion criteria assessment, addition of ECG assessment at week 12, efficacy measures/rating scales were better aligned to key visits in TP2, addition of blood chemistry assessments to week 60 and week 68 of LTE, adding questionnaire and clarification of questionnaire timing; Analysis of iron inclusion bodies and completion of iron related parameters; Correction of blood volumes; Clarification of reporting of serious adverse events; Clarification of non-serious adverse events of special interest and reporting process; Addition of risk benefit section; Clarification of restricted and prohibited concomitant medication.

20 February 2012	Amendment D: Addition of biomarker defined subpopulation as secondary objective; Clarification of timing of screening and prospective stabilization period; Clarification of exclusion criterion 3: decrease of exclusionary hemoglobin criterion in males; Updated dosing of concomitant antipsychotics for inclusion criterion 12; Clarification of exclusion criterion for body mass index; Revision of caregiver definition in inclusion criterion 5; Additional follow-up for treatment withdrawal and at week 52 initiation of washout and clarification of withdrawal process; clarified exclusion criterion regarding concomitant medication; Updated requirements for past use of clozapine; Added eszopiclone to list of restricted medications; Updated definition of postmenopausal; Inclusion of description of exploratory substudy open to eligible patients from certain sites in United Kingdom; Addition of new guidelines regarding withdrawal for hepatic laboratory abnormalities.
18 October 2012	Amendment E: Modification of caregiver burden assessment/ questionnaire; Inclusion of a futility analysis; Addition of biomarker defined subpopulation analysis to the objectives; Change in data safety monitoring board; Modification of exclusion criteria 2: update to patient demographics in Asian countries; Modification of exclusion criteria 18: clarification on eligibility of patients with prior history of clozapine; Addition of 12-Lead ECG assessment in long-term extension period; Change in serious adverse event (SAE) reporting to require SAEs to be reported within 24 hours of investigator becoming aware of event; Change in definition of safety population; Changes in definition of study duration; Removal of reference to per protocol population as all efficacy analyses will be performed on intent-to-treat population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported