

**Clinical trial results:**

A Phase III, Multi-Center, Randomized, 24 week, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate Efficacy and Safety of RO4917838 in Stable Patients with Persistent, Predominant Negative Symptoms of Schizophrenia Treated with Antipsychotics Followed by a 28 Week Double-Blind Treatment Period.

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2010-020370-42
Trial protocol	GB HU FI SE
Global end of trial date	26 May 2014

Results information

Result version number	v2 (current)
This version publication date	26 May 2016
First version publication date	06 August 2015
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Quality Control of data already entered before access for sponsors was blocked on 31 July 2015

Trial information**Trial identification**

Sponsor protocol code	NN25310
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01192867
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 May 2014
Global end of trial reached?	Yes
Global end of trial date	26 May 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Evaluate efficacy of 24 weeks treatment with RO4917838 in the Positive and Negative Syndrome Scale (PANSS) negative symptom factor score in subjects with persistent, predominant negative symptoms of schizophrenia treated with antipsychotics. Evaluate safety and tolerability of 24 weeks treatment with RO4917838 in subjects with persistent, predominant negative symptoms of schizophrenia treated with antipsychotics.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy:

Stable antipsychotic treatment

Evidence for comparator: -

Actual start date of recruitment	19 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	Romania: 36
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Hungary: 59
Country: Number of subjects enrolled	Russian Federation: 138
Country: Number of subjects enrolled	United States: 79
Country: Number of subjects enrolled	Argentina: 70
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Colombia: 27
Country: Number of subjects enrolled	India: 53
Country: Number of subjects enrolled	Korea, Republic of: 45
Country: Number of subjects enrolled	Mexico: 50
Worldwide total number of subjects	626
EEA total number of subjects	157

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)	616
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Diagnosis of schizophrenia, paranoid, disorganised, residual, undifferentiated or catatonic subtype. A score of 40 or greater on the sum of the 14 Positive and Negative Syndrome Scale (PANSS) negative and disorganised thought factor items and a score of 22 or less on the sum of the 8 PANSS positive symptom factor items.

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 only for Arms with the following designation in the name of the arm: Treatment period 1, Treatment period 2 and Washout period. Not applicable/not blinded for Longterm extension period and Safety follow-up period arms.

Arms

Are arms mutually exclusive?	No
Arm title	Placebo - Treatment period 1

Arm description:

Matching placebo adjunct to stable antipsychotic treatment for 24 weeks

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

Dosage and administration details:

Matching placebo oral use (p.o.) once daily (q.d.) for 24 weeks

Arm title	Bitopertin 10 mg - Treatment period 1
------------------	---------------------------------------

Arm description:

Bitopertin/RO4917838 10 mg adjunct to stable antipsychotic treatment for 24 weeks

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

Dosage and administration details:

10 mg oral use (p.o.) once daily (q.d.) for 24 weeks

Arm title	Bitopertin 20 mg - Treatment period 1
------------------	---------------------------------------

Arm description:

Bitopertin/RO4917838 20 mg adjunct to stable antipsychotic treatment for 24 weeks

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
20 mg oral use (p.o.) once daily (q.d.) for 24 weeks	
Arm title	Placebo - Treatment period 2
Arm description:	
Matching placebo adjunct to stable antipsychotic treatment for 28 weeks	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Matching placebo oral use (p.o.) once daily (q.d.) for 28 weeks	
Arm title	Bitopertin 10 mg - Treatment period 2
Arm description:	
Bitopertin/RO4917838 10 mg adjunct to stable antipsychotic treatment for 28 weeks	
Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
10 mg oral use (p.o.) once daily (q.d.) for 28 weeks	
Arm title	Bitopertin 20 mg - Treatment period 2
Arm description:	
Bitopertin/RO4917838 20 mg adjunct to stable antipsychotic treatment for 28 weeks	
Arm type	Experimental
Investigational medicinal product name	bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
20 mg oral use (p.o.) once daily (q.d.) for 28 weeks	
Arm title	Placebo - Washout period
Arm description:	
Matching placebo adjunct to stable antipsychotic treatment for 4 weeks	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo oral use (p.o.) once daily (q.d.) for 4 weeks

Arm title	Bitopertin 10 mg - Washout period
------------------	-----------------------------------

Arm description:

Bitopertin/RO4917838 10 mg adjunct to stable antipsychotic treatment for 4 weeks

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

Dosage and administration details:

10 mg oral use (p.o.) once daily (q.d.) for 4 weeks

Arm title	Bitopertin 10 mg to placebo - Washout period
------------------	--

Arm description:

Bitopertin/RO4917838 10 mg switched to placebo for duration of washout period; adjunct to stable antipsychotic treatment for 4 weeks

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

Dosage and administration details:

Matching placebo oral use (p.o.) once daily (q.d.) for 4 weeks

Arm title	Bitopertin 20 mg - Washout period
------------------	-----------------------------------

Arm description:

Bitopertin/RO4917838 20 mg adjunct to stable antipsychotic treatment for 4 weeks

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

Dosage and administration details:

20 mg oral use (p.o.) once daily (q.d.) for 4 weeks

Arm title	Bitopertin 20 mg to placebo - Washout period
------------------	--

Arm description:

Bitopertin/RO4917838 20 mg switched to placebo for duration of washout period; adjunct to antipsychotic treatment for 4 weeks

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

Dosage and administration details:

Matching placebo oral use (p.o.) once daily (q.d.) for 4 weeks

Arm title	Placebo - Longterm extension period
Arm description: Matching placebo during previous periods: switched to Bitopertin/RO4917838 10 mg adjunct to stable antipsychotic treatment up to 3 years	
Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 10 mg oral use (p.o.) once daily (q.d.) for up to 3 years	
Arm title	Bitopertin 10 mg - Longterm extension period
Arm description: Bitopertin/RO4917838 10 mg adjunct to stable antipsychotic treatment for up to 3 years	
Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 10 mg oral use (p.o.) once daily (q.d.) for up to 3 years	
Arm title	Bitopertin 20 mg - Longterm extension period
Arm description: Bitopertin/RO4917838 20 mg adjunct to stable antipsychotic treatment for up to 3 years	
Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	RO4917838
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 20 mg oral use (p.o.) once daily (q.d.) for up to 3 years	
Arm title	Placebo - Safety follow-up period
Arm description: Matching placebo during previous periods: no intervention during this period; adjunct to stable antipsychotic treatment	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Bitopertin 10 mg - Safety follow-up period
Arm description: Bitopertin/RO4917838 10 mg during previous periods: no intervention during this period; adjunct to antipsychotic treatment	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Bitopertin 20 mg - Safety follow-up period
Arm description: 20 mg Bitopertin/RO4917838 during previous periods: no intervention during this period; adjunct to stable antipsychotic treatment	
Arm type	No intervention

Number of subjects in period 1	Placebo - Treatment period 1	Bitopertin 10 mg - Treatment period 1	Bitopertin 20 mg - Treatment period 1
Started	210	208	208
Completed	163	174	180
Not completed	47	34	28
Consent withdrawn by subject	9	11	12
Administrative	4	4	4
Adverse event, non-fatal	19	7	5
Death	-	1	-
Non-compliance	7	4	1
Lost to follow-up	2	3	5
Lack of efficacy	1	2	-
Protocol deviation	5	2	1

Number of subjects in period 1	Placebo - Treatment period 2	Bitopertin 10 mg - Treatment period 2	Bitopertin 20 mg - Treatment period 2
Started	160	174	177
Completed	119	142	155
Not completed	41	32	22
Consent withdrawn by subject	7	2	3
Administrative	23	21	12
Adverse event, non-fatal	9	5	3
Death	-	1	-
Non-compliance	2	1	2
Lost to follow-up	-	1	-
Lack of efficacy	-	-	1
Protocol deviation	-	1	1

Number of subjects in period 1	Placebo - Washout period	Bitopertin 10 mg - Washout period	Bitopertin 10 mg to placebo - Washout period
Started	119	71	71
Completed	113	68	68
Not completed	6	3	3
Consent withdrawn by subject	-	-	-
Administrative	3	3	3

Adverse event, non-fatal	-	-	-
Death	2	-	-
Non-compliance	1	-	-
Lost to follow-up	-	-	-
Lack of efficacy	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Bitopertin 20 mg - Washout period	Bitopertin 20 mg to placebo - Washout period	Placebo - Longterm extension period
Started	78	77	102
Completed	73	71	0
Not completed	5	6	102
Consent withdrawn by subject	-	-	4
Administrative	5	3	93
Adverse event, non-fatal	-	1	3
Death	-	1	-
Non-compliance	-	1	-
Lost to follow-up	-	-	1
Lack of efficacy	-	-	1
Protocol deviation	-	-	-

Number of subjects in period 1	Bitopertin 10 mg - Longterm extension period	Bitopertin 20 mg - Longterm extension period	Placebo - Safety follow-up period
Started	116	120	108
Completed	0	0	61
Not completed	116	120	47
Consent withdrawn by subject	1	6	18
Administrative	109	106	11
Adverse event, non-fatal	3	4	5
Death	-	-	1
Non-compliance	1	-	-
Lost to follow-up	2	3	12
Lack of efficacy	-	1	-
Protocol deviation	-	-	-

Number of subjects in period 1	Bitopertin 10 mg - Safety follow-up period	Bitopertin 20 mg - Safety follow-up period
Started	310	208
Completed	234	148
Not completed	76	60
Consent withdrawn by subject	25	15
Administrative	17	15
Adverse event, non-fatal	1	2

Death	2	2
Non-compliance	-	-
Lost to follow-up	31	26
Lack of efficacy	-	-
Protocol deviation	-	-

Baseline characteristics

Reporting groups

Reporting group title	Overall period
-----------------------	----------------

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	626	626	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	616	616	
From 65-84 years	10	10	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	39.3		
standard deviation	± 11.9	-	
Gender categorical			
Units: Subjects			
Female	203	203	
Male	423	423	

End points

End points reporting groups

Reporting group title	Placebo - Treatment period 1
Reporting group description: Matching placebo adjunct to stable antipsychotic treatment for 24 weeks	
Reporting group title	Bitopertin 10 mg - Treatment period 1
Reporting group description: Bitopertin/RO4917838 10 mg adjunct to stable antipsychotic treatment for 24 weeks	
Reporting group title	Bitopertin 20 mg - Treatment period 1
Reporting group description: Bitopertin/RO4917838 20 mg adjunct to stable antipsychotic treatment for 24 weeks	
Reporting group title	Placebo - Treatment period 2
Reporting group description: Matching placebo adjunct to stable antipsychotic treatment for 28 weeks	
Reporting group title	Bitopertin 10 mg - Treatment period 2
Reporting group description: Bitopertin/RO4917838 10 mg adjunct to stable antipsychotic treatment for 28 weeks	
Reporting group title	Bitopertin 20 mg - Treatment period 2
Reporting group description: Bitopertin/RO4917838 20 mg adjunct to stable antipsychotic treatment for 28 weeks	
Reporting group title	Placebo - Washout period
Reporting group description: Matching placebo adjunct to stable antipsychotic treatment for 4 weeks	
Reporting group title	Bitopertin 10 mg - Washout period
Reporting group description: Bitopertin/RO4917838 10 mg adjunct to stable antipsychotic treatment for 4 weeks	
Reporting group title	Bitopertin 10 mg to placebo - Washout period
Reporting group description: Bitopertin/RO4917838 10 mg switched to placebo for duration of washout period; adjunct to stable antipsychotic treatment for 4 weeks	
Reporting group title	Bitopertin 20 mg - Washout period
Reporting group description: Bitopertin/RO4917838 20 mg adjunct to stable antipsychotic treatment for 4 weeks	
Reporting group title	Bitopertin 20 mg to placebo - Washout period
Reporting group description: Bitopertin/RO4917838 20 mg switched to placebo for duration of washout period; adjunct to antipsychotic treatment for 4 weeks	
Reporting group title	Placebo - Longterm extension period
Reporting group description: Matching placebo during previous periods: switched to Bitopertin/RO4917838 10 mg adjunct to stable antipsychotic treatment up to 3 years	
Reporting group title	Bitopertin 10 mg - Longterm extension period
Reporting group description: Bitopertin/RO4917838 10 mg adjunct to stable antipsychotic treatment for up to 3 years	
Reporting group title	Bitopertin 20 mg - Longterm extension period
Reporting group description: Bitopertin/RO4917838 20 mg adjunct to stable antipsychotic treatment for up to 3 years	
Reporting group title	Placebo - Safety follow-up period
Reporting group description: Matching placebo during previous periods: no intervention during this period; adjunct to stable antipsychotic treatment	

Reporting group title	Bitopertin 10 mg - Safety follow-up period
Reporting group description: Bitopertin/RO4917838 10 mg during previous periods: no intervention during this period; adjunct to antipsychotic treatment	
Reporting group title	Bitopertin 20 mg - Safety follow-up period
Reporting group description: 20 mg Bitopertin/RO4917838 during previous periods: no intervention during this period; adjunct to stable antipsychotic treatment	

Primary: Mean Change from Baseline Positive and Negative Syndrome Scale (PANSS)

End point title	Mean Change from Baseline Positive and Negative Syndrome Scale (PANSS) ^[1]
End point description: Mean change from baseline to week 24 in the Positive and Negative Syndrome Scale (PANSS) Negative Symptom Factor Score (NSFS) in subjects with persistent, predominant negative symptoms of schizophrenia treated with antipsychotics.	
End point type	Primary
End point timeframe: Baseline to week 24	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Since this study has an adaptive trial design all periods had to be reported in the Overall Period to avoid errors in the subject disposition section. As indicated in the arm titles data were reported for all arms in the baseline period (Treatment period 1).

End point values	Placebo - Treatment period 1	Bitopertin 10 mg - Treatment period 1	Bitopertin 20 mg - Treatment period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	197	200	197	
Units: Score				
arithmetic mean (standard error)	-6.11 (± 0.369)	-5.77 (± 0.335)	-6.08 (± 0.379)	

Statistical analyses

Statistical analysis title	Difference from Placebo: 10 mg RO4917838 MMRM
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	Placebo - Treatment period 1 v Bitopertin 10 mg - Treatment period 1
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2706
Method	MMRM

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 - Treatment period 1 v Bitopertin 20 mg - Treatment period 1
Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6425
Method	MMRM

Statistical analysis title	Difference from placebo: 10 mg RO4917838 ANCOVA
Statistical analysis description: Difference of treatment with 10 mg RO4917838 from placebo using analysis of covariance (ANCOVA) model	
Comparison groups	Bitopertin 10 mg - Treatment period 1 v Placebo - Treatment period 1
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3692
Method	ANCOVA

Statistical analysis title	Difference from placebo: 20 mg RO4917838 ANCOVA
Statistical analysis description: Difference of treatment with 20 mg RO4917838 from placebo using analysis of covariance (ANCOVA) model	
Comparison groups	Placebo - Treatment period 1 v Bitopertin 20 mg - Treatment period 1
Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	ANCOVA

Secondary: Mean change from baseline in the Personal and Social Performance (PSP) total score

End point title	Mean change from baseline in the Personal and Social Performance (PSP) total score ^[2]
-----------------	---

End point description:

Mean change from baseline at week 24 in personal and social functioning using Personal and Social Performance (PSP) total score in subjects with persistent, predominant negative symptoms of

schizophrenia treated with antipsychotics.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline to week 24

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Since this study has an adaptive trial design all periods had to be reported in the Overall Period to avoid errors in the subject disposition section. As indicated in the arm titles data were reported for all arms in the baseline period (Treatment period 1).

End point values	Placebo - Treatment period 1	Bitopertin 10 mg - Treatment period 1	Bitopertin 20 mg - Treatment period 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	197	200	197	
Units: Score				
arithmetic mean (standard error)	8.41 (± 0.802)	9.48 (± 0.848)	8.38 (± 0.804)	

Statistical analyses

Statistical analysis title	Difference from placebo: 10 mg RO4917838 MMRM
-----------------------------------	---

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	Placebo - Treatment period 1 v Bitopertin 10 mg - Treatment period 1
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4697
Method	MMRM

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 - Treatment period 1 v Bitopertin 20 mg - Treatment period 1
Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8982
Method	MMRM

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization to the end of the study (up to 4 years, 2 months)

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	17.0
--------------------	------

Reporting groups

Reporting group title	Placebo - Treatment periods 1 and 2
-----------------------	-------------------------------------

Reporting group description:

Matching placebo, Treatment periods 1 and 2: 52 weeks

Reporting group title	Bitopertin 10 mg - Treatment periods 1 and 2
-----------------------	--

Reporting group description:

Bitopertin 10 mg, Treatment periods 1 and 2: 52 weeks

Reporting group title	Bitopertin 20 mg - Treatment periods 1 and 2
-----------------------	--

Reporting group description:

Bitopertin 20 mg, Treatment periods 1 and 2: 52 weeks

Reporting group title	Placebo - Washout period
-----------------------	--------------------------

Reporting group description:

Matching placebo, oral administration, once daily for 4 weeks following the treatment period 2 starting at week 52

Reporting group title	Bitopertin 10 mg - Washout period
-----------------------	-----------------------------------

Reporting group description:

Bitopertin 10 mg, oral administration, once daily for 4 weeks following treatment period 2 starting at week 52

Reporting group title	Bitopertin 10 mg to Placebo - Washout period
-----------------------	--

Reporting group description:

Bitopertin 10 mg switched to placebo: oral administration, once daily for 4 weeks following treatment period 2 starting at week 52

Reporting group title	Bitopertin 20 mg - Washout period
-----------------------	-----------------------------------

Reporting group description:

Bitopertin 20 mg, oral administration, once daily for 4 weeks following treatment period 2 starting at week 52

Reporting group title	Bitopertin 20 mg to Placebo - Washout period
-----------------------	--

Reporting group description:

Bitopertin 20 mg switched to placebo: oral administration, once daily for 4 weeks following treatment period 2 starting at week 52

Reporting group title	Placebo - Long term extension period
-----------------------	--------------------------------------

Reporting group description:

Placebo group in treatment and washout periods switched to Bitopertin/RO4917838 10 mg, oral administration, once daily for up to 3 years following washout period

Reporting group title	Bitopertin 10 mg - Long term extension period
-----------------------	---

Reporting group description:

Bitopertin 10 mg, oral administration, once daily up to 3 years following washout period

Reporting group title	Bitopertin 20 mg - Long term extension period
-----------------------	---

Reporting group description:

Bitopertin 20 mg, oral administration, once daily up to 3 years following the washout period

Reporting group title	Placebo - Safety follow up period
-----------------------	-----------------------------------

Reporting group description:

Placebo group in prior periods: no intervention during 4 week safety follow up period

Reporting group title	Bitopertin 10 mg - Safety follow up period
Reporting group description:	
Bitopertin 10 mg in prior periods: no intervention during 4 week safety follow up period	
Reporting group title	Bitopertin 20 mg - Safety follow up period
Reporting group description:	
Bitopertin 20 mg in prior periods: no intervention during 4 week safety follow up period	

Serious adverse events	Placebo - Treatment periods 1 and 2	Bitopertin 10 mg - Treatment periods 1 and 2	Bitopertin 20 mg - Treatment periods 1 and 2
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 210 (8.10%)	13 / 208 (6.25%)	7 / 208 (3.37%)
number of deaths (all causes)	1	2	1
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid cancer			
subjects affected / exposed	0 / 210 (0.00%)	1 / 208 (0.48%)	0 / 208 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 210 (0.00%)	1 / 208 (0.48%)	0 / 208 (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
Papillary thyroid cancer			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Thrombosis			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Physical assault			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social problem			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 210 (0.00%)	1 / 208 (0.48%)	0 / 208 (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
Uterine polyp			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizophrenia			

subjects affected / exposed	7 / 210 (3.33%)	3 / 208 (1.44%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	4 / 7	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	2 / 208 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 210 (0.00%)	1 / 208 (0.48%)	0 / 208 (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
Completed suicide			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	0 / 210 (0.00%)	1 / 208 (0.48%)	0 / 208 (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
Investigations			
Pancreatic enzymes increased			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fall			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gun shot wound			
subjects affected / exposed	0 / 210 (0.00%)	1 / 208 (0.48%)	0 / 208 (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
Joint dislocation			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 210 (0.00%)	1 / 208 (0.48%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Stab wound			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 210 (0.00%)	1 / 208 (0.48%)	0 / 208 (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
Toxicity to various agents			

subjects affected / exposed	2 / 210 (0.95%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye contusion			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardio-respiratory arrest			
subjects affected / exposed	0 / 210 (0.00%)	1 / 208 (0.48%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Bradycardia			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 210 (0.00%)	1 / 208 (0.48%)	0 / 208 (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-injection delirium sedation			

syndrome			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oromandibular dystonia			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Oculogyric crisis			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 210 (0.00%)	1 / 208 (0.48%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Tuberculosis			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 210 (0.00%)	1 / 208 (0.48%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 210 (0.48%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatitis A			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicitis			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis chronic			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 210 (0.00%)	0 / 208 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo - Washout period	Bitopertin 10 mg - Washout period	Bitopertin 10 mg to Placebo - Washout period
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 119 (0.00%)	1 / 71 (1.41%)	0 / 71 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid cancer			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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 neoplasm			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Physical assault			

subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social problem			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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 / 119 (0.00%)	1 / 71 (1.41%)	0 / 71 (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
Anxiety			

subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Pancreatic enzymes increased			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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			
Upper limb fracture			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gun shot wound			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stab wound			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye contusion			

subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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			
Epilepsy			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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-injection delirium sedation syndrome			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oromandibular dystonia			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Oculogyric crisis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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			
Tuberculosis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatitis A			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicitis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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 chronic			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
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			
Dehydration			
subjects affected / exposed	0 / 119 (0.00%)	0 / 71 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Bitopertin 20 mg - Washout period	Bitopertin 20 mg to Placebo - Washout period	Placebo - Long term extension period
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 78 (1.28%)	2 / 77 (2.60%)	1 / 102 (0.98%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid cancer			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			

subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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 neoplasm			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Physical assault			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social problem			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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 / 78 (0.00%)	1 / 77 (1.30%)	0 / 102 (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	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Suicide attempt			

subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Pancreatic enzymes increased			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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			
Upper limb fracture			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gun shot wound			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Radius fracture			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stab wound			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye contusion			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			

subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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			
Epilepsy			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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-injection delirium sedation syndrome			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oromandibular dystonia			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Oculogyric crisis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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			
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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			
Tuberculosis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatitis A			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 102 (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
Cervicitis			

subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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 chronic			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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			
Dehydration			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 102 (0.00%)
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	Biopertin 10 mg - Long term extension period	Bitopertin 20 mg - Long term extension period	Placebo - Safety follow up period
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 116 (6.03%)	5 / 120 (4.17%)	7 / 108 (6.48%)
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)			
Thyroid cancer			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 116 (0.00%)	1 / 120 (0.83%)	0 / 108 (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
Metastases to lung			

subjects affected / exposed	1 / 116 (0.86%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	1 / 116 (0.86%)	0 / 120 (0.00%)	0 / 108 (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
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Physical assault			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social problem			
subjects affected / exposed	1 / 116 (0.86%)	0 / 120 (0.00%)	0 / 108 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			

subjects affected / exposed	0 / 116 (0.00%)	1 / 120 (0.83%)	0 / 108 (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			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
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 / 116 (0.86%)	0 / 120 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 116 (0.00%)	1 / 120 (0.83%)	2 / 108 (1.85%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 116 (0.00%)	1 / 120 (0.83%)	0 / 108 (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
Completed suicide			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 116 (0.86%)	0 / 120 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Pancreatic enzymes increased			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gun shot wound			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Stab wound			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	0 / 116 (0.00%)	1 / 120 (0.83%)	0 / 108 (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
Eye contusion			
subjects affected / exposed	1 / 116 (0.86%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Epilepsy			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
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-injection delirium sedation syndrome			
subjects affected / exposed	1 / 116 (0.86%)	0 / 120 (0.00%)	0 / 108 (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
Oromandibular dystonia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Oculogyric crisis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
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			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
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			

subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
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			
Tuberculosis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
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 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
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 / 116 (0.00%)	0 / 120 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatitis A			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 120 (0.00%)	0 / 108 (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
Bronchitis chronic			
subjects affected / exposed	0 / 116 (0.00%)	0 / 120 (0.00%)	0 / 108 (0.00%)
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			

Dehydration			
subjects affected / exposed	1 / 116 (0.86%)	0 / 120 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Bitopertin 10 mg - Safety follow up period	Bitopertin 20 mg - Safety follow up period	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 310 (0.65%)	2 / 208 (0.96%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid cancer			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 310 (0.00%)	1 / 208 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombosis			

subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Physical assault			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social problem			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			

subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 310 (0.32%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Pancreatic enzymes increased			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gun shot wound			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stab wound			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			

subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye contusion			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-injection delirium sedation			

syndrome			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oromandibular dystonia			
subjects affected / exposed	1 / 310 (0.32%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Oculogyric crisis			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Tuberculosis			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatitis A			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicitis			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 310 (0.00%)	1 / 208 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 310 (0.00%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo - Treatment periods 1 and 2	Bitopertin 10 mg - Treatment periods 1 and 2	Bitopertin 20 mg - Treatment periods 1 and 2
Total subjects affected by non-serious adverse events subjects affected / exposed	116 / 210 (55.24%)	23 / 208 (11.06%)	105 / 208 (50.48%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	15 / 210 (7.14%) 20	11 / 208 (5.29%) 16	6 / 208 (2.88%) 6
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	5 / 210 (2.38%) 6	3 / 208 (1.44%) 3	11 / 208 (5.29%) 11
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 210 (4.29%) 10	9 / 208 (4.33%) 11	8 / 208 (3.85%) 10

Non-serious adverse events	Placebo - Washout period	Bitopertin 10 mg - Washout period	Bitopertin 10 mg to Placebo - Washout period
Total subjects affected by non-serious adverse events subjects affected / exposed	16 / 119 (13.45%)	0 / 71 (0.00%)	15 / 71 (21.13%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 119 (0.84%) 1	0 / 71 (0.00%) 0	1 / 71 (1.41%) 1
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 119 (0.00%) 0	0 / 71 (0.00%) 0	0 / 71 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 119 (1.68%) 2	0 / 71 (0.00%) 0	2 / 71 (2.82%) 2

Non-serious adverse events	Bitopertin 20 mg - Washout period	Bitopertin 20 mg to Placebo - Washout period	Placebo - Long term extension period
Total subjects affected by non-serious adverse events subjects affected / exposed	14 / 78 (17.95%)	9 / 77 (11.69%)	33 / 102 (32.35%)
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	1 / 78 (1.28%) 1	1 / 77 (1.30%) 1	1 / 102 (0.98%) 1
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 78 (1.28%) 1	0 / 77 (0.00%) 0	0 / 102 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 78 (2.56%) 2	0 / 77 (0.00%) 0	7 / 102 (6.86%) 8

Non-serious adverse events	Biopertin 10 mg - Long term extension period	Bitopertin 20 mg - Long term extension period	Placebo - Safety follow up period
Total subjects affected by non-serious adverse events subjects affected / exposed	38 / 116 (32.76%)	39 / 120 (32.50%)	14 / 108 (12.96%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 116 (1.72%) 2	2 / 120 (1.67%) 2	3 / 108 (2.78%) 3
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 116 (1.72%) 2	1 / 120 (0.83%) 1	0 / 108 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	2 / 120 (1.67%) 2	1 / 108 (0.93%) 1

Non-serious adverse events	Bitopertin 10 mg - Safety follow up period	Bitopertin 20 mg - Safety follow up period	
Total subjects affected by non-serious adverse events subjects affected / exposed	19 / 310 (6.13%)	23 / 208 (11.06%)	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 310 (0.97%) 3	2 / 208 (0.96%) 2	
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	0 / 310 (0.00%) 0	1 / 208 (0.48%) 1	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 310 (0.32%) 1	1 / 208 (0.48%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2010	Amendment B: Addition of creatine phosphokinase for laboratory testing; Clarification on procedures collecting data for the Roche Clinical Repository (RCR) for exploratory objective; Changes to Work Readiness Questionnaire (WoRQ); Changes to schedule of assessments and procedures: physical examination changed from Week 28 to Week 24, during Long Term Extension period examination of vital signs were added at Week 68, Week 80 and to be assessed every 12 weeks; Clarification of data collection: no details required on non-psychotropic medication; Clarification of urinalysis: to be performed at central laboratory; Liver enzymes: changes to exclusion criteria excluding subjects with hepatic dysfunction
21 April 2011	Amendment C: Further information on Long Term Extension period regarding safety and tolerability of long term use (beyond 56 weeks) of RO4917838 in combination with antipsychotics as well as long-term treatment effects (beyond 56 weeks) on the symptoms, functioning, quality of life and caregivers' burden; Addition of questionnaire; Initiation of psychosocial and/or rehabilitative therapy permitted from Treatment Period 2 (TP2) onwards; Adding of exclusion criterion 22: as glycine supplementation and other products may have an effect on the N-methyl-D aspartate (NMDA)-type glutamate receptors these substances will be prohibited during the study participation to avoid confounding the study results; Clarification of reporting of serious adverse events: elective hospitalisation or hospitalisation due to social reasons does not meet the criteria of Serious Adverse Event; Inclusion of risk and benefit assessment section: during this clinical development program the subject's safety profile will be closely monitored. The risk for the individual subject due to treatment with RO4917838 or study related procedures are considered low because of the proposed doses and careful monitoring of all critical safety parameters. The current risk/benefit profile of the drug justifies continued assessment of RO4917838 in Phase III clinical studies. The participation in the study itself will not deprive subjects from standard treatment as their antipsychotic therapy is maintained.
04 October 2011	Amendment C-1: Description of the proton Magnetic Resonance Spectroscopy (1H-MRS) and functional magnetic resonance imaging (fMRI) sub study.
20 February 2012	Amendment D: Addition of biomarker defined subpopulations as a secondary objective; Clarification of timing of screening and prospective stabilisation period; Clarification of exclusion criterion 3 decreasing the exclusionary hemoglobin criterion in males from 13 g/dL to 12g/dL as per Data and Safety Monitoring Board (DSMB) endorsement; Updated dosing of concomitant antipsychotics for inclusion criterion 12: equivalent dose of the primary and secondary antipsychotic treatments can be the same; Clarification of exclusion criterion for Body Mass Index (BMI) < 18.5 or > 40; Revision of the definition of caregiver in inclusion criterion 5 to someone being able to support the subject through the study and who has sufficient knowledge and understanding of the subject to be able to identify changes in the subject's condition or symptoms; Additional follow-up for treatment withdrawal and at week-52 initiation of wash-out, and clarification of withdrawal process to ensure close monitoring of reported adverse events; Definition of postmenopausal; New guidelines regarding withdrawal for hepatic laboratory abnormalities.
30 May 2012	Amendment D-1: Modification of caregiver burden assessment/questionnaire in the following countries: Canada, United Kingdom (UK), United States (USA), Australia, Finland, France, Germany, Italy, Netherlands, Spain and Sweden

18 October 2012	Amendment E: Modification of the caregiver burden assessment/questionnaire combining the approach related to Protocol version D and Protocol version D-1, the latest one applying locally to the following countries: Canada, United Kingdom, United States, Australia, Finland, France, Germany, Italy, Netherlands, Spain, and Sweden.
-----------------	--

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 May 2014	Study was terminated prematurely after the primary analysis at Week 24. The study ended once the last randomised subject completed the last assessment (LPLV), which was planned for 4 weeks after the last dose taken, i.e., at the 4-week safety follow-up visit.	-

Notes:

Limitations and caveats

None reported