



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | WN25308 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01192880 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 21 November 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 08 July 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

This was a Phase III, multi-center, randomized, 24 week, double-blind, parallel-group, placebo-controlled study to evaluate efficacy and safety of bitopertin (RO4917838) in stable participants with persistent, predominant negative symptoms of schizophrenia treated with anti-psychotics followed by a 28-week, double-blind placebo-controlled treatment period.

Protection of trial subjects:

The investigator ensured that this study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study fully adhered to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it afforded greater protection to the participant. For studies conducted in the European Union/European Economic Area (EU/EEA) countries, the investigator ensured compliance with the EU Clinical Trial Directive [2001/20/EC]. For studies conducted in the United States of America (USA) or under US Investigational New Drug (IND), the investigator additionally ensured adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 Code of Federal Regulations (CFR), subchapter D, part 312, "Responsibilities of sponsors and Investigators", part 50, "Protection of Human Patients", and part 56, "Institutional Review Boards".

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 615 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

| | |
|------------------------------|----|
| Are arms mutually exclusive? | No |
|------------------------------|----|

| | |
|------------------|----------------------------|
| Arm title | Placebo-Treatment Period 1 |
|------------------|----------------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|-------------------------------------|
| Arm title | Bitopertin 10 mg-Treatment Period 1 |
|------------------|-------------------------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|-------------------------------------|
| Arm title | Bitopertin 20 mg-Treatment Period 1 |
|------------------|-------------------------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|----------------------------|
| Arm title | Placebo-Treatment Period 2 |
|------------------|----------------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|-------------------------------------|
| Arm title | Bitopertin 10 mg-Treatment Period 2 |
|------------------|-------------------------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|-------------------------------------|
| Arm title | Bitopertin 20 mg-Treatment Period 2 |
|------------------|-------------------------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|------------------------|
| Arm title | Placebo-Washout Period |
|------------------|------------------------|

Arm description:

Matching oral placebo doses (10 mg or 20 mg) in the morning with/without food adjunct to stable antipsychotic treatment for 4 weeks.

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

Dosage and administration details:

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

| | |
|------------------|---------------------------------|
| Arm title | Bitopertin 10 mg-Washout Period |
|------------------|---------------------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|--|
| Arm title | Bitopertin 10 mg to Placebo-Washout Period |
|------------------|--|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|---------------------------------|
| Arm title | Bitopertin 20 mg-Washout Period |
|------------------|---------------------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|--|
| Arm title | Bitopertin 20 mg to Placebo-Washout Period |
|------------------|--|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|--|
| Arm title | Placebo to Bitopertin 10 mg-LTE Period |
|------------------|--|

Arm description:

Placebo during previous periods: switched to bitopertin 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:

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

| | |
|------------------|-----------------------------|
| Arm title | Bitopertin 10 mg-LTE Period |
|------------------|-----------------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|-----------------------------|
| Arm title | Bitopertin 20 mg-LTE Period |
|------------------|-----------------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|-----------------------------------|
| Arm title | Placebo – Safety Follow-up Period |
|------------------|-----------------------------------|

Arm description:

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

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

| | |
|------------------|--|
| Arm title | Bitopertin 10 mg – Safety Follow-up Period |
|------------------|--|

Arm description:

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

| | |
|---|--|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Bitopertin 20 mg – Safety Follow-up Period |
| Arm description: | |
| Participants who were on bitopertin 20 mg treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment. | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

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

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

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

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

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

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

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

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description: -

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

End points

End points reporting groups

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

| | |
|---|--|
| Reporting group title | Bitopertin 20 mg-LTE Period |
| Reporting group description: Bitopertin 20 mg adjunct to stable antipsychotic treatment for up to 3 years. | |
| Reporting group title | Placebo – Safety Follow-up Period |
| Reporting group description: Participants who were on placebo treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment. | |
| Reporting group title | Bitopertin 10 mg – Safety Follow-up Period |
| Reporting group description: Participants who were on bitopertin 10 mg treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment. | |
| Reporting group title | Bitopertin 20 mg – Safety Follow-up Period |
| Reporting group description: Participants who were on bitopertin 20 mg treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment. | |

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

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

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 24

Notes:

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

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

Statistical analyses

| Statistical analysis title | Statistical analysis I |
|---|--|
| Statistical analysis description: | |
| Primary analysis population was ITT population. For all analyses of PANSS data, scores were transformed into 0-6 points to express "absent" as 0. Mean change from baseline in PANSS NSFS at Week 24 was analyzed using an MMRM incorporating data collected up to 24 weeks of treatment to assess all data collected over time with consideration of the variance-covariance matrix of repeated measures. No imputations for missing data were used in primary analyses. | |
| Comparison groups | Placebo-Treatment Period 1 v Bitopertin 10 mg-Treatment Period 1 |
| Number of subjects included in analysis | 399 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9008 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.89 |
| upper limit | 1.01 |

| Statistical analysis title | Statistical analysis II |
|---|--|
| Statistical analysis description: | |
| Primary analysis population was ITT population. For all analyses of PANSS data, scores were transformed into 0-6 points to express "absent" as 0. Mean change from baseline in PANSS NSFS at Week 24 was analyzed using an MMRM incorporating data collected up to 24 weeks of treatment to assess all data collected over time with consideration of the variance-covariance matrix of repeated measures. No imputations for missing data were used in primary analyses. | |
| Comparison groups | Placebo-Treatment Period 1 v Bitopertin 20 mg-Treatment Period 1 |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6844 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.76 |
| upper limit | 1.15 |

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

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

End point description:

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

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

End point timeframe:

Baseline, Week 24

Notes:

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

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

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis I |
|----------------------------|------------------------|

Statistical analysis description:

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

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

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

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis II |
|-----------------------------------|-------------------------|

Statistical analysis description:

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

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Placebo – Treatment Periods 1 and 2 |
|-----------------------|-------------------------------------|

Reporting group description:

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

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

Reporting group description:

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

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

Reporting group description:

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

| | |
|-----------------------|--------------------------|
| Reporting group title | Placebo – Washout Period |
|-----------------------|--------------------------|

Reporting group description:

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

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Bitopertin 10 mg – Washout Period |
|-----------------------|-----------------------------------|

Reporting group description:

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

| | |
|-----------------------|--|
| Reporting group title | Bitopertin 10 mg to Placebo – Washout Period |
|-----------------------|--|

Reporting group description:

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

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Bitopertin 20 mg – Washout Period |
|-----------------------|-----------------------------------|

Reporting group description:

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

| | |
|-----------------------|--|
| Reporting group title | Bitopertin 20 mg to Placebo – Washout Period |
|-----------------------|--|

Reporting group description:

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

| | |
|-----------------------|--|
| Reporting group title | Placebo to Bitopertin 10 mg – LTE period |
|-----------------------|--|

Reporting group description:

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

| | |
|-----------------------|-------------------------------|
| Reporting group title | Bitopertin 10 mg – LTE Period |
|-----------------------|-------------------------------|

Reporting group description:

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

| | |
|-----------------------|-------------------------------|
| Reporting group title | Bitopertin 20 mg – LTE Period |
|-----------------------|-------------------------------|

Reporting group description:

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

| | |
|--|--|
| Reporting group title | Placebo – Safety Follow-up Period |
| Reporting group description: Participants who were on placebo treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment. Adverse event data reported are for safety follow-up period. | |
| Reporting group title | Bitopertin 10 mg – Safety Follow-up Period |
| Reporting group description: Participants who were on bitopertin 10 mg treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment. Adverse event data reported are for safety follow-up period. | |
| Reporting group title | Bitopertin 20 mg – Safety Follow-up Period |
| Reporting group description: Participants who were on bitopertin 20 mg treatment at the time of discontinuation from study treatment but came for 4-week safety follow-up period were included. No intervention during this period; adjunct to stable antipsychotic treatment. Adverse event data reported are for safety follow-up period. | |

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

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

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

| | | | |
|---|-----------------|-----------------|-----------------|
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 206 (0.00%) | 0 / 206 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | 0 / 206 (0.00%) | 0 / 208 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Schizophrenia | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental disorder | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychotic disorder | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Persecutory delusion | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tension | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 0 / 57 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------------------------|----------------------------------|----------------------------------|
| Infections and infestations Bronchopneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 113 (0.00%) 0 / 0 0 / 0 | 0 / 57 (0.00%) 0 / 0 0 / 0 | 0 / 58 (0.00%) 0 / 0 0 / 0 |
|---|-----------------------------------|----------------------------------|----------------------------------|

| Serious adverse events | Bitopertin 20 mg – Washout Period | Bitopertin 20 mg to Placebo – Washout Period | Placebo to Bitopertin 10 mg – LTE period |
|--|-----------------------------------|--|--|
| Total subjects affected by serious adverse events subjects affected / exposed number of deaths (all causes) number of deaths resulting from adverse events | 1 / 56 (1.79%) 0 | 0 / 57 (0.00%) 0 | 3 / 94 (3.19%) 0 |
| Injury, poisoning and procedural complications Wrist fracture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 56 (0.00%) 0 / 0 0 / 0 | 0 / 57 (0.00%) 0 / 0 0 / 0 | 0 / 94 (0.00%) 0 / 0 0 / 0 |
| Chemical poisoning subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 56 (0.00%) 0 / 0 0 / 0 | 0 / 57 (0.00%) 0 / 0 0 / 0 | 0 / 94 (0.00%) 0 / 0 0 / 0 |
| Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 56 (0.00%) 0 / 0 0 / 0 | 0 / 57 (0.00%) 0 / 0 0 / 0 | 0 / 94 (0.00%) 0 / 0 0 / 0 |
| Atrioventricular block second degree subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 56 (0.00%) 0 / 0 0 / 0 | 0 / 57 (0.00%) 0 / 0 0 / 0 | 0 / 94 (0.00%) 0 / 0 0 / 0 |
| Myocarditis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 56 (0.00%) 0 / 0 0 / 0 | 0 / 57 (0.00%) 0 / 0 0 / 0 | 0 / 94 (0.00%) 0 / 0 0 / 0 |
| Nervous system disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 57 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Psoriasis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Schizophrenia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 1 / 94 (1.06%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental disorder | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychotic disorder | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 1 / 94 (1.06%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Persecutory delusion | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 1 / 94 (1.06%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tension | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 57 (0.00%) | 0 / 94 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Bitopertin 10 mg – LTE Period | Bitopertin 20 mg – LTE Period | Placebo – Safety Follow-up Period |
|--|----------------------------------|----------------------------------|--------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 102 (2.94%) | 1 / 98 (1.02%) | 2 / 113 (1.77%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chemical poisoning | | | |
| subjects affected / exposed | 1 / 102 (0.98%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocarditis | | | |
| subjects affected / exposed | 1 / 102 (0.98%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 102 (0.98%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastritis | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 102 (0.00%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 102 (0.98%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | 1 / 98 (1.02%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 102 (0.98%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Schizophrenia | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 102 (0.98%) | 0 / 98 (0.00%) | 2 / 113 (1.77%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental disorder | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychotic disorder | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Persecutory delusion | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tension | | | |
| subjects affected / exposed | 1 / 102 (0.98%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 102 (0.98%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | 0 / 98 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Bitopertin 10 mg – Safety Follow-up Period | Bitopertin 20 mg – Safety Follow-up Period | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 299 (0.67%) | 4 / 208 (1.92%) | |
| number of deaths (all causes) | 0 | 0 | |

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

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

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 208 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychotic disorder | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 208 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Persecutory delusion | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 208 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tension | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 208 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 208 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 208 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo – Treatment Periods 1 and 2 | Bitopertin 10 mg – Treatment Periods 1 and 2 | Bitopertin 20 mg – Treatment Periods 1 and 2 |
|---|-------------------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 30 / 206 (14.56%) | 34 / 206 (16.50%) | 26 / 208 (12.50%) |
| Nervous system disorders | | | |
| Headache | | | |

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

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

Notes:

Limitations and caveats

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

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

Notes:

