



## 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.**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2010-020467-21    |
| Trial protocol           | ES DE LT LV SK NL |
| Global end of trial date | 09 June 2014      |

### Results information

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

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | WN25309 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01192906 |
| 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<br>, 41 61 6878333, global.trial_information@roche.com |
| Scientific contact           | Roche Trial Information Hotline, F. Hoffmann-La Roche AG<br>, 41 61 6878333, global.trial_information@roche.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 09 June 2014 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 09 June 2014 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

The main objectives of this study are :

- To evaluate the efficacy of 24 weeks treatment with bitopertin in the Positive and Negative Syndrome Scale (PANSS) Negative Symptom Factor Score (NSFS) in patients with persistent, predominant negative symptoms of schizophrenia treated with antipsychotics
- To evaluate the safety and tolerability of 24 weeks of treatment with bitopertin in patients with persistent, predominant negative symptoms of schizophrenia treated with antipsychotics

Protection of trial subjects:

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

Background therapy:

This is an add-on therapy to selected typical and atypical antipsychotics treatment.

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 27 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 | Netherlands: 3    |
| Country: Number of subjects enrolled | Poland: 85        |
| Country: Number of subjects enrolled | Slovakia: 10      |
| Country: Number of subjects enrolled | Spain: 38         |
| Country: Number of subjects enrolled | Germany: 18       |
| Country: Number of subjects enrolled | Latvia: 12        |
| Country: Number of subjects enrolled | Lithuania: 40     |
| Country: Number of subjects enrolled | Turkey: 25        |
| Country: Number of subjects enrolled | Ukraine: 58       |
| Country: Number of subjects enrolled | Canada: 51        |
| Country: Number of subjects enrolled | United States: 73 |
| Country: Number of subjects enrolled | Brazil: 155       |
| Country: Number of subjects enrolled | Chile: 26         |
| Country: Number of subjects enrolled | Taiwan: 27        |
| Worldwide total number of subjects   | 621               |
| EEA total number of subjects         | 206               |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 609 |
| From 65 to 84 years                       | 12  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study enrolled outpatients aged 18 and above with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) diagnosis of schizophrenia with persistent, predominant negative symptoms and on current stable antipsychotic treatment.

### 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                | Investigator, Subject           |

Blinding implementation details:

Subjects and investigators remained blinded to the treatment they received throughout the study. In the Follow-up, subjects did not receive drug but they remained blinded to the treatment they had received previously.

### Arms

|                              |                              |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | No                           |
| <b>Arm title</b>             | Placebo - Treatment Period 1 |

Arm description:

Participants received placebo orally once daily 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 dose of 5 or 10 mg tablet taken once daily in the morning, with or without food

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Bitopertin 5 mg - Treatment Period 1 |
|------------------|--------------------------------------|

Arm description:

Participants received bitopertin 5 mg orally once daily 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:

5 mg taken orally once daily in the morning, with or without food

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | Bitopertin 10 mg - Treatment Period 1 |
|------------------|---------------------------------------|

Arm description:

Participants received bitopertin 10 mg orally once daily 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 taken orally once daily in the morning, with or without food                       |                                       |
| <b>Arm title</b>   | Placebo - Treatment Period 2          |
| Arm description:   |                                       |
| Participants received placebo orally once daily 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 dose of 5 or 10 mg tablet taken once daily in the morning, with or without food |                                       |
| <b>Arm title</b>   | Bitopertin 5 mg - Treatment Period 2  |
| Arm description:   |                                       |
| Participants received bitopertin 5 mg orally once daily 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:   |                                       |
| 5 mg taken orally once daily in the morning, with or without food                        |                                       |
| <b>Arm title</b>   | Bitopertin 10 mg - Treatment Period 2 |
| Arm description:   |                                       |
| Participants received bitopertin 10 mg orally once daily 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 taken orally once daily in the morning, with or without food                       |                                       |
| <b>Arm title</b>   | Placebo - Washout Period              |
| Arm description:   |                                       |
| Participants received placebo orally once daily 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 dose of 5 or 10 mg tablet taken once daily in the morning, with or without food

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | Bitopertin 5 mg - Washout Period |
|------------------|----------------------------------|

Arm description:

Participants received bitopertin 5 mg orally once daily 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:

5 mg taken orally once daily in the morning, with or without food

|                  |   |
|------------------|---|
| <b>Arm title</b> | Bitopertin 5 mg to placebo - Washout Period |
|------------------|---|

Arm description:

Participants received placebo orally once daily 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 dose of 5 or 10 mg tablet taken once daily in the morning, with or without food

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | Bitopertin 10 mg - Washout Period |
|------------------|-----------------------------------|

Arm description:

Participants received bitopertin 10 mg orally once daily 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 taken orally once daily in the morning, with or without food

|                  |  |
|------------------|--|
| <b>Arm title</b> | Bitopertin 10 mg to placebo - Washout Period |
|------------------|--|

Arm description:

Participants received placebo orally once daily 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 dose of 10 mg tablet taken once daily in the morning, with or without food

|                  |   |
|------------------|---|
| <b>Arm title</b> | Placebo to Bitopertin 10 mg - Long-Term Extension |
|------------------|---|

|  |   |
|--|---|
| Arm description:   |   |
| Participants received bitopertin 10 mg orally once daily 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 taken orally once daily in the morning, with or without food         |   |
| <b>Arm title</b>   | Bitopertin 5 mg to Bitopertin 10 mg - Long-Term Extension |
| Arm description:   |   |
| Participants received bitopertin 10 mg orally once daily 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 taken orally once daily in the morning, with or without food         |   |
| <b>Arm title</b>   | Bitopertin 10 mg - Long-Term Extension                    |
| Arm description:   |   |
| Participants received bitopertin 10 mg orally once daily 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 taken orally once daily in the morning, with or without food         |   |
| <b>Arm title</b>   | Placebo - Safety Follow-Up Period                         |
| Arm description:   |   |
| Participants were not treated during the follow-up period                  |   |
| Arm type   | No intervention   |
| No investigational medicinal product assigned in this arm                  |   |
| <b>Arm title</b>   | Bitopertin 5 mg - Safety Follow-Up Period                 |
| Arm description:   |   |
| Participants were not treated during the follow-up period                  |   |
| Arm type   | No intervention   |
| No investigational medicinal product assigned in this arm                  |   |
| <b>Arm title</b>   | Bitopertin 10 mg - Safety Follow-Up Period                |
| Arm description:   |   |
| Participants were not treated during the follow-up period                  |   |
| Arm type   | No intervention   |
| No investigational medicinal product assigned in this arm                  |   |

| <b>Number of subjects in period 1</b> | Placebo - Treatment Period 1 | Bitopertin 5 mg - Treatment Period 1 | Bitopertin 10 mg - Treatment Period 1 |
|---------------------------------------|------------------------------|--------------------------------------|---------------------------------------|
| Started                               | 209                          | 211                                  | 201                                   |
| Completed                             | 181                          | 185                                  | 166                                   |
| Not completed                         | 28                           | 26                                   | 35                                    |
| Adverse event, non-fatal              | 20                           | 12                                   | 10                                    |
| Protocol violation                    | -                            | 2                                    | 2                                     |
| Death                                 | -                            | -                                    | -                                     |
| Non-compliance                        | 2                            | 1                                    | 7                                     |
| Administrative/Other                  | -                            | 3                                    | 1                                     |
| Lost to follow-up                     | 2                            | -                                    | 1                                     |
| Withdrawal by subject                 | 3                            | 6                                    | 12                                    |
| Lack of efficacy                      | 1                            | 2                                    | 2                                     |

| <b>Number of subjects in period 1</b> | Placebo - Treatment Period 2 | Bitopertin 5 mg - Treatment Period 2 | Bitopertin 10 mg - Treatment Period 2 |
|---------------------------------------|------------------------------|--------------------------------------|---------------------------------------|
| Started                               | 178                          | 181                                  | 165                                   |
| Completed                             | 134                          | 136                                  | 127                                   |
| Not completed                         | 44                           | 45                                   | 38                                    |
| Adverse event, non-fatal              | 6                            | 7                                    | 5                                     |
| Protocol violation                    | 1                            | 1                                    | -                                     |
| Death                                 | 1                            | -                                    | -                                     |
| Non-compliance                        | 4                            | -                                    | 2                                     |
| Administrative/Other                  | 28                           | 28                                   | 23                                    |
| Lost to follow-up                     | 1                            | 1                                    | 5                                     |
| Withdrawal by subject                 | 3                            | 6                                    | 1                                     |
| Lack of efficacy                      | -                            | 2                                    | 2                                     |

| <b>Number of subjects in period 1</b> | Placebo - Washout Period | Bitopertin 5 mg - Washout Period | Bitopertin 5 mg to placebo - Washout Period |
|---------------------------------------|--------------------------|----------------------------------|---|
| Started                               | 133                      | 66                               | 66  |
| Completed                             | 129                      | 62                               | 66  |
| Not completed                         | 4                        | 4                                | 0   |
| Adverse event, non-fatal              | 1                        | 1                                | -   |
| Protocol violation                    | -                        | -                                | -   |
| Death                                 | -                        | -                                | -   |
| Non-compliance                        | -                        | 1                                | -   |
| Administrative/Other                  | 2                        | 2                                | -   |
| Lost to follow-up                     | -                        | -                                | -   |
| Withdrawal by subject                 | -                        | -                                | -   |
| Lack of efficacy                      | 1                        | -                                | -   |



| Number of subjects in period 1 | Bitopertin 10 mg - Washout Period | Bitopertin 10 mg to placebo - Washout Period | Placebo to Bitopertin 10 mg - Long-Term Extension |
|--------------------------------|-----------------------------------|--|---|
|                                |                                   |  |   |
| Started                        | 63                                | 63   | 121   |
| Completed                      | 61                                | 61   | 0   |
| Not completed                  | 2                                 | 2  | 121   |
| Adverse event, non-fatal       | -                                 | 1  | 1   |
| Protocol violation             | -                                 | -  | 1   |
| Death                          | -                                 | -  | -   |
| Non-compliance                 | -                                 | -  | 2   |
| Administrative/Other           | 2                                 | -  | 112   |
| Lost to follow-up              | -                                 | -  | -   |
| Withdrawal by subject          | -                                 | 1  | 2   |
| Lack of efficacy               | -                                 | -  | 3   |

| Number of subjects in period 1 | Bitopertin 5 mg to Bitopertin 10 mg - Long-Term Extension | Bitopertin 10 mg - Long-Term Extension | Placebo - Safety Follow-Up Period |
|--------------------------------|---|--|-----------------------------------|
|                                |   |  |                                   |
| Started                        | 116   | 114                                    | 88                                |
| Completed                      | 0   | 0                                      | 53                                |
| Not completed                  | 116   | 114                                    | 35                                |
| Adverse event, non-fatal       | 4   | 7                                      | 5                                 |
| Protocol violation             | -   | -                                      | -                                 |
| Death                          | -   | -                                      | 2                                 |
| Non-compliance                 | 1   | 1                                      | -                                 |
| Administrative/Other           | 100   | 100                                    | 5                                 |
| Lost to follow-up              | 1   | -                                      | 8                                 |
| Withdrawal by subject          | 8   | 4                                      | 15                                |
| Lack of efficacy               | 2   | 2                                      | -                                 |

| Number of subjects in period 1 | Bitopertin 5 mg - Safety Follow-Up Period | Bitopertin 10 mg - Safety Follow-Up Period |
|--------------------------------|---|--|
| Started                        | 95  | 438  |
| Completed                      | 60  | 370  |
| Not completed                  | 35  | 68   |
| Adverse event, non-fatal       | 4   | 4  |
| Protocol violation             | -   | -  |
| Death                          | 1   | -  |
| Non-compliance                 | -   | -  |
| Administrative/Other           | 14  | 13   |
| Lost to follow-up              | 7   | 22   |
| Withdrawal by subject          | 9   | 29   |
| Lack of efficacy               | -   | -  |



## Baseline characteristics

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Overall period (overall period) |
|-----------------------|---------------------------------|

Reporting group description: -

| Reporting group values  | Overall period<br>(overall period) | Total |  |
|---|------------------------------------|-------|--|
| Number of subjects  | 621                                | 621   |  |
| Age categorical<br>Units: Subjects                                      |                                    |       |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 41.4<br>± 11.7                     | -     |  |
| Gender categorical<br>Units: Subjects                                   |                                    |       |  |
| Female  | 191                                | 191   |  |
| Male  | 430                                | 430   |  |

## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Placebo - Treatment Period 1                              |
| Reporting group description:   |   |
| Participants received placebo orally once daily for 24 weeks               |   |
| Reporting group title  | Bitopertin 5 mg - Treatment Period 1                      |
| Reporting group description:   |   |
| Participants received bitopertin 5 mg orally once daily for 24 weeks       |   |
| Reporting group title  | Bitopertin 10 mg - Treatment Period 1                     |
| Reporting group description:   |   |
| Participants received bitopertin 10 mg orally once daily for 24 weeks      |   |
| Reporting group title  | Placebo - Treatment Period 2                              |
| Reporting group description:   |   |
| Participants received placebo orally once daily for 28 weeks               |   |
| Reporting group title  | Bitopertin 5 mg - Treatment Period 2                      |
| Reporting group description:   |   |
| Participants received bitopertin 5 mg orally once daily for 28 weeks       |   |
| Reporting group title  | Bitopertin 10 mg - Treatment Period 2                     |
| Reporting group description:   |   |
| Participants received bitopertin 10 mg orally once daily for 28 weeks      |   |
| Reporting group title  | Placebo - Washout Period                                  |
| Reporting group description:   |   |
| Participants received placebo orally once daily for 4 weeks                |   |
| Reporting group title  | Bitopertin 5 mg - Washout Period                          |
| Reporting group description:   |   |
| Participants received bitopertin 5 mg orally once daily for 4 weeks        |   |
| Reporting group title  | Bitopertin 5 mg to placebo - Washout Period               |
| Reporting group description:   |   |
| Participants received placebo orally once daily for 4 weeks                |   |
| Reporting group title  | Bitopertin 10 mg - Washout Period                         |
| Reporting group description:   |   |
| Participants received bitopertin 10 mg orally once daily for 4 weeks       |   |
| Reporting group title  | Bitopertin 10 mg to placebo - Washout Period              |
| Reporting group description:   |   |
| Participants received placebo orally once daily for 4 weeks                |   |
| Reporting group title  | Placebo to Bitopertin 10 mg - Long-Term Extension         |
| Reporting group description:   |   |
| Participants received bitopertin 10 mg orally once daily for up to 3 years |   |
| Reporting group title  | Bitopertin 5 mg to Bitopertin 10 mg - Long-Term Extension |
| Reporting group description:   |   |
| Participants received bitopertin 10 mg orally once daily for up to 3 years |   |
| Reporting group title  | Bitopertin 10 mg - Long-Term Extension                    |
| Reporting group description:   |   |
| Participants received bitopertin 10 mg orally once daily for up to 3 years |   |
| Reporting group title  | Placebo - Safety Follow-Up Period                         |
| Reporting group description:   |   |
| Participants were not treated during the follow-up period                  |   |
| Reporting group title  | Bitopertin 5 mg - Safety Follow-Up Period                 |

Reporting group description:

Participants were not treated during the follow-up period

|                       |  |
|-----------------------|--|
| Reporting group title | Bitopertin 10 mg - Safety Follow-Up Period |
|-----------------------|--|

Reporting group description:

Participants were not treated during the follow-up period

## Primary: Mean Change from Baseline in the PANSS Negative Symptom Factor Score at Week 24

|                 |  |
|-----------------|--|
| End point title | Mean Change from Baseline in the PANSS Negative Symptom Factor Score at Week 24 <sup>[1]</sup> |
|-----------------|--|

End point description:

The PANSS is a 30-item scale designed to capture the degree of severity for many symptoms in schizophrenia. Each of the 30 items is rated on a 7-point scale, from 1 to 7 (absence of to extreme psychopathology). The negative symptom subscale is composed of 7 items: Blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking. The score on the negative symptom subscale can range from 0 to 49, with a higher score indicating more negative symptom psychopathology. A negative change score indicates improvement.

Intent-to-treat population: All randomized participants who received at least 1 dose of double-blind study drug and had at least one post-baseline assessment of the primary efficacy variable.

For all analyses of PANSS data, the scores were transformed into 0-6 points to express "absent" as 0.

|                |         |
|----------------|---------|
| 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: This final abbreviated Clinical Study Report (CSR) presents the data at Week 24 for the key primary endpoint, Positive and Negative Syndrome Scale (PANSS) Negative Symptom Factor Score (NSFS), and the key secondary endpoint, Personal and Social Performance (PSP) total score. The study did not meet its primary endpoint.

| End point values                 | Placebo - Treatment Period 1 | Bitopertin 5 mg - Treatment Period 1 | Bitopertin 10 mg - Treatment Period 1 |  |
|----------------------------------|------------------------------|--------------------------------------|---------------------------------------|--|
| Subject group type               | Reporting group              | Reporting group                      | Reporting group                       |  |
| Number of subjects analysed      | 203                          | 205                                  | 197                                   |  |
| Units: number                    |                              |                                      |                                       |  |
| arithmetic mean (standard error) | -5.25 (± 0.365)              | -5.53 (± 0.33)                       | -5.87 (± 0.366)                       |  |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Placebo vs. Bitopertin 5 mg - PANSS at Week 24 |
|----------------------------|--|

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 and PSP 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 imputation for missing data were used in primary analyses.

|                   |   |
|-------------------|---|
| Comparison groups | Placebo - Treatment Period 1 v Bitopertin 5 mg - Treatment Period 1 |
|-------------------|---|

|   |   |
|---|---|
| Number of subjects included in analysis | 408                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.4742                                |
| Method                                  | Mixed Models Repeated Measures Analysis |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Placebo vs. Bitopertin 10 mg - PANSS at Week 24 |
|-----------------------------------|---|

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 and PSP 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 imputation for missing data was used in primary analyses.

|   |  |
|---|--|
| Comparison groups                       | Placebo - Treatment Period 1 v Bitopertin 10 mg - Treatment Period 1 |
| Number of subjects included in analysis | 400  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.0989   |
| Method                                  | Mixed Models Repeated Measures Analysis                              |

## **Secondary: Mean Change from Baseline in the Personal and Social Performance (PSP) Total Score at Week 24**

|                 |  |
|-----------------|--|
| End point title | Mean Change from Baseline in the Personal and Social Performance (PSP) Total Score at Week 24 <sup>[2]</sup> |
|-----------------|--|

End point description:

The PSP is a clinician-rated 100-point rating scale subdivided into 10 equal intervals, enabling the determination of small changes in levels of functioning. The ratings are based upon assessment of the patient's functioning in 4 areas: 1) Socially useful activities; 2) personal and social relationships; 3) self-care; and 4) disturbing and aggressive behaviors. Each of the 4 areas is rated in 6 degrees of severity (absent, mild, manifest, marked, severe, very severe). Higher scores represent better personal and social functioning, with ratings from 91-100 referring to more than adequate functioning, while scores under 30 refer to poor functioning that intensive supervision is required. A higher score indicates better functioning. A positive change score indicates improvement.

Intent-to-treat population: All randomized participants who received at least 1 dose of double-blind study drug and had at least one post-baseline assessment of the primary efficacy variable.

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

End point timeframe:

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: This final abbreviated Clinical Study Report (CSR) presents the data at Week 24 for the key primary endpoint, Positive and Negative Syndrome Scale (PANSS) Negative Symptom Factor Score (NSFS), and the key secondary endpoint, Personal and Social Performance (PSP) total score. The study did not meet its primary endpoint.

| <b>End point values</b>          | Placebo - Treatment Period 1 | Bitopertin 5 mg - Treatment Period 1 | Bitopertin 10 mg - Treatment Period 1 |  |
|----------------------------------|------------------------------|--------------------------------------|---------------------------------------|--|
| Subject group type               | Reporting group              | Reporting group                      | Reporting group                       |  |
| Number of subjects analysed      | 203                          | 205                                  | 197                                   |  |
| Units: number                    |                              |                                      |                                       |  |
| arithmetic mean (standard error) | 8.64 (± 0.752)               | 6.64 (± 0.712)                       | 8.24 (± 0.733)                        |  |

## Statistical analyses

| <b>Statistical analysis title</b> | Placebo vs. Bitopertin 5 mg - PSP at Week 24 |
|-----------------------------------|--|
|-----------------------------------|--|

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 PSP 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 imputation for missing data were used in primary analyses.

|   |   |
|---|---|
| Comparison groups                       | Placebo - Treatment Period 1 v Bitopertin 5 mg - Treatment Period 1 |
| Number of subjects included in analysis | 408   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.1288  |
| Method                                  | Mixed Models Repeated Measures Analysis                             |

| <b>Statistical analysis title</b> | Placebo vs. Bitopertin 10 mg - PSP at Week 24 |
|-----------------------------------|---|
|-----------------------------------|---|

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 PSP 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 imputation 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 | 400  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.6471   |
| Method                                  | Mixed Models Repeated Measures Analysis                              |

## 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 |
|--------------------|----|

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Placebo through Week 52 |
|-----------------------|-------------------------|

Reporting group description: -

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Bitopertin 5 mg through Week 52 |
|-----------------------|---------------------------------|

Reporting group description: -

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Bitopertin 10 mg through Week 52 |
|-----------------------|----------------------------------|

Reporting group description: -

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Placebo during washout period |
|-----------------------|-------------------------------|

Reporting group description: -

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Bitopertin 5 mg during washout period |
|-----------------------|---------------------------------------|

Reporting group description: -

|                       |  |
|-----------------------|--|
| Reporting group title | Bitopertin 5 mg to Placebo during washout period |
|-----------------------|--|

Reporting group description: -

|                       |  |
|-----------------------|--|
| Reporting group title | Bitopertin 10 mg during washout period |
|-----------------------|--|

Reporting group description: -

|                       |   |
|-----------------------|---|
| Reporting group title | Bitopertin 10 mg to placebo during washout period |
|-----------------------|---|

Reporting group description: -

|                       |  |
|-----------------------|--|
| Reporting group title | Placebo to bitopertin 10 mg during long-term extension |
|-----------------------|--|

Reporting group description: -

|                       |  |
|-----------------------|--|
| Reporting group title | Bitopertin 5 mg to bitopertin 10 mg during long-term extension |
|-----------------------|--|

Reporting group description: -

|                       |   |
|-----------------------|---|
| Reporting group title | Bitopertin 10 mg during long-term extension |
|-----------------------|---|

Reporting group description: -

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Placebo during follow-up period |
|-----------------------|---------------------------------|

Reporting group description: -

|                       |   |
|-----------------------|---|
| Reporting group title | Bitopertin 5 mg during follow-up period |
|-----------------------|---|

Reporting group description: -

|                       |  |
|-----------------------|--|
| Reporting group title | Bitopertin 10 mg during follow-up period |
|-----------------------|--|

Reporting group description: -

| Serious adverse events                            | Placebo through Week 52 | Bitopertin 5 mg through Week 52 | Bitopertin 10 mg through Week 52 |
|---|-------------------------|---------------------------------|----------------------------------|
| Total subjects affected by serious adverse events |                         |                                 |                                  |
| subjects affected / exposed                       | 15 / 209 (7.18%)        | 11 / 211 (5.21%)                | 16 / 201 (7.96%)                 |
| 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) |                 |                 |                 |
| Acute myeloid leukaemia   |                 |                 |                 |
| subjects affected / exposed   | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Benign ovarian tumour   |                 |                 |                 |
| subjects affected / exposed   | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| 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   | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 201 (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           |
| Vascular disorders  |                 |                 |                 |
| Aortic dissection   |                 |                 |                 |
| subjects affected / exposed   | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions                |                 |                 |                 |
| Mass  |                 |                 |                 |
| subjects affected / exposed   | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Sudden death  |                 |                 |                 |
| subjects affected / exposed   | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| occurrences causally related to treatment / all                     | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 1 / 1           | 0 / 0           | 0 / 0           |
| Social circumstances  |                 |                 |                 |
| Victim of homicide  |                 |                 |                 |
| subjects affected / exposed   | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| 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 failure                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic obstructive pulmonary disease           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 201 (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           |
| Psychiatric disorders                           |                 |                 |                 |
| Psychotic disorder                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 3 / 201 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Schizophrenia                                   |                 |                 |                 |
| subjects affected / exposed                     | 5 / 209 (2.39%) | 3 / 211 (1.42%) | 3 / 201 (1.49%) |
| occurrences causally related to treatment / all | 2 / 5           | 0 / 3           | 2 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Alcohol abuse                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 201 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anxiety disorder                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 201 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hallucination                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 201 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Thinking abnormal                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 201 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anxiety   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 201 (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           |
| Suicidal Ideation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 201 (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           |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| 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  |                 |                 |                 |
| Ankle fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| 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 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Foot fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hand fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 201 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Wound   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 201 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Carbon monoxide poisoning                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 201 (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           |
| Tendon injury                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 201 (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           |
| Congenital, familial and genetic disorders      |                 |                 |                 |
| Dermoid Cyst                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 201 (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                               |                 |                 |                 |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiomyopathy                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| 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 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 201 (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           |
| Nervous system disorders                        |                 |                 |                 |
| Altered state of consciousness                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 201 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhagic stroke                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 201 (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           |
| Subarachnoid haemorrhage                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 201 (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           |
| Eye disorders                                   |                 |                 |                 |
| Angle closure glaucoma                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 201 (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                      |                 |                 |                 |
| Small intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 201 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Duodenal ulcer                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 201 (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           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 201 (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           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholecystitis chronic                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 201 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Renal and urinary disorders                     |                 |                 |                 |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 201 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Rhabdomyolysis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Jaw cyst  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 201 (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           |
| Infections and infestations                     |                 |                 |                 |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 2 / 201 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroenteritis viral                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 201 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Necrotising fasciitis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 1 / 201 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 201 (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           |
| Ehinococciasis                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 209 (0.48%) | 0 / 211 (0.00%) | 0 / 201 (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           |
| <b>Pneumonia</b>                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 201 (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           |
| <b>Pulmonary tuberculosis</b>                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 1 / 211 (0.47%) | 0 / 201 (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           |
| <b>Subcutaneous abscess</b>                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 0 / 211 (0.00%) | 0 / 201 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>  | Placebo during washout period | Bitopertin 5 mg during washout period | Bitopertin 5 mg to Placebo during washout period |
|--|-------------------------------|---------------------------------------|--|
| <b>Total subjects affected by serious adverse events</b>                   |                               |                                       |  |
| subjects affected / exposed  | 1 / 133 (0.75%)               | 0 / 66 (0.00%)                        | 2 / 66 (3.03%)                                   |
| number of deaths (all causes)  | 0                             | 0                                     | 0  |
| number of deaths resulting from adverse events                             | 0                             | 0                                     | 0  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                               |                                       |  |
| <b>Acute myeloid leukaemia</b>   |                               |                                       |  |
| subjects affected / exposed  | 0 / 133 (0.00%)               | 0 / 66 (0.00%)                        | 0 / 66 (0.00%)                                   |
| occurrences causally related to treatment / all                            | 0 / 0                         | 0 / 0                                 | 0 / 0  |
| deaths causally related to treatment / all                                 | 0 / 0                         | 0 / 0                                 | 0 / 0  |
| <b>Benign ovarian tumour</b>   |                               |                                       |  |
| subjects affected / exposed  | 0 / 133 (0.00%)               | 0 / 66 (0.00%)                        | 0 / 66 (0.00%)                                   |
| occurrences causally related to treatment / all                            | 0 / 0                         | 0 / 0                                 | 0 / 0  |
| deaths causally related to treatment / all                                 | 0 / 0                         | 0 / 0                                 | 0 / 0  |
| <b>Uterine leiomyoma</b>   |                               |                                       |  |

|  |                 |                |                |
|--|-----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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                                   |                 |                |                |
| Aortic dissection                                    |                 |                |                |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                 |                |                |
| Mass   |                 |                |                |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0          |
| Sudden death   |                 |                |                |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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                                 |                 |                |                |
| Victim of homicide                                   |                 |                |                |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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 failure                            |                 |                |                |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0          |
| Chronic obstructive pulmonary disease                |                 |                |                |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0          |
| Pulmonary embolism                                   |                 |                |                |



|   |                 |                |                |
|---|-----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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                           |                 |                |                |
| Psychotic disorder                              |                 |                |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 66 (0.00%) | 0 / 66 (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          |
| Schizophrenia                                   |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Alcohol abuse                                   |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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 disorder                                |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Thinking abnormal                               |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Suicidal Ideation                               |                 |                |                |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Depression                                      |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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  |                 |                |                |
| Ankle fracture                                  |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Foot fracture                                   |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Hand fracture                                   |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Wound   |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Carbon monoxide poisoning                       |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Tendon injury                                   |                 |                |                |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Congenital, familial and genetic disorders      |                 |                |                |
| Dermoid Cyst                                    |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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                               |                 |                |                |
| Cardiac failure congestive                      |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Cardiomyopathy                                  |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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                        |                 |                |                |
| Altered state of consciousness                  |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Haemorrhagic stroke                             |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Subarachnoid haemorrhage                        |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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                                   |                 |                |                |
| Angle closure glaucoma                          |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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                      |                 |                |                |
| Small intestinal obstruction                    |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Duodenal ulcer                                  |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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 haemorrhage                    |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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                         |                 |                |                |
| Cholecystitis chronic                           |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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                     |                 |                |                |
| Nephrolithiasis                                 |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                 |                |                |
| Rhabdomyolysis                                  |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 1 / 66 (1.52%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Jaw cyst  |                 |                |                |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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                     |                 |                |                |
| Cellulitis                                      |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 1 / 66 (1.52%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Gastroenteritis viral                           |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Necrotising fasciitis                           |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Echinococcosis                                  |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| 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 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Pulmonary tuberculosis                          |                 |                |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 0 / 66 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Subcutaneous abscess                            |                 |                |                |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 66 (0.00%) | 1 / 66 (1.52%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                                       | Bitopertin 10 mg during washout period | Bitopertin 10 mg to placebo during washout period | Placebo to bitopertin 10 mg during long-term extension |
|---|--|---|--|
| Total subjects affected by serious adverse events                   |  |   |  |
| subjects affected / exposed   | 0 / 63 (0.00%)                         | 1 / 63 (1.59%)                                    | 2 / 121 (1.65%)  |
| 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) |  |   |  |
| Acute myeloid leukaemia   |  |   |  |
| subjects affected / exposed   | 0 / 63 (0.00%)                         | 0 / 63 (0.00%)                                    | 1 / 121 (0.83%)  |
| occurrences causally related to treatment / all                     | 0 / 0                                  | 0 / 0   | 0 / 1  |
| deaths causally related to treatment / all                          | 0 / 0                                  | 0 / 0   | 0 / 0  |
| Benign ovarian tumour   |  |   |  |
| subjects affected / exposed   | 0 / 63 (0.00%)                         | 0 / 63 (0.00%)                                    | 0 / 121 (0.00%)  |
| 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 / 63 (0.00%)                         | 0 / 63 (0.00%)                                    | 0 / 121 (0.00%)  |
| 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  |  |   |  |
| Aortic dissection   |  |   |  |
| subjects affected / exposed   | 0 / 63 (0.00%)                         | 0 / 63 (0.00%)                                    | 0 / 121 (0.00%)  |
| occurrences causally related to treatment / all                     | 0 / 0                                  | 0 / 0   | 0 / 0  |
| deaths causally related to treatment / all                          | 0 / 0                                  | 0 / 0   | 0 / 0  |
| General disorders and administration site conditions                |  |   |  |
| Mass  |  |   |  |
| subjects affected / exposed   | 0 / 63 (0.00%)                         | 0 / 63 (0.00%)                                    | 1 / 121 (0.83%)  |
| occurrences causally related to treatment / all                     | 0 / 0                                  | 0 / 0   | 0 / 1  |
| deaths causally related to treatment / all                          | 0 / 0                                  | 0 / 0   | 0 / 0  |
| Sudden death  |  |   |  |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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                            |                |                |                 |
| Victim of homicide                              |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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 failure                       |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Chronic obstructive pulmonary disease           |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pulmonary embolism                              |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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                           |                |                |                 |
| Psychotic disorder                              |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 63 (1.59%) | 0 / 121 (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           |
| Schizophrenia                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Alcohol abuse                                   |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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 disorder                                |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Thinking abnormal                               |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Suicidal Ideation                               |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Depression                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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  |                |                |                 |
| Ankle fracture                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Foot fracture                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 1 / 121 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hand fracture                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Wound   |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Carbon monoxide poisoning                       |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Tendon injury                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Congenital, familial and genetic disorders      |                |                |                 |
| Dermoid Cyst                                    |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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                               |                |                |                 |
| Cardiac failure congestive                      |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Cardiomyopathy                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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                        |                |                |                 |
| Altered state of consciousness                  |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Haemorrhagic stroke                             |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Subarachnoid haemorrhage                        |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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                                   |                |                |                 |
| Angle closure glaucoma                          |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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                      |                |                |                 |
| Small intestinal obstruction                    |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Duodenal ulcer                                  |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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 haemorrhage                    |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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                         |                |                |                 |
| Cholecystitis chronic                           |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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                     |                |                |                 |
| Nephrolithiasis                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                |                |                 |
| Rhabdomyolysis                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Jaw cyst  |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| 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                     |                |                |                 |
| Cellulitis                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastroenteritis viral                           |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Necrotising fasciitis</b>                    |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Bronchitis</b>                               |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Ehinococciasis</b>                           |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Pneumonia</b>                                |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 1 / 121 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Pulmonary tuberculosis</b>                   |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Subcutaneous abscess</b>                     |                |                |                 |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

| <b>Serious adverse events</b>                            | Bitopertin 5 mg to bitopertin 10 mg during long-term extension | Bitopertin 10 mg during long-term extension | Placebo during follow-up period |
|--|--|---|---------------------------------|
| <b>Total subjects affected by serious adverse events</b> |  |   |                                 |
| subjects affected / exposed                              | 3 / 116 (2.59%)  | 5 / 114 (4.39%)                             | 5 / 88 (5.68%)                  |
| number of deaths (all causes)                            | 0  | 0   | 1                               |
| number of deaths resulting from adverse events           | 0  | 0   |                                 |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |                |
| Acute myeloid leukaemia   |                 |                 |                |
| subjects affected / exposed   | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0          |
| Benign ovarian tumour   |                 |                 |                |
| subjects affected / exposed   | 1 / 116 (0.86%) | 0 / 114 (0.00%) | 0 / 88 (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          |
| Uterine leiomyoma   |                 |                 |                |
| subjects affected / exposed   | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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  |                 |                 |                |
| Aortic dissection   |                 |                 |                |
| subjects affected / exposed   | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0          |
| General disorders and administration site conditions                |                 |                 |                |
| Mass  |                 |                 |                |
| subjects affected / exposed   | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0          |
| Sudden death  |                 |                 |                |
| subjects affected / exposed   | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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  |                 |                 |                |
| Victim of homicide  |                 |                 |                |
| subjects affected / exposed   | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 1          |
| Respiratory, thoracic and mediastinal disorders                     |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Acute respiratory failure                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Chronic obstructive pulmonary disease           |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pulmonary embolism                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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                           |                 |                 |                |
| Psychotic disorder                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 116 (0.86%) | 1 / 114 (0.88%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Schizophrenia                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 2 / 114 (1.75%) | 3 / 88 (3.41%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Alcohol abuse                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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 disorder                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Thinking abnormal                               |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Suicidal Ideation                               |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Depression                                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 116 (0.86%) | 0 / 114 (0.00%) | 0 / 88 (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          |
| Injury, poisoning and procedural complications  |                 |                 |                |
| Ankle fracture                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 1 / 114 (0.88%) | 0 / 88 (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          |
| Multiple fractures                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 1 / 114 (0.88%) | 0 / 88 (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          |
| Foot fracture                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hand fracture                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Wound   |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Carbon monoxide poisoning                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Tendon injury                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Congenital, familial and genetic disorders      |                 |                 |                |
| Dermoid Cyst                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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                               |                 |                 |                |
| Cardiac failure congestive                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiomyopathy                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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                        |                 |                 |                |
| Altered state of consciousness                  |                 |                 |                |



|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haemorrhagic stroke                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Subarachnoid haemorrhage                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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                                   |                 |                 |                |
| Angle closure glaucoma                          |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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                      |                 |                 |                |
| Small intestinal obstruction                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Duodenal ulcer                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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 haemorrhage                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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                         |                 |                 |                |
| Cholecystitis chronic                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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                     |                 |                 |                |
| Nephrolithiasis                                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                 |                 |                |
| Rhabdomyolysis                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Jaw cyst  |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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                     |                 |                 |                |
| Cellulitis                                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastroenteritis viral                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Necrotising fasciitis                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| 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 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Ehinococciasis                                  |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| <b>Pneumonia</b>                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| <b>Pulmonary tuberculosis</b>                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| <b>Subcutaneous abscess</b>                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 116 (0.00%) | 0 / 114 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

| <b>Serious adverse events</b>  | Bitopertin 5 mg<br>during follow-up<br>period | Bitopertin 10 mg<br>during follow-up<br>period |  |
|--|---|--|--|
| <b>Total subjects affected by serious adverse events</b>                   |   |  |  |
| subjects affected / exposed  | 4 / 95 (4.21%)                                | 9 / 438 (2.05%)                                |  |
| number of deaths (all causes)  | 0   | 0  |  |
| number of deaths resulting from adverse events                             | 0   | 0  |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |   |  |  |
| <b>Acute myeloid leukaemia</b>   |   |  |  |
| subjects affected / exposed  | 0 / 95 (0.00%)                                | 0 / 438 (0.00%)                                |  |
| occurrences causally related to treatment / all                            | 0 / 0   | 0 / 0  |  |
| deaths causally related to treatment / all                                 | 0 / 0   | 0 / 0  |  |
| <b>Benign ovarian tumour</b>   |   |  |  |
| subjects affected / exposed  | 0 / 95 (0.00%)                                | 0 / 438 (0.00%)                                |  |
| occurrences causally related to treatment / all                            | 0 / 0   | 0 / 0  |  |
| deaths causally related to treatment / all                                 | 0 / 0   | 0 / 0  |  |
| <b>Uterine leiomyoma</b>   |   |  |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Vascular disorders                                   |                |                 |  |
| Aortic dissection                                    |                |                 |  |
| subjects affected / exposed                          | 0 / 95 (0.00%) | 1 / 438 (0.23%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| General disorders and administration site conditions |                |                 |  |
| Mass   |                |                 |  |
| subjects affected / exposed                          | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Sudden death   |                |                 |  |
| subjects affected / exposed                          | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Social circumstances                                 |                |                 |  |
| Victim of homicide                                   |                |                 |  |
| subjects affected / exposed                          | 0 / 95 (0.00%) | 0 / 438 (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 failure                            |                |                 |  |
| subjects affected / exposed                          | 0 / 95 (0.00%) | 1 / 438 (0.23%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Chronic obstructive pulmonary disease                |                |                 |  |
| subjects affected / exposed                          | 0 / 95 (0.00%) | 1 / 438 (0.23%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Pulmonary embolism                                   |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Psychiatric disorders                           |                |                 |  |
| Psychotic disorder                              |                |                 |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 2 / 438 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Schizophrenia                                   |                |                 |  |
| subjects affected / exposed                     | 2 / 95 (2.11%) | 3 / 438 (0.68%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Alcohol abuse                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Anxiety disorder                                |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 438 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hallucination                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Thinking abnormal                               |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 438 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Anxiety   |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Suicidal Ideation                               |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Depression                                      |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (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  |                |                 |  |
| Ankle fracture                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (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 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Foot fracture                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hand fracture                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Wound   |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Carbon monoxide poisoning                       |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Tendon injury                                   |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                |                 |  |
| Dermoid Cyst                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiac disorders                               |                |                 |  |
| Cardiac failure congestive                      |                |                 |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiomyopathy                                  |                |                 |  |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardio-respiratory arrest                       |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (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                        |                |                 |  |
| Altered state of consciousness                  |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Haemorrhagic stroke                             |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Subarachnoid haemorrhage                        |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Eye disorders                                   |                |                 |  |
| Angle closure glaucoma                          |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrointestinal disorders                      |                |                 |  |
| Small intestinal obstruction                    |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Duodenal ulcer                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hepatobiliary disorders                         |                |                 |  |
| Cholecystitis chronic                           |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (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                     |                |                 |  |
| Nephrolithiasis                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                |                 |  |
| Rhabdomyolysis                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Jaw cyst  |                |                 |  |



|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (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                     |                |                 |  |
| Cellulitis                                      |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 438 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastroenteritis viral                           |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Necrotising fasciitis                           |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (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 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Ehinococciasis                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (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                     | 2 / 95 (2.11%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pulmonary tuberculosis                          |                |                 |  |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Subcutaneous abscess                            |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 95 (0.00%) | 0 / 438 (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 %

| <b>Non-serious adverse events</b>                     | Placebo through Week 52 | Bitopertin 5 mg through Week 52 | Bitopertin 10 mg through Week 52 |
|---|-------------------------|---------------------------------|----------------------------------|
| Total subjects affected by non-serious adverse events |                         |                                 |                                  |
| subjects affected / exposed                           | 153 / 209 (73.21%)      | 138 / 211 (65.40%)              | 122 / 201 (60.70%)               |
| Investigations  |                         |                                 |                                  |
| Weight increased                                      |                         |                                 |                                  |
| subjects affected / exposed                           | 12 / 209 (5.74%)        | 9 / 211 (4.27%)                 | 8 / 201 (3.98%)                  |
| occurrences (all)                                     | 14                      | 10                              | 10                               |
| Nervous system disorders                              |                         |                                 |                                  |
| Headache  |                         |                                 |                                  |
| subjects affected / exposed                           | 22 / 209 (10.53%)       | 18 / 211 (8.53%)                | 13 / 201 (6.47%)                 |
| occurrences (all)                                     | 32                      | 39                              | 24                               |
| Somnolence  |                         |                                 |                                  |
| subjects affected / exposed                           | 11 / 209 (5.26%)        | 9 / 211 (4.27%)                 | 10 / 201 (4.98%)                 |
| occurrences (all)                                     | 11                      | 10                              | 11                               |
| Dizziness   |                         |                                 |                                  |
| subjects affected / exposed                           | 11 / 209 (5.26%)        | 5 / 211 (2.37%)                 | 8 / 201 (3.98%)                  |
| occurrences (all)                                     | 11                      | 6                               | 8                                |
| Gastrointestinal disorders                            |                         |                                 |                                  |
| Nausea  |                         |                                 |                                  |
| subjects affected / exposed                           | 11 / 209 (5.26%)        | 11 / 211 (5.21%)                | 3 / 201 (1.49%)                  |
| occurrences (all)                                     | 13                      | 12                              | 3                                |
| Psychiatric disorders                                 |                         |                                 |                                  |
| Anxiety   |                         |                                 |                                  |
| subjects affected / exposed                           | 10 / 209 (4.78%)        | 11 / 211 (5.21%)                | 10 / 201 (4.98%)                 |
| occurrences (all)                                     | 13                      | 18                              | 16                               |
| Insomnia  |                         |                                 |                                  |
| subjects affected / exposed                           | 11 / 209 (5.26%)        | 10 / 211 (4.74%)                | 6 / 201 (2.99%)                  |
| occurrences (all)                                     | 14                      | 12                              | 6                                |
| Infections and infestations                           |                         |                                 |                                  |

|   |                        |                        |                        |
|---|------------------------|------------------------|------------------------|
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 20 / 209 (9.57%)<br>23 | 17 / 211 (8.06%)<br>19 | 13 / 201 (6.47%)<br>19 |
|---|------------------------|------------------------|------------------------|

| <b>Non-serious adverse events</b>  | Placebo during washout period | Bitopertin 5 mg during washout period | Bitopertin 5 mg to Placebo during washout period |
|--|-------------------------------|---------------------------------------|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed               | 0 / 133 (0.00%)               | 0 / 66 (0.00%)                        | 0 / 66 (0.00%)                                   |
| Investigations<br>Weight increased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 133 (0.00%)<br>0          | 0 / 66 (0.00%)<br>0                   | 0 / 66 (0.00%)<br>0                              |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)           | 0 / 133 (0.00%)<br>0          | 0 / 66 (0.00%)<br>0                   | 0 / 66 (0.00%)<br>0                              |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 133 (0.00%)<br>0          | 0 / 66 (0.00%)<br>0                   | 0 / 66 (0.00%)<br>0                              |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 133 (0.00%)<br>0          | 0 / 66 (0.00%)<br>0                   | 0 / 66 (0.00%)<br>0                              |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)           | 0 / 133 (0.00%)<br>0          | 0 / 66 (0.00%)<br>0                   | 0 / 66 (0.00%)<br>0                              |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)               | 0 / 133 (0.00%)<br>0          | 0 / 66 (0.00%)<br>0                   | 0 / 66 (0.00%)<br>0                              |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 133 (0.00%)<br>0          | 0 / 66 (0.00%)<br>0                   | 0 / 66 (0.00%)<br>0                              |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 133 (0.00%)<br>0          | 0 / 66 (0.00%)<br>0                   | 0 / 66 (0.00%)<br>0                              |

|  |                  |                     |                       |
|--|------------------|---------------------|-----------------------|
|  | Bitopertin 10 mg | Bitopertin 10 mg to | Placebo to bitopertin |
|--|------------------|---------------------|-----------------------|

| <b>Non-serious adverse events</b>   | during washout period   | placebo during washout period   | 10 mg during long-term extension   |
|---|---|---|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed  | 0 / 63 (0.00%)  | 0 / 63 (0.00%)  | 47 / 121 (38.84%)  |
| Investigations<br>Weight increased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 63 (0.00%)<br>0   | 0 / 63 (0.00%)<br>0   | 0 / 121 (0.00%)<br>0   |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Somnolence<br>subjects affected / exposed<br>occurrences (all)<br><br>Dizziness<br>subjects affected / exposed<br>occurrences (all) | 0 / 63 (0.00%)<br>0<br><br>0 / 63 (0.00%)<br>0<br><br>0 / 63 (0.00%)<br>0 | 0 / 63 (0.00%)<br>0<br><br>0 / 63 (0.00%)<br>0<br><br>0 / 63 (0.00%)<br>0 | 7 / 121 (5.79%)<br>7<br><br>0 / 121 (0.00%)<br>0<br><br>0 / 121 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)  | 0 / 63 (0.00%)<br>0   | 0 / 63 (0.00%)<br>0   | 0 / 121 (0.00%)<br>0   |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)<br><br>Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 63 (0.00%)<br>0<br><br>0 / 63 (0.00%)<br>0                            | 0 / 63 (0.00%)<br>0<br><br>0 / 63 (0.00%)<br>0                            | 0 / 121 (0.00%)<br>0<br><br>0 / 121 (0.00%)<br>0                             |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 63 (0.00%)<br>0   | 0 / 63 (0.00%)<br>0   | 7 / 121 (5.79%)<br>8   |

| <b>Non-serious adverse events</b>  | Bitopertin 5 mg to bitopertin 10 mg during long-term extension | Bitopertin 10 mg during long-term extension | Placebo during follow-up period |
|--|--|---|---------------------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 49 / 116 (42.24%)  | 40 / 114 (35.09%)                           | 0 / 88 (0.00%)                  |

|  |                      |                      |                     |
|--|----------------------|----------------------|---------------------|
| Investigations<br>Weight increased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 116 (0.00%)<br>0 | 0 / 114 (0.00%)<br>0 | 0 / 88 (0.00%)<br>0 |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)           | 4 / 116 (3.45%)<br>4 | 3 / 114 (2.63%)<br>3 | 0 / 88 (0.00%)<br>0 |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 116 (0.00%)<br>0 | 0 / 114 (0.00%)<br>0 | 0 / 88 (0.00%)<br>0 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 116 (0.00%)<br>0 | 0 / 114 (0.00%)<br>0 | 0 / 88 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)           | 0 / 116 (0.00%)<br>0 | 0 / 114 (0.00%)<br>0 | 0 / 88 (0.00%)<br>0 |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)               | 3 / 116 (2.59%)<br>3 | 6 / 114 (5.26%)<br>6 | 0 / 88 (0.00%)<br>0 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 116 (0.00%)<br>0 | 0 / 114 (0.00%)<br>0 | 0 / 88 (0.00%)<br>0 |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 5 / 116 (4.31%)<br>6 | 2 / 114 (1.75%)<br>3 | 0 / 88 (0.00%)<br>0 |

|   |   |  |  |
|---|---|--|--|
| <b>Non-serious adverse events</b>   | Bitopertin 5 mg<br>during follow-up<br>period | Bitopertin 10 mg<br>during follow-up<br>period |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 0 / 95 (0.00%)                                | 0 / 438 (0.00%)                                |  |
| Investigations<br>Weight increased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 95 (0.00%)<br>0                           | 0 / 438 (0.00%)<br>0                           |  |
| Nervous system disorders  |   |  |  |

|                             |                |                 |  |
|-----------------------------|----------------|-----------------|--|
| Headache                    |                |                 |  |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences (all)           | 0              | 0               |  |
| Somnolence                  |                |                 |  |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences (all)           | 0              | 0               |  |
| Dizziness                   |                |                 |  |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences (all)           | 0              | 0               |  |
| Gastrointestinal disorders  |                |                 |  |
| Nausea                      |                |                 |  |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences (all)           | 0              | 0               |  |
| Psychiatric disorders       |                |                 |  |
| Anxiety                     |                |                 |  |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences (all)           | 0              | 0               |  |
| Insomnia                    |                |                 |  |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences (all)           | 0              | 0               |  |
| Infections and infestations |                |                 |  |
| Nasopharyngitis             |                |                 |  |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 438 (0.00%) |  |
| occurrences (all)           | 0              | 0               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 30 June 2010      | Version A: Staggered start approach was removed, increased safety monitoring per Special Protocol Assessment (SPA) feedback, various sections of the protocol were clarified.  |
| 15 September 2010 | Version B: Clarification for dosing during Long-term Extension Period, addition of criteria to exclude patients who may have pre-existing potentially clinically significant hepatic dysfunction, addition of creatinine phosphokinase (was not listed in the standard laboratory list by error), clarification on procedures for Roche Clinical Repository (RCR), Work Readiness Questionnaire included as exploratory efficacy endpoint, corrected errors in the schedule of assessments and procedures.   |
| 21 April 2011     | Version C: Inclusion of FDA's requirements for analysis of iron inclusion bodies, changes to safety reporting of adverse events, clarification of screening/rescreening procedures, minor changes to study design (permission of psychosocial/rehabilitative therapies, addition of questionnaire to ensure exclusion of treatment resistant patients, minor changes to schedule of assessments and procedures), description of the VERIFIED™ system (Video Enhancement of Rater Interviewing for Independent Evaluation of Data) part of the rater quality assurance program. |
| 30 May 2012       | Version D: Addition of biomarker defined subpopulations as a secondary objective, clarification of hemoglobin exclusion criterion, additional follow-up for treatment withdrawal and at Week 52 initiation of washout, and clarification of withdrawal process, clarification of timing of screening and prospective stabilization period  |
| 25 January 2013   | Version E: Inclusion of futility analysis, addition of biomarker defined subpopulation analysis as a key secondary objective, change in Data Safety Monitoring Board (DSMB) to Independent Data Monitoring Committee (IDMC), modification of body mass index (BMI) criterion, changes in serious adverse event (SAE) reporting timeframe, and other changes (addition of electrocardiogram [ECG] at Week 58, clarification of safety population, clarification of length of study, removal of analysis of the per protocol population)   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date             | Interruption   | Restart date |
|------------------|--|--------------|
| 27 November 2013 | While bitopertin was generally well tolerated and its overall safety profile was similar to that seen in the previously reported phase II trial (NN20372), the study failed to meet its primary endpoint at week 24 (treatment period 1). These results do not support continuation of patients' treatment (treatment period 2, until week 56 and long-term extension), and the decision was made to terminate this study early. | -            |

Notes:

## Limitations and caveats

None reported