# Clinical trial results:
# A Double-blind, Randomised, Placebo-controlled, Phase 3 Trial in Patients with Chronic Idiopathic Constipation to Demonstrate the Efficacy and Safety of Elobixibat 5 mg and 10 mg for 12 Weeks Followed by a 4-week Withdrawal Period

## Summary

| | |
|---|---|
| EudraCT number | 2012-005588-28 |
| Trial protocol | SE DE SK HU CZ GB PL |
| Global end of trial date | 26 April 2014 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 30 August 2018 |
| First version publication date | 02 August 2015 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 000080 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01833065 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Ferring International Pharmascience Center US, Inc. |
| Sponsor organisation address | 100 Interpace Parkway Unite, Parsippany, NJ , United States, 07054 |
| Public contact | Clinical Development Support, Ferring Pharmaceuticals, DK0-Disclosure@ferring.com |
| Scientific contact | Clinical Development Support, Ferring Pharmaceuticals, DK0-Disclosure@ferring.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 | 19 May 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 March 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 April 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate efficacy of elobixibat treatment - at 5 mg and 10 mg daily doses - assessed as overall Complete Spontaneous Bowel Movement (CSBM) response, in patients with Chronic Idiopathic Constipation (CIC) during 12 Week Treatment Period followed by a 4 Week Withdrawal Period.

Protection of trial subjects:

Before obtaining the consent from patients, the Investigator appropriately explained the aims, methods, anticipated benefits, potential hazards, and any other aspects of the trial which are relevant to the patient's decision to participate, in a language understood by the patient. The Investigator explained to the patients about their right of freedom to refuse to enter the trial or to withdraw from it at any time, without any consequences on their further care and without the need to justify their decision. The trial was conducted in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines.

Bisacodyl 10 mg suppository (DULCOLAX) was used as rescue medication. It was allowed for treatment of significantly worsened constipation and its use was recorded in the PDA.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 30 April 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Canada: 4 |
| Country: Number of subjects enrolled | Czech Republic: 4 |
| Country: Number of subjects enrolled | Germany: 13 |
| Country: Number of subjects enrolled | Hungary: 42 |
| Country: Number of subjects enrolled | Poland: 10 |
| Country: Number of subjects enrolled | Sweden: 6 |
| Country: Number of subjects enrolled | South Africa: 32 |
| Country: Number of subjects enrolled | Slovakia: 13 |
| Country: Number of subjects enrolled | United Kingdom: 32 |
| Country: Number of subjects enrolled | United States: 158 |
| Worldwide total number of subjects | 314 |
| EEA total number of subjects | 120 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 262 |
| From 65 to 84 years | 52 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

For this trial,  total of 86 sites in the Canada, Czech Republic, Germany, Hungary, Poland, Slovakia, Sweden, United Kingdom (UK), Unites States of America (USA), and South Africa were initiated. Of these, 79 sites enrolled the patients from 30th April 2013 to 26th April 2014.

### Pre-assignment

Screening details:

The trial included a 4-week Screening Period and a 2-week Pretreatment Period prior to patient randomisation to a 12-week Treatment Period. A total of 797 patients were screened while 483 patients were excluded due to screening failure in the trial.

### Period 1

| | |
|---|---|
| Period 1 title | Baseline Visit |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | EBX 10 |

Arm description:

Elobixibat 10 mg/day was administered orally in a tablet form.

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

Dosage and administration details:

Elobixibat 10 mg/day was administered orally in a tablet form.

| | |
|---|---|
| **Arm title** | EBX 5 |

Arm description:

Elobixibat 5 mg/day was administered orally in a tablet form.

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

Dosage and administration details:

Elobixibat 5 mg/day was administered orally in a tablet form.

| | |
|---|---|
| **Arm title** | PLCBO |

Arm description:

Placebo was administered orally in a tablet form.

| | |
|---|---|
| Arm type | Placebo |

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

Dosage and administration details:

Placebo was administered orally in a tablet form.

| **Number of subjects in period 1** | EBX 10 | EBX 5 | PLCBO |
|---|---|---|---|
| Started | 103 | 100 | 111 |
| Completed | 103 | 100 | 111 |

## Period 2

| | |
|---|---|
| Period 2 title | Treatment and Withdrawal Period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | EBX 10 |

Arm description:

Elobixibat 10 mg/day was administered orally in a tablet form.

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

Dosage and administration details:

Elobixibat 10 mg/day was administered orally in a tablet form.

| | |
|---|---|
| **Arm title** | EBX 5 |

Arm description:

Elobixibat 5 mg/day was administered orally in a tablet form.

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

Dosage and administration details:

Elobixibat 5 mg/day was administered orally in a tablet form.

| **Arm title** | PLCBO |
|---|---|

Arm description:

Placebo was administered orally in a tablet form.

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

Dosage and administration details:

Placebo was administered orally in a tablet form.

| **Number of subjects in period 2[1]** | EBX 10 | EBX 5 | PLCBO |
|---|---|---|---|
| Started | 118 | 85 | 110 |
| Completed | 81 | 64 | 74 |
| Not completed | 37 | 21 | 36 |
| Trial terminated by sponsor | 16 | 10 | 13 |
| Consent withdrawn by subject | 8 | 7 | 11 |
| Others | 3 | 2 | 4 |
| Adverse event, non-fatal | 7 | 2 | 3 |
| Patient's substantial non-compliance | 1 | - | - |
| Lost to follow-up | 1 | - | 3 |
| Protocol deviation | 1 | - | 2 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: After Baseline Visit, few patients randomised to elobixibat 5 mg/day treatment received 10 mg/day treatment in actual - due to distribution issue with the trial medication - and hence counted in elobixiabt 10 mg/day group.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | EBX 10 |
| Reporting group description: | |
| Elobixibat 10 mg/day was administered orally in a tablet form. | |
| Reporting group title | EBX 5 |
| Reporting group description: | |
| Elobixibat 5 mg/day was administered orally in a tablet form. | |
| Reporting group title | PLCBO |
| Reporting group description: | |
| Placebo was administered orally in a tablet form. | |

| Reporting group values | EBX 10 | EBX 5 | PLCBO |
|---|---|---|---|
| Number of subjects | 103 | 100 | 111 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 87 | 87 | 88 |
| From 65-84 years | 16 | 13 | 23 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 49.6 | 49.5 | 48 |
| standard deviation | ± 14.3 | ± 13.5 | ± 16.1 |
| Gender, Male/Female<br>Units: participants | | | |
| Female | 84 | 85 | 97 |
| Male | 19 | 15 | 14 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 9 | 9 | 11 |
| Not Hispanic or Latino | 94 | 91 | 100 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 2 | 1 | 2 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 16 | 13 | 16 |
| White | 85 | 86 | 93 |
| More than one race | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Unknown or Not Reported | 0 | 0 | 0 |
| Region of Enrollment<br>Units: Subjects | | | |
| Canada | 1 | 2 | 1 |
| Czech Republic | 2 | 2 | 0 |
| Sweden | 1 | 2 | 3 |
| Hungary | 15 | 13 | 14 |
| United States | 49 | 54 | 55 |
| Poland | 3 | 4 | 3 |
| South Africa | 12 | 7 | 13 |
| United Kingdom | 11 | 9 | 12 |
| Slovakia | 5 | 3 | 5 |
| Germany | 4 | 4 | 5 |
| Weekly number of CSBM | | | |
| Complete Spontaneous Bowel Movement (CSBM) was defined as a spontaneous (occurring without laxative within the preceding 24 hours, including no rescue medication within the preceding 24 hours) bowel movement (as interpreted by the patient, with a beginning and an end, including single or multiple stools), accompanied by a patient reported sense of complete evacuation ('complete'). | | | |
| Units: Number | | | |
| arithmetic mean | 0.33 | 0.32 | 0.43 |
| standard deviation | ± 0.62 | ± 0.62 | ± 0.68 |
| Weekly number of SBM | | | |
| Spontaneous Bowel movement (SBM) was defined as a bowel movement that occurs in the absence of a laxative use or manual disimpaction. | | | |
| Units: Number | | | |
| arithmetic mean | 2.31 | 2.19 | 2.45 |
| standard deviation | ± 1.27 | ± 1.13 | ± 1.35 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 314 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 262 | | |
| From 65-84 years | 52 | | |
| 85 years and over | 0 | | |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender, Male/Female<br>Units: participants | | | |
| Female | 266 | | |
| Male | 48 | | |

| | | | |
|---|---|---|---|
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 29 | | |
| Not Hispanic or Latino | 285 | | |
| Unknown or Not Reported | 0 | | |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | | |
| Asian | 5 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 45 | | |
| White | 264 | | |
| More than one race | 0 | | |
| Unknown or Not Reported | 0 | | |
| Region of Enrollment<br>Units: Subjects | | | |
| Canada | 4 | | |
| Czech Republic | 4 | | |
| Sweden | 6 | | |
| Hungary | 42 | | |
| United States | 158 | | |
| Poland | 10 | | |
| South Africa | 32 | | |
| United Kingdom | 32 | | |
| Slovakia | 13 | | |
| Germany | 13 | | |
| Weekly number of CSBM | | | |
| Complete Spontaneous Bowel Movement (CSBM) was defined as a spontaneous (occurring without laxative within the preceding 24 hours, including no rescue medication within the preceding 24 hours) bowel movement (as interpreted by the patient, with a beginning and an end, including single or multiple stools), accompanied by a patient reported sense of complete evacuation (‘complete’). | | | |
| Units: Number<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Weekly number of SBM | | | |
| Spontaneous Bowel movement (SBM) was defined as a bowel movement that occurs in the absence of a laxative use or manual disimpaction. | | | |
| Units: Number<br>arithmetic mean<br>standard deviation | -<br>- | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | EBX 10 |
| Reporting group description: | |
| Elobixibat 10 mg/day was administered orally in a tablet form. | |
| Reporting group title | EBX 5 |
| Reporting group description: | |
| Elobixibat 5 mg/day was administered orally in a tablet form. | |
| Reporting group title | PLCBO |
| Reporting group description: | |
| Placebo was administered orally in a tablet form. | |
| Reporting group title | EBX 10 |
| Reporting group description: | |
| Elobixibat 10 mg/day was administered orally in a tablet form. | |
| Reporting group title | EBX 5 |
| Reporting group description: | |
| Elobixibat 5 mg/day was administered orally in a tablet form. | |
| Reporting group title | PLCBO |
| Reporting group description: | |
| Placebo was administered orally in a tablet form. | |

### Primary: Overall CSBM Response (Rate)

| | |
|---|---|
| End point title | Overall CSBM Response (Rate)[1] |
| End point description: | |
| This measure is a rate where a CSBM responder was defined as a patient with ≥3 CSBMs per week and an increase of ≥1 CSBM per week from Baseline, for at least 9 of the 12 weeks in the 12-week Treatment Period, including at least 3 weeks during Weeks 9-12. | |
| End point type | Primary |
| End point timeframe: | |
| For the overall 12-week Treatment Period | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the early termination of the study, outcomes were presented only for descriptive purposes.

| End point values | EBX 10 | EBX 5 | PLCBO | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 103 | 100 | 111 | |
| Units: Percentage of patients | | | | |
| number (confidence interval 95%) | 12.6 (7.5 to 20.6) | 14.9 (9.2 to 23.4) | 7.9 (4.1 to 14.5) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Occurrence of CSBM Response (Rate)

| End point title | Occurrence of CSBM Response (Rate) |
|---|---|

End point description:

This measure is a rate where a CSBM was defined as a spontaneous (occurring without laxative within the preceding 24 hours, including no rescue medication within the preceding 24 hours) bowel movement (as interpreted by the patient, with a beginning and an end, including single or multiple stools), accompanied by a patient reported sense of complete evacuation ('complete').

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

End point timeframe:

Within first 24 hours of treatment initiation

| End point values | EBX 10 | EBX 5 | PLCBO | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 103 | 100 | 111 | |
| Units: Percentage of patients | | | | |
| number (confidence interval 95%) | 20.9 (14 to 30) | 12.6 (7.4 to 20.8) | 12.2 (7.3 to 19.6) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in weekly frequency of SBMs

| End point title | Change from Baseline in weekly frequency of SBMs |
|---|---|

End point description:

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

End point timeframe:

For the overall 12-week Treatment Period

| End point values | EBX 10 | EBX 5 | PLCBO | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 103 | 100 | 111 | |
| Units: Number | | | | |
| least squares mean (confidence interval 95%) | 2.25 (1.78 to 2.71) | 2.4 (1.92 to 2.88) | 1.2 (0.74 to 1.66) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in weekly stool consistency of SBMs

| End point title | Change from Baseline in weekly stool consistency of SBMs |
|---|---|

End point description:

The stool consistency is measured using the seven-point ordinal Bristol Stool Form Scale (BSFS) score. The BSFS classifies human stool into seven types and points them accordingly.
The seven types of stool are: Type 1: Separate hard lumps, like nuts (hard to pass); Type 2: Sausage shaped, but lumpy; Type 3: Like a sausage but with cracks on its surface; Type 4: Like a sausage or snake, smooth and soft; Type 5: Soft blobs with clear cut edges (passed easily); Type 6: Fluffy pieces with ragged edges, a mushy stool; Type 7: Watery, no solid pieces, entirely liquid
Types 1 and 2 indicate constipation, with 3 and 4 represents the ideal stool form (especially the latter), as they are easy to defecate while not containing excess liquid, and 5, 6 and 7 points tends towards diarrhoea.

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

End point timeframe:

For the overall 12-week Treatment Period

| End point values | EBX 10 | EBX 5 | PLCBO | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 103 | 100 | 111 | |
| Units: Units on BSFS | | | | |
| least squares mean (confidence interval 95%) | 1.56 (1.35 to 1.77) | 1.45 (1.24 to 1.66) | 0.8 (0.6 to 1) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Total Patient Assessment of Constipation - Quality of Life (PAC-QOL) score responder (Rate)

| End point title | Total Patient Assessment of Constipation - Quality of Life (PAC-QOL) score responder (Rate) |
|---|---|

End point description:

This measure is a rate where a PAC-QOL score responder was defined as a patient with ≥50% reduction in total PAC-QOL score from Baseline at Week 12.

PAC-QOL is a 28-item questionnaire for psychometric assessment of disease-specific quality of life. The questionnaire is based on 5-point Likert scale; ranging from 0 [none of the time or not at all] to 4 [all of the time or extremely]). A lower score indicates a better Quality of Life. The PAC-QOL questionnaire is developed specifically for patients with constipation.

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

End point timeframe:

At Week 12

| End point values | EBX 10 | EBX 5 | PLCBO | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 103 | 100 | 111 | |
| Units: Percentage of patients | | | | |
| number (confidence interval 95%) | 32.6 (24 to 42.4) | 31.5 (22.8 to 41.8) | 19.2 (12.7 to 27.9) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in weekly degree of straining of SBMs

| End point title | Change from Baseline in weekly degree of straining of SBMs |
|---|---|

End point description:

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

End point timeframe:

For the overall 12-week Treatment Period

| End point values | EBX 10 | EBX 5 | PLCBO | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 103 | 100 | 111 | |
| Units: Units on a scale | | | | |
| least squares mean (confidence interval 95%) | -0.9 (-1.03 to -0.77) | -0.84 (-0.97 to -0.71) | -0.63 (-0.76 to -0.5) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in weekly abdominal bloating score

| End point title | Change from Baseline in weekly abdominal bloating score |
|---|---|

End point description:

The abdominal bloating score was measured using the five-point ordinal scale (1=None, 2=Mild, 3=Moderate, 4=Severe, and 5=Very severe).

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

End point timeframe:

For the overall 12-weekTreatment Period

| End point values | EBX 10 | EBX 5 | PLCBO | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 103 | 100 | 111 | |
| Units: Units on a scale | | | | |
| least squares mean (confidence interval 95%) | -0.46 (-0.56 to -0.36) | -0.35 (-0.46 to -0.25) | -0.3 (-0.4 to -0.2) | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in weekly abdominal discomfort score

| End point title | Change from Baseline in weekly abdominal discomfort score |
|---|---|

End point description:

The abdominal discomfort score was measured using the five-point ordinal scale (1=None, 2=Mild, 3=Moderate, 4=Severe, and 5=Very severe).

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

End point timeframe:

For the overall 12-week Treatment Period

| End point values | EBX 10 | EBX 5 | PLCBO | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 103 | 100 | 111 | |
| Units: Units on a scale | | | | |
| least squares mean (confidence interval 95%) | -0.37 (-0.48 to -0.27) | -0.32 (-0.43 to -0.22) | -0.25 (-0.36 to -0.15) | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

6 months

Adverse event reporting additional description:

The Investigator monitored the condition of the patient and recorded all AEs throughout the trial from the time of obtaining informed consent until the last visit (i.e. the end of the follow-up period, as applicable) in the AEs Log. Information on AEs was collected at each trial visit.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | EBX 10/EBX 10 |

Reporting group description:

Patients in this arm received Elobixibat 10 mg/day during the 12-week Treatment Period and also received Elobixibat 10 mg/day during the 4-week Withdrawal Period.

| | |
|---|---|
| Reporting group title | EBX 10/PLCBO |

Reporting group description:

Patients in this arm received Elobixibat 10 mg/day during the 12-week Treatment Period and received placebo during the 4-week Withdrawal Period.

| | |
|---|---|
| Reporting group title | EBX 5/EBX 5 |

Reporting group description:

Patients in this arm received Elobixibat 5 mg/day during the 12-week Treatment Period and also received Elobixibat 5 mg/day during the 4-week Withdrawal Period.

| | |
|---|---|
| Reporting group title | EBX 5/PLCBO |

Reporting group description:

Patients in this arm received Elobixibat 5 mg/day during the 12-week Treatment Period and received placebo during the 4-week Withdrawal Period.

| | |
|---|---|
| Reporting group title | PLCBO/EBX 10 |

Reporting group description:

Patients in this arm received placebo during the 12-week Treatment Period and received Elobixibat 10 mg/day during the 4-week Withdrawal Period.

| **Serious adverse events** | EBX 10/EBX 10 | EBX 10/PLCBO | EBX 5/EBX 5 |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 0 / 53 (0.00%) | 0 / 35 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 0 / 53 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 0 / 53 (0.00%) | 0 / 35 (0.00%) |
| 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 | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 0 / 53 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Hysterectomy | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 0 / 53 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 0 / 53 (0.00%) | 0 / 35 (0.00%) |
| 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 | | | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 0 / 53 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | EBX 5/PLCBO | PLCBO/EBX 10 | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 3 / 110 (2.73%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 110 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 110 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 110 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Hysterectomy | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 110 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 110 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 110 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | EBX 10/EBX 10 | EBX 10/PLCBO | EBX 5/EBX 5 |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 25 / 65 (38.46%) | 11 / 53 (20.75%) | 13 / 35 (37.14%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | 0 / 53 (0.00%) | 2 / 35 (5.71%) |
| occurrences (all) | 3 | 0 | 5 |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Pain | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 0 / 53 (0.00%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 0 | 2 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 13 / 65 (20.00%) | 2 / 53 (3.77%) | 1 / 35 (2.86%) |
| occurrences (all) | 17 | 12 | 2 |
| Abdominal pain | | | |
| subjects affected / exposed | 9 / 65 (13.85%) | 3 / 53 (5.66%) | 2 / 35 (5.71%) |
| occurrences (all) | 11 | 3 | 2 |
| Nausea | | | |
| subjects affected / exposed | 6 / 65 (9.23%) | 0 / 53 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all) | 6 | 0 | 1 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | 1 / 53 (1.89%) | 0 / 35 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 2 / 65 (3.08%) | 0 / 53 (0.00%) | 2 / 35 (5.71%) |
| occurrences (all) | 2 | 0 | 3 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 65 (3.08%) | 2 / 53 (3.77%) | 1 / 35 (2.86%) |
| occurrences (all) | 2 | 2 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | 3 / 53 (5.66%) | 0 / 35 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 1 / 53 (1.89%) | 2 / 35 (5.71%) |
| occurrences (all) | 1 | 1 | 2 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 53 (1.89%) | 1 / 35 (2.86%) |
| occurrences (all) | 0 | 1 | 1 |

| **Non-serious adverse events** | EBX 5/PLCBO | PLCBO/EBX 10 | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 20 / 50 (40.00%) | 24 / 110 (21.82%) | |

| | | | |
|---|---|---|---|
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 110 (1.82%) | |
| occurrences (all) | 0 | 2 | |
| General disorders and administration site conditions | | | |
| Pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 110 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 50 (10.00%) | 4 / 110 (3.64%) | |
| occurrences (all) | 7 | 5 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 6 / 110 (5.45%) | |
| occurrences (all) | 1 | 9 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 110 (1.82%) | |
| occurrences (all) | 0 | 2 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 1 / 110 (0.91%) | |
| occurrences (all) | 3 | 1 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 110 (1.82%) | |
| occurrences (all) | 0 | 2 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 5 / 110 (4.55%) | |
| occurrences (all) | 4 | 5 | |
| Sinusitis | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 1 / 110 (0.91%) | |
| occurrences (all) | 3 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 3 / 110 (2.73%) | |
| occurrences (all) | 3 | 3 | |
| Nasopharyngitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 4 / 50 (8.00%)<br>5 | 3 / 110 (2.73%)<br>3 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 21 February 2013 | A substantial amendment was made which included -<br>Adjustment of the visit window of Visit 2, Adjustment of inclusion/exclusion criteria, Addition of exploratory endpoints<br>Clarification of IMP intake (last day of IMP intake, instruction on missed IMP intake), Clarifications of treatment and withdrawal periods<br>Statistical methods: PDA to be used for formal analysis of compliance; change in statistical model for the analysis of key secondary endpoints and handling of missing doses (and other minor changes). Addition of two secondary efficacy endpoints related to QoL. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 08 January 2014 | The trial was early terminated due to a distribution issue with the trial medication. | - |

Notes:

## Limitations and caveats

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

| |
|---|
| Due to the early termination of the study, outcomes were presented only for descriptive purposes. |

Notes: