Clinical trial results:
A Multicenter, Open-label, Safety and Tolerability Extension Trial of 5 mg and 10 mg Elobixibat Daily in the Treatment of Chronic Idiopathic Constipation

Summary

EudraCT number	2012-005601-46
Trial protocol	BE SE SK HU CZ GB PL
Global end of trial date	13 May 2015

Results information

Result version number	v1 (current)
This version publication date	26 May 2016
First version publication date	26 May 2016

Trial information

Trial identification

Sponsor protocol code	000081

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01895543
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ferring International Pharmascience Center US, Inc.
Sponsor organisation address	100 Interpace Parkway, 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	04 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2015
Global end of trial reached?	Yes
Global end of trial date	13 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Safety and Tolerability Extension Trial for Patients with Chronic Idiopathic Constipation (CIC)

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 the Declaration of Helsinki and in compliance with the International Conference on Harmonization-Good Clinical Practice guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 September 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: 17
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Slovakia: 12
Country: Number of subjects enrolled	South Africa: 30
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 38
Country: Number of subjects enrolled	United States: 250
Worldwide total number of subjects	411
EEA total number of subjects	114

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)	362
From 65 to 84 years	49
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial enrolled patients from two lead-in, double-blind efficacy trials (000079 and 000080).

Pre-assignment

Screening details:

Enrolled patient (with CIC) completed at least 12 weeks of double-blind treatment in either of the lead-in efficacy trials (Trial codes 000079 or 000080). The patients agreed to refrain from making any new, major life-style changes that may affect CIC symptoms from the time of signing the informed consent form through to the last trial visit.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	EBX10

Arm description:

Elobixibat 10 mg

Elobixibat 10 mg: 10 mg Elobixibat daily, with possibility for dose adjustment to 5 mg daily.

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:

10 mg Elobixibat daily, with possibility for dose adjustment to 5 mg daily.

Number of subjects in period 1	EBX10
Started	411
Completed	282
Not completed	129
Consent withdrawn by subject	43
Subject's substantial non-compliance	6
Physician decision	2
Adverse event, non-fatal	28
Other (Not fulfilling above criteria)	24
Lost to follow-up	25
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	EBX10
Reporting group description: Elobixibat 10 mg Elobixibat 10 mg: 10 mg Elobixibat daily, with possibility for dose adjustment to 5 mg daily.	

Reporting group values	EBX10	Total	
Number of subjects	411	411	
Age Categorical Units: participants			
<=18 years	0	0	
Between 18 and 65 years	362	362	
>=65 years	49	49	
Age Continuous Units: Years			
arithmetic mean	48.6		
standard deviation	± 14.13	-	
Gender, Male/Female Units: participants			
Female	351	351	
Male	60	60	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	2	
Asian	10	10	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	74	74	
White	324	324	
More than one race	1	1	
Unknown or Not Reported	0	0	
Height Units: Meters (m)			
arithmetic mean	1.654		
standard deviation	± 0.0834	-	
Weight Units: Kilogram (Kg)			
arithmetic mean	73.61		
standard deviation	± 14.159	-	
Body Mass Index (BMI) Units: Kg/m^2			
arithmetic mean	26.87		
standard deviation	± 4.284	-	

End points

End points reporting groups

Reporting group title	EBX10
Reporting group description:	
Elobixibat 10 mg Elobixibat 10 mg: 10 mg Elobixibat daily, with possibility for dose adjustment to 5 mg daily.	
Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description:	
Set included all enrolled patients who had no major protocol deviations and included 380 patients.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Set included all enrolled patients who took at least one dose of Investigational Medicinal Product (IMP) and included 409 patients.	

Primary: Number of patients with adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of patients with adverse events (AEs) and serious adverse events (SAEs)[1]
End point description:	
The Investigator recorded all AEs throughout the trial from the time of obtaining informed consent till the last visit (i.e., Visit 6). Information on AE was collected and recorded at each visit. The data are presented for the Safety Analysis Set.	
End point type	Primary
End point timeframe:	
For the overall 52-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: The data were presented using descriptive statistics. No statistical analysis was performed.	

End point values	EBX10			
Subject group type	Reporting group			
Number of subjects analysed	409			
Units: Number of patients				
AEs	241			
SAEs	14			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of markedly abnormal changes in clinical safety laboratory variables

End point title	Incidence of markedly abnormal changes in clinical safety laboratory variables[2]

End point description:

Outcome measure include laboratory parameters from haematology, coagulation and clinical chemistry. The data are presented for the Safety Analysis Set.

End point type	Primary

End point timeframe:

For the overall 52-week Treatment Period

Notes:

[2] - 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: The data were presented using descriptive statistics. No statistical analysis was performed.

End point values	EBX10			
Subject group type	Reporting group			
Number of subjects analysed	409			
Units: Number of patients				
Gamma Glutamyl Transferase (Units/Litre): >3*ULN	6			
Triglycerides : >3.39 millimoles/Litre	5			
LDL Cholesterol : >4.1 millimoles/Litre	3			
Glucose : <2.2 (F) and <2.8 (M) millimoles/Litre	3			
Activated Partial Thromboplastin Time : >70 second	3			
Prothrombin Time : >25 seconds	2			
Sodium : >155 millimoles/Litre	2			
Chloride : <90 millimoles/Litre	2			
Alanine Aminotransferase : >3*ULN	1			
Erythrocytes (10^12/L) : <3.1	1			
Potassium : >6.5 millimoles/Litre	1			
Glucose : >22.2 millimoles/Litre	1			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of markedly abnormal changes in electrocardiograms (ECGs)

End point title	Incidence of markedly abnormal changes in electrocardiograms (ECGs)[3]

End point description:

A routine 12-lead ECG was performed at all visits. The ECG included heart rate, PR, QRS, and QT intervals assessment. The data are presented for the Safety Analysis Set.

End point type	Primary

End point timeframe:

For the overall 52-week Treatment Period

Notes:

[3] - 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: The data were presented using descriptive statistics. No statistical analysis was performed.

End point values	EBX10			
Subject group type	Reporting group			
Number of subjects analysed	409			
Units: Number of patients	3			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of markedly abnormal changes in body weight and vital signs

End point title	Incidence of markedly abnormal changes in body weight and vital signs[4]

End point description:

Vital signs were measured at all visits and included blood pressure (BP: measured after the patient had been in a seated position for ≥3 minutes of rest), pulse, respiration rate, body temperature, and body weight. The data are presented for the Safety Analysis Set.

End point type	Primary

End point timeframe:

For the overall 52-week Treatment Period

Notes:

[4] - 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: The data were presented using descriptive statistics. No statistical analysis was performed.

End point values	EBX10			
Subject group type	Reporting group			
Number of subjects analysed	409			
Units: Number of patients				
Temperature - <35 degree celsius	2			
Diastolic BP - >105 mmHg	2			
Diastolic BP - <50 mmHg	1			
Systolic BP - <85 mmHg	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients using concomitant medications

End point title	Number of patients using concomitant medications[5]

End point description:

The concomitant medications details were collected throughout the trial at all visits. Data were obtained at scheduled or unscheduled trial visits based on information provided spontaneously by the patient or as a result of questioning the patient. The data are presented for the Safety Analysis Set.

End point type	Primary

End point timeframe:

For the overall 52-week Treatment Period

Notes:

[5] - 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: The data were presented using descriptive statistics. No statistical analysis was performed.

End point values	EBX10			
Subject group type	Reporting group			
Number of subjects analysed	409			
Units: Number of patients	340			

Statistical analyses

No statistical analyses for this end point

Secondary: Use of concomitant over-the-counter (OTC) laxatives

End point title	Use of concomitant over-the-counter (OTC) laxatives

End point description:

The use of OTC laxatives during the trial was assessed based upon the concomitant medication module of the electronic Case Report Form (eCRF). The data are presented for the Safety Analysis Set.

End point type	Secondary

End point timeframe:

For the overall 52-week Treatment Period

End point values	EBX10			
Subject group type	Reporting group			
Number of subjects analysed	409			
Units: Number of patients				
Contact laxatives	33			
Osmotically acting laxatives	14			
Softeners, Emollients	11			
Bulk Producers	6			
Enemas	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in global evaluation of constipation severity

End point title	Change from Baseline in global evaluation of constipation severity

End point description:

The constipation severity score was measured on a 5-point scale (1: none to 5: very severe). The data are presented for the Safety Analysis Set.

End point type	Secondary

End point timeframe:

At Week 12, 24, 36, and 52

End point values	EBX10			
Subject group type	Reporting group			
Number of subjects analysed	409			
Units: Unit on a scale				
arithmetic mean (standard deviation)				
At Week 12	-0.2 (± 1.1)			
At Week 24	-0.2 (± 1.1)			
At Week 36	-0.1 (± 1.11)			
At Week 52	-0.2 (± 1.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in global evaluation of treatment effectiveness

End point title	Change from Baseline in global evaluation of treatment effectiveness

End point description:

The treatment effectiveness score was measured on a 5-point scale (1: extremely effective, 2: quite a bit effective, 3: moderately effective, 4: little bit effective, 5: not at all effective). The data are presented for the the Safety Analysis Set.

End point type	Secondary

End point timeframe:

At Week 12, 24, 36, and 52

End point values	EBX10			
Subject group type	Reporting group			
Number of subjects analysed	409			
Units: Unit on a scale				
arithmetic mean (standard deviation)				
At Week 12	-0.6 (± 1.43)			
At Week 24	-0.6 (± 1.36)			
At Week 36	-0.7 (± 1.24)			
At Week 52	-0.7 (± 1.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Patient assessment of constipation - Quality of Life (PAC-QOL): Overall score

End point title	Change from Baseline in Patient assessment of constipation - Quality of Life (PAC-QOL): Overall score

End point description:

PAC-QOL is a 28-item questionnaire for psychometric assessment of disease-specific QOL. The questionnaire is based on a 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 QOL. The PAC-QOL questionnaire is developed specifically for patients with constipation. PAC-QOL has four sub-scales: 'Worries and Concerns', 'Physical Discomfort', 'Psychosocial Discomfort', and 'Dissatisfaction'. The data are presented for the Safety Analysis Set.

End point type	Secondary

End point timeframe:

At Week 12, 24, 36 and 52

End point values	EBX10			
Subject group type	Reporting group			
Number of subjects analysed	409			
Units: Unit on a scale				
arithmetic mean (standard deviation)				
At Week 12	-0.24 (± 0.677)			
At Week 24	-0.21 (± 0.639)			
At Week 36	-0.16 (± 0.687)			
At Week 52	-0.22 (± 0.644)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol Group 5-Dimensions 5-Level Questionnaire (EQ-5D-5L) scores

End point title	Change from Baseline in EuroQol Group 5-Dimensions 5-Level Questionnaire (EQ-5D-5L) scores

End point description:

EQ-5D-5L is a standardised measure of health status developed to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L descriptive system comprises the following five dimensions: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels (1-5 denotes): no problems, slight problems, moderate problems, severe problems, and extreme problems, respectively. A unique health state was defined by combining 1 level from each of the 5 dimensions. Each health state was converted into a single EQ-5D-5L index value. The index values are country specific and values specified for United Kingdom (UK) were used for this study. The index value range for UK lies between -0.594 - 1.000. A positive index value represents better health status while the negative value represents poor health status. The data are presented for the Safety Analysis Set.

End point type	Secondary

End point timeframe:

At Week 12, 24, 36 and 52

End point values	EBX10			
Subject group type	Reporting group			
Number of subjects analysed	409			
Units: Unit on a scale				
arithmetic mean (standard deviation)				
At Week 12	0 (± 0.14)			
At Week 24	0 (± 0.14)			
At Week 36	0 (± 0.15)			
At Week 52	0 (± 0.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol Group Visual Analog Scale (EQ-VAS) score

End point title	Change from Baseline in EuroQol Group Visual Analog Scale (EQ-VAS) score

End point description:

The EQ VAS presents the participant's self-evaluated health on a 20 cm vertical, visual analogue scale with endpoints labelled ‘the best health you can imagine’ and ‘the worst health you can imagine’. This scale is numbered from 0 to 100, where '100' means best health you can imagine and '0' means worst health you can imagine. The participant simply mark an 'X' on the scale to indicate "how his/her health is TODAY" and mention the same number in a box provided. The data are presented for the Safety Analysis Set.

End point type	Secondary

End point timeframe:

At Week 12, 24, 36 and 52

End point values	EBX10			
Subject group type	Reporting group			
Number of subjects analysed	409			
Units: Unit on a scale				
arithmetic mean (standard deviation)				
At Week 12	0.7 (± 13.43)			
At Week 24	1.2 (± 11.95)			
At Week 36	1 (± 12.44)			
At Week 52	0.8 (± 12.35)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For the overall 52-week Treatment Period and the 2-week Follow-up Period

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. Visit 6 - the end of the follow-up period) in the AEs Log . During the trial, a total of 26 patients were down-titrated to 5 mg a day and most of these had diarrhea.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	EBX 10

Reporting group description:

Elobixibat 10 mg

Elobixibat 10 mg: 10 mg Elobixibat daily, with possibility for dose adjustment to 5 mg daily.

Serious adverse events	EBX 10		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 409 (3.42%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 409 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 409 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphangioma			
subjects affected / exposed	1 / 409 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Aortic dissection			
subjects affected / exposed	1 / 409 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 409 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 409 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 409 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 409 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 409 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Emotional distress			
subjects affected / exposed	1 / 409 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Nephrolithiasis			
subjects affected / exposed	1 / 409 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 409 (0.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breast abscess			
subjects affected / exposed	1 / 409 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 409 (0.24%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	EBX 10		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 409 (18.83%)		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	57 / 409 (13.94%)		
occurrences (all)	69		
Abdominal pain			
subjects affected / exposed	28 / 409 (6.85%)		
occurrences (all)	31		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2013	The majority of the changes in this amendment were clarifications to the initial protocol (dated 21 Feb 2013 in all participating countries except in the UK where the original protocol was dated 24 May 2013). The changes included e.g. adjustments of secondary analyses and endpoints, adjustment of exclusion criteria, clarification of administration and documentation of first IMP intake, and correction of wording and minor errors. This amendment was applicable for all sites.
24 February 2014	The main change in this amendment was the updated inclusion and exclusion criteria following the termination of the lead in efficacy trials (Echo 1 and Echo 2; protocols 000079 and 000080, respectively), to allow eligible patients to roll over into this trial (Echo 3) at the earliest convenience, and without interruption of treatment. Amendment 3 for South Africa corresponds to amendment 2 for all other participating countries. This amendment was applicable for all sites in South Africa.
12 September 2014	The main change in this amendment was the updated recruitment projections for this trial due to Sponsor's early termination of the lead in efficacy trials (Echo 1 and Echo 2; protocols 000079 and 000080, respectively) that significantly lowered the number of potential patients who could roll over into this trial. This amendment was applicable for all sites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported