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 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 Units: Years			
arithmetic mean	49.6	49.5	48
standard deviation	± 14.3	± 13.5	± 16.1
Gender, Male/Female Units: participants			
Female	84	85	97
Male	19	15	14
Ethnicity (NIH/OMB) 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) 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 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 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 Units: Years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: participants			
Female	266		
Male	48		

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	29		
Not Hispanic or Latino	285		
Unknown or Not Reported	0		
Race (NIH/OMB) 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 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 arithmetic mean standard deviation	- -		
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 standard deviation	- -		

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 occurrences (all)	4 / 50 (8.00%) 5	3 / 110 (2.73%) 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 - Adjustment of the visit window of Visit 2, Adjustment of inclusion/exclusion criteria, Addition of exploratory endpoints Clarification of IMP intake (last day of IMP intake, instruction on missed IMP intake), Clarifications of treatment and withdrawal periods 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: