



**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 26 Weeks.**

**Summary**

EudraCT number	2012-005587-94
Trial protocol	BE DE CZ GB PL
Global end of trial date	15 May 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	000079
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01827592
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	28 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2014
Global end of trial reached?	Yes
Global end of trial date	15 May 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 26 Week Treatment 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: 17
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	South Africa: 39
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	United States: 228
Worldwide total number of subjects	376
EEA total number of subjects	92

Notes:

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**Subjects enrolled per age group**

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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)	335
From 65 to 84 years	41
85 years and over	0

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## Subject disposition

### Recruitment

Recruitment details:

For this trial, a total of 84 sites were initiated in Belgium, Canada, Czech Republic, Germany, Israel, United Kingdom (UK), Poland, United States of America (USA) and South Africa. Of these, 71 sites screened patients from 30th April 2013 to 15th May 2104.

### Pre-assignment

Screening details:

The trial included a 4-week Screening Period and a 2-week Pretreatment Period prior to patient randomisation to a 26-week Treatment Period. A total of 909 patients were screened in the trial and of these 533 patients were excluded due to screening failure.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	EBX 10

Arm description:

Elobixibat 10 mg/day was administered orally in a tablet form starting from Baseline visit till End of the Treatment (EoT) visit.

Arm type	Experimental
Investigational medicinal product name	Elobixibat 10 mg
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 starting from Baseline visit till EoT visit.

<b>Arm title</b>	EBX 5
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Arm description:

Elobixibat 5 mg/day was administered orally in a tablet form starting from Baseline visit till EoT visit.

Arm type	Experimental
Investigational medicinal product name	Elobixibat 5 mg
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 starting from Baseline visit till EoT visit.

<b>Arm title</b>	PLCBO
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Arm description:

Placebo was administered orally in a tablet form starting from Baseline visit till EoT visit.

Arm type	Placebo
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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 starting from Baseline visit till EoT visit.

<b>Number of subjects in period 1</b>	EBX 10	EBX 5	PLCBO
Started	126	126	124
Safety Analysis set	125	126	124
Completed	52	46	48
Not completed	74	80	76
Consent withdrawn by subject	12	11	11
Physician decision	-	2	1
Others	-	1	3
Adverse event, non-fatal	11	9	2
Patient's substantial non-compliance	1	1	6
Lost to follow-up	1	2	2
Protocol deviation	2	1	-
Trial terminated by Sponsor	47	53	51

## Baseline characteristics

### Reporting groups

Reporting group title	EBX 10
Reporting group description: Elobixibat 10 mg/day was administered orally in a tablet form starting from Baseline visit till End of the Treatment (EoT) visit.	
Reporting group title	EBX 5
Reporting group description: Elobixibat 5 mg/day was administered orally in a tablet form starting from Baseline visit till EoT visit.	
Reporting group title	PLCBO
Reporting group description: Placebo was administered orally in a tablet form starting from Baseline visit till EoT visit.	

Reporting group values	EBX 10	EBX 5	PLCBO
Number of subjects	126	126	124
Age Categorical Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	110	113	112
>=65 years	16	13	12
Age Continuous Units: Years			
arithmetic mean	48	45.8	46.1
standard deviation	± 14.3	± 14.1	± 14.4
Gender, Male/Female Units: participants			
Female	104	107	103
Male	22	19	21
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	26	32	28
Not Hispanic or Latino	100	94	96
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	2	4	7
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	28	23	29
White	95	97	87
More than one race	0	2	0
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Canada	6	6	5
Czech Republic	2	2	2
Belgium	2	2	2

United States	73	78	77
Poland	2	1	0
United Kingdom	12	10	9
South Africa	14	11	14
Germany	15	16	15
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	0.36	0.44	0.54
standard deviation	± 0.66	± 0.75	± 0.82
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	2.2	2.13	2.31
standard deviation	± 1.34	± 1.27	± 1.43

<b>Reporting group values</b>	Total		
Number of subjects	376		
Age Categorical			
Units: participants			
<=18 years	0		
Between 18 and 65 years	335		
>=65 years	41		
Age Continuous			
Units: Years			
arithmetic mean	-		
standard deviation			
Gender, Male/Female			
Units: participants			
Female	314		
Male	62		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	86		
Not Hispanic or Latino	290		
Unknown or Not Reported	0		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	2		
Asian	13		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	80		
White	279		
More than one race	2		
Unknown or Not Reported	0		
Region of Enrollment			
Units: Subjects			
Canada	17		

Czech Republic	6		
Belgium	6		
United States	228		
Poland	3		
United Kingdom	31		
South Africa	39		
Germany	46		
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 starting from Baseline visit till End of the Treatment (EoT) visit.
Reporting group title	EBX 5
Reporting group description:	Elobixibat 5 mg/day was administered orally in a tablet form starting from Baseline visit till EoT visit.
Reporting group title	PLCBO
Reporting group description:	Placebo was administered orally in a tablet form starting from Baseline visit till EoT visit.

### Primary: Overall CSBM Response (Rate)

End point title	Overall CSBM Response (Rate) <sup>[1]</sup>
End point description:	This measure is a rate where a CSBM responder was defined as a patient with $\geq 3$ CSBMs per week and an increase of $\geq 1$ CSBM per week from Baseline, for at least 9 of the first 12-weeks of the 26-week Treatment Period, including at least 3 weeks in Weeks 9-12.
End point type	Primary
End point timeframe:	During the first 12 weeks

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	126	126	124	
Units: Percentage of patients				
number (confidence interval 95%)	15.9 (10.5 to 23.5)	22.3 (15.8 to 30.5)	10.7 (6.4 to 17.4)	

### 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 the first 24 hours of treatment initiation

<b>End point values</b>	EBX 10	EBX 5	PLCBO	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126	126	124	
Units: Percentage of patients				
number (confidence interval 95%)	20.7 (14.3 to 28.9)	23.3 (16.6 to 31.8)	9.8 (5.7 to 16.3)	

### 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 first 12 weeks	

<b>End point values</b>	EBX 10	EBX 5	PLCBO	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126	126	124	
Units: Number				
least squares mean (confidence interval 95%)	2.04 (1.64 to 2.44)	2.44 (2.04 to 2.84)	1.55 (1.15 to 1.95)	

### 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 first 12 weeks	

End point values	EBX 10	EBX 5	PLCBO	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126	126	124	
Units: Units on BSFS				
least squares mean (confidence interval 95%)	1.41 (1.24 to 1.58)	1.35 (1.18 to 1.52)	0.83 (0.66 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)
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End point description:

This measure is a rate where a PAC-QOL score responder was defined as a patient with  $\geq 50\%$  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 12 weeks	

End point values	EBX 10	EBX 5	PLCBO	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126	126	124	
Units: Percentage of patients				
number (confidence interval 95%)	34.9 (27 to 43.8)	33.3 (25.6 to 42.1)	25.7 (18.7 to 34.2)	

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The degree of straining was measured using the five-point ordinal scale (1=Not at all, 2=A little bit, 3=A moderate amount, 4=A great deal, and 5=An extreme amount).

End point type | Secondary

End point timeframe:

For the overall first 12 weeks

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<b>End point values</b>	EBX 10	EBX 5	PLCBO	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126	126	124	
Units: Units on a scale				
least squares mean (confidence interval 95%)	-1.01 (-1.15 to -0.88)	-1.04 (-1.17 to -0.91)	-0.91 (-1.05 to -0.78)	

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**Statistical analyses**

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No statistical analyses for this end point

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

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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 first 12 weeks

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<b>End point values</b>	EBX 10	EBX 5	PLCBO	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126	126	124	
Units: Units on a scale				
least squares mean (confidence interval 95%)	-0.49 (-0.61 to -0.38)	-0.52 (-0.63 to -0.4)	-0.35 (-0.47 to -0.24)	

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**Statistical analyses**

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No statistical analyses for this end point

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

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End point title	Change from Baseline in weekly abdominal discomfort score
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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
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End point timeframe:

For the overall first 12 weeks

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<b>End point values</b>	EBX 10	EBX 5	PLCBO	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126	126	124	
Units: Units on a scale				
least squares mean (confidence interval 95%)	-0.43 (-0.54 to -0.32)	-0.46 (-0.57 to -0.35)	-0.38 (-0.49 to -0.27)	

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

34 weeks

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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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### Reporting groups

Reporting group title	EBX 10
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Reporting group description:

Elobixibat 10 mg/day was administered orally in a tablet form starting from Baseline visit till EoT visit.

Reporting group title	EBX 5
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Reporting group description:

Elobixibat 5 mg/day was administered orally in a tablet form starting from Baseline visit till EoT visit.

Reporting group title	PLCBO
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Reporting group description:

Placebo was administered orally in a tablet form starting from Baseline visit till EoT visit.

<b>Serious adverse events</b>	EBX 10	EBX 5	PLCBO
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 125 (2.40%)	3 / 126 (2.38%)	1 / 124 (0.81%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 125 (0.00%)	1 / 126 (0.79%)	0 / 124 (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
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 125 (0.80%)	0 / 126 (0.00%)	0 / 124 (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			
Haemorrhoids			

subjects affected / exposed	0 / 125 (0.00%)	0 / 126 (0.00%)	1 / 124 (0.81%)
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>Hepatobiliary disorders</b>			
Cholecystitis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 126 (0.79%)	0 / 124 (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>Respiratory, thoracic and mediastinal disorders</b>			
Dyspnoea			
subjects affected / exposed	1 / 125 (0.80%)	0 / 126 (0.00%)	0 / 124 (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>Musculoskeletal and connective tissue disorders</b>			
Back pain			
subjects affected / exposed	1 / 125 (0.80%)	0 / 126 (0.00%)	0 / 124 (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
Osteochondrosis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 126 (0.79%)	0 / 124 (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

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

<b>Non-serious adverse events</b>	EBX 10	EBX 5	PLCBO
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	42 / 125 (33.60%)	28 / 126 (22.22%)	23 / 124 (18.55%)
<b>Nervous system disorders</b>			
Headache			
subjects affected / exposed	6 / 125 (4.80%)	7 / 126 (5.56%)	5 / 124 (4.03%)
occurrences (all)	7	7	5
<b>Gastrointestinal disorders</b>			

Abdominal pain subjects affected / exposed occurrences (all)	18 / 125 (14.40%) 22	6 / 126 (4.76%) 6	7 / 124 (5.65%) 11
Diarrhoea subjects affected / exposed occurrences (all)	11 / 125 (8.80%) 21	9 / 126 (7.14%) 14	3 / 124 (2.42%) 4
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	10 / 125 (8.00%) 10	7 / 126 (5.56%) 7	11 / 124 (8.87%) 12
Urinary tract infection subjects affected / exposed occurrences (all)	7 / 125 (5.60%) 8	5 / 126 (3.97%) 6	3 / 124 (2.42%) 3

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 November 2013	A substantial amendment was made which included - Addition of two secondary efficacy endpoints related to QoL, Clarifications of Inclusion/Exclusion criteria Clarification of definition of treatment periods and visit-related procedures related to specific treatment periods; adjustment of visit window (Visit 2) Clarification of IMP intake (last day of IMP intake, instruction on missed IMP intake), Change in number of allowed rescue medication during Pretreatment Period. Statistical methods: PDA to be used for formal analysis of compliance; change in statistical model for the analysis of key secondary endpoints (and other minor changes).

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: