

**Clinical trial results:**  
**Safety and efficacy of eslicarbazepine acetate (ESL) as adjunctive therapy for partial seizures in elderly patients****Summary**

EudraCT number	2009-012587-14
Trial protocol	ES CZ AT PT DE BG
Global end of trial date	08 October 2013

**Results information**

Result version number	v1 (current)
This version publication date	08 April 2016
First version publication date	06 August 2015

**Trial information****Trial identification**

Sponsor protocol code	BIA-2093-401
-----------------------	--------------

**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01422720
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	BIAL - Portela & CA, S.A.
Sponsor organisation address	À Av. Siderurgia Nacional, Coronado, Portugal, 4745-457
Public contact	André Garrido, BIAL - Portela & C <sup>a</sup> , S.A., 00351 229866100, andre.garrido@bial.com
Scientific contact	José Francisco Rocha, BIAL - Portela & C <sup>a</sup> , S.A., 00351 229866100, jose.rocha@bial.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	24 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 October 2013
Global end of trial reached?	Yes
Global end of trial date	08 October 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Primary: To evaluate the safety and tolerability of ESL as adjunctive therapy in patients aged  $\geq 65$  years with partial epilepsy, over a 26-week Treatment Period.

Secondary: To explore the efficacy of ESL as adjunctive therapy in patients aged  $\geq 65$  years with partial epilepsy, over a 26-week Treatment Period.

Protection of trial subjects:

The trial was conducted in accordance with the International Conference on Harmonisation (ICH), Good Clinical Practices (GCP), Good Manufacturing Practice (GMP), the ethical principles of the Declaration of Helsinki and with applicable local regulations. This trial was conducted by qualified persons who respected the rights and welfare of the subjects and after the review and approval of the protocol by an EC. Adverse events were collected during the trial and subject was followed by 4 weeks after last treatment visit.

Background therapy:

-

Evidence for comparator: -

Actual start date of recruitment	19 April 2010
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	Austria: 2
Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Czech Republic: 17
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Thailand: 3
Worldwide total number of subjects	72
EEA total number of subjects	60

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	72
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The recruitment period duration is expected to be approximately 9 months.  
Planned Number of Study Centres: 40 study centres in Austria, Croatia, Czech Republic, France, Germany, Poland, Portugal, Romania and Spain. Other countries may be added.

### Pre-assignment

Screening details:

Subjects who met all the inclusion criteria and none of the exclusion criteria. 99 subjects were enrolled to the trial and 27 subjects were screening failures.

### Pre-assignment period milestones

Number of subjects started	99 <sup>[1]</sup>
Number of subjects completed	72

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, serious non-fatal: 1
Reason: Number of subjects	Consent withdrawn by subject: 8
Reason: Number of subjects	Ineligibility: 16
Reason: Number of subjects	Patient's non-compliance: 1
Reason: Number of subjects	Due the anual hospitalization: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects reported to have started the pre-assignment period is the number of enrolled subjects; The worldwide number is number of treated subjects.

### Period 1

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

### Arms

<b>Arm title</b>	Eslicarbazepine acetate
------------------	-------------------------

Arm description:

Eslicarbazepine acetate (ESL);  
ESL tablets (800 mg) QD;  
Other Name: Zebinix

Arm type	Experimental
Investigational medicinal product name	Eslicarbazepine acetate
Investigational medicinal product code	
Other name	Zebinix
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For patients with CLCR above 60 mL/min the recommended starting dose is 400 mg once daily for two weeks. Thereafter, investigators are free to uptitrate the drug in 400 mg steps until a maximum of 1200 mg once daily. Titration can be upwards or downwards based on individual response. In this study the maximum daily dose allowed will be 1200 mg and the minimum dose will be 400 mg. At the end of the treatment period the dose of ESL will be tapered off at 400 mg steps each week and standard anti-epileptic treatment will be introduced.

<b>Number of subjects in period 1</b>	Eslicarbazepine acetate
Started	72
Completed	50
Not completed	22
Adverse event, serious fatal	3
Consent withdrawn by subject	4
Adverse event, non-fatal	10
Adverse event, serious non-fatal	3
Ineligibility	1
Lack of efficacy	1

## Baseline characteristics

### Reporting groups

Reporting group title	Eslicarbazepine acetate
-----------------------	-------------------------

Reporting group description:

Eslicarbazepine acetate (ESL);

ESL tablets (800 mg) QD;

Other Name: Zebinix

Reporting group values	Eslicarbazepine acetate	Total	
Number of subjects	72	72	
Age Categorical			
Age Categorical Characteristic			
Units: Subjects			
In Utero	0	0	
Preterm newborn- gestational age < 37 wk	0	0	
Newborns (0-27days)	0	0	
Infants and toddlers (28days – 23months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 year)	0	0	
From 18 - 64 years	0	0	
From 65 – 84 years	72	72	
Over 85 years	0	0	
Age Continuous			
Age Continuous Characteristic			
Units: Years			
arithmetic mean	71.6		
standard deviation	± 5.4	-	
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	34	34	
Male	38	38	

## End points

### End points reporting groups

Reporting group title	Eslicarbazepine acetate
Reporting group description: Eslicarbazepine acetate (ESL); ESL tablets (800 mg) QD; Other Name: Zebinix	
Subject analysis set title	ESL x Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: The FAS will consist of all patients who received at least 1 dose of study medication and had at least 1 day of seizure evaluation reported in the patient diary after Visit 2.	
Subject analysis set title	ESL x Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety set will consist of all patients who received at least 1 dose of study medication.	
Subject analysis set title	ESL x Per protocol population
Subject analysis set type	Per protocol
Subject analysis set description: The PP set will consist of all patients in the FAS who have completed the Treatment Period and do not have any protocol deviation (e.g. poor compliance, diaries not properly filled) in a sufficiently serious manner to warrant data (but not patient) exclusion.	

### Primary: Number of Subjects With Reported Adverse Events (AE)

End point title	Number of Subjects With Reported Adverse Events (AE) <sup>[1]</sup>
End point description: Number of Subjects With Reported Adverse Events (AE)	
End point type	Primary
End point timeframe: Throughout the study	

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: No statistical analyses were foreseen.

End point values	ESL x Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	72			
Units: Number of Subjects				
number (not applicable)				
who died	3			
who died due to TEAE	3			
with at least one SAE	11			
with at least one TESAE	10			
who prematurely terminated the study due to TEAE	16			
with at least one TEAE	47			
with at least one related TEAE	31			
with at least one severe TEAE	12			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute change from baseline of seizure frequency standardised to a frequency per 4 weeks

End point title	Absolute change from baseline of seizure frequency standardised to a frequency per 4 weeks
End point description:	Absolute change from baseline of seizure frequency standardised to a frequency per 4 weeks
End point type	Secondary
End point timeframe:	8-week Baseline Period and 26-week Treatment Period

End point values	ESL x Full analysis set	ESL x Per protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	55		
Units: Number of seizures				
arithmetic mean (standard deviation)				
Number of seizures	-1.3 ( $\pm$ 4.17)	-0.9 ( $\pm$ 3.41)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Relative change from baseline of seizure frequency standardised to a frequency per 4 weeks

End point title	Relative change from baseline of seizure frequency standardised to a frequency per 4 weeks
End point description:	Relative change from baseline of seizure frequency standardised to a frequency per 4 weeks
End point type	Secondary
End point timeframe:	8-week Baseline Period and 26-week Treatment Period

<b>End point values</b>	ESL x Full analysis set	ESL x Per protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	55		
Units: Number of seizures				
arithmetic mean (standard deviation)				
Number of seizures	-35 ( $\pm$ 65.31)	-37.5 ( $\pm$ 61.26)		

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the study

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

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	16.0
--------------------	------

### Reporting groups

Reporting group title	ESL x Safety population
-----------------------	-------------------------

Reporting group description:

Subjects in Safety population

<b>Serious adverse events</b>	ESL x Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 72 (15.28%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma multiforme			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Prostate cancer			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			

subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac disorders</b>			
<b>Cardiac failure</b>			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Coronary artery disease</b>			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Nervous system disorders</b>			
<b>Altered state of consciousness</b>			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Grand mal convulsion</b>			
subjects affected / exposed	3 / 72 (4.17%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
<b>Ischaemic stroke</b>			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Lacunar infarction</b>			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Presyncope</b>			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Respiratory, thoracic and mediastinal</b>			

disorders			
Upper airway obstruction			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Postictal psychosis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	ESL x Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 72 (65.28%)		

Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 72 (4.17%)		
occurrences (all)	3		
Orthostatic hypotension			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Gait disturbance			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	7 / 72 (9.72%)		
occurrences (all)	8		
Localised oedema			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Puncture site reaction			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	2		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Hiccups			

subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2		
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
Sneezing subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2		
Confusional state subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
Depressed mood subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
Insomnia subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
Depression subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
Sleep disorder subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
Investigations			
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
Blood creatine phosphokinase increased			

<p>subjects affected / exposed occurrences (all)</p> <p>Blood potassium decreased subjects affected / exposed occurrences (all)</p> <p>Blood urea increased subjects affected / exposed occurrences (all)</p> <p>Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)</p> <p>White blood cell count decreased subjects affected / exposed occurrences (all)</p>	<p>3 / 72 (4.17%) 3</p> <p>1 / 72 (1.39%) 1</p> <p>1 / 72 (1.39%) 1</p> <p>3 / 72 (4.17%) 3</p> <p>1 / 72 (1.39%) 1</p>		
<p>Injury, poisoning and procedural complications</p> <p>Contusion subjects affected / exposed occurrences (all)</p> <p>Injury corneal subjects affected / exposed occurrences (all)</p>	<p>1 / 72 (1.39%) 1</p> <p>1 / 72 (1.39%) 1</p>		
<p>Cardiac disorders</p> <p>Atrial fibrillation subjects affected / exposed occurrences (all)</p> <p>Cardiac failure chronic subjects affected / exposed occurrences (all)</p> <p>Cardiopulmonary failure subjects affected / exposed occurrences (all)</p> <p>Hypertensive heart disease subjects affected / exposed occurrences (all)</p> <p>Palpitations</p>	<p>1 / 72 (1.39%) 1</p> <p>1 / 72 (1.39%) 1</p> <p>1 / 72 (1.39%) 1</p> <p>1 / 72 (1.39%) 1</p>		

subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
<b>Nervous system disorders</b>			
<b>Ataxia</b>			
subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
<b>Convulsion</b>			
subjects affected / exposed occurrences (all)	6 / 72 (8.33%) 6		
<b>Dizziness</b>			
subjects affected / exposed occurrences (all)	10 / 72 (13.89%) 13		
<b>Dysgeusia</b>			
subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2		
<b>Headache</b>			
subjects affected / exposed occurrences (all)	4 / 72 (5.56%) 7		
<b>Hypersomnia</b>			
subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
<b>Lethargy</b>			
subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
<b>Hypoaesthesia</b>			
subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
<b>Migraine</b>			
subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
<b>Paraesthesia</b>			
subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1		
<b>Somnolence</b>			
subjects affected / exposed occurrences (all)	7 / 72 (9.72%) 7		

<p>Ear and labyrinth disorders</p> <p>Vestibular disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 72 (1.39%)</p> <p>1</p>		
<p>Eye disorders</p> <p>Lacrimation increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vision blurred</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 72 (1.39%)</p> <p>1</p> <p>1 / 72 (1.39%)</p> <p>1</p>		
<p>Gastrointestinal disorders</p> <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dental caries</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysphagia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epigastric discomfort</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Eructation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p>	<p>2 / 72 (2.78%)</p> <p>2</p> <p>2 / 72 (2.78%)</p> <p>2</p> <p>1 / 72 (1.39%)</p> <p>1</p> <p>3 / 72 (4.17%)</p> <p>4</p> <p>1 / 72 (1.39%)</p> <p>1</p>		

<p>subjects affected / exposed occurrences (all)</p> <p>Toothache subjects affected / exposed occurrences (all)</p>	<p>2 / 72 (2.78%) 2</p> <p>1 / 72 (1.39%) 1</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Purpura subjects affected / exposed occurrences (all)</p> <p>Rash subjects affected / exposed occurrences (all)</p> <p>Skin burning sensation subjects affected / exposed occurrences (all)</p>	<p>1 / 72 (1.39%) 1</p> <p>2 / 72 (2.78%) 2</p> <p>1 / 72 (1.39%) 1</p>		
<p>Renal and urinary disorders</p> <p>Urinary retention subjects affected / exposed occurrences (all)</p>	<p>1 / 72 (1.39%) 1</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Back pain subjects affected / exposed occurrences (all)</p> <p>Joint stiffness subjects affected / exposed occurrences (all)</p> <p>Musculoskeletal chest pain subjects affected / exposed occurrences (all)</p> <p>Neck pain subjects affected / exposed occurrences (all)</p>	<p>2 / 72 (2.78%) 2</p> <p>1 / 72 (1.39%) 1</p> <p>1 / 72 (1.39%) 1</p> <p>1 / 72 (1.39%) 1</p>		
<p>Infections and infestations</p> <p>Bacteriuria subjects affected / exposed occurrences (all)</p>	<p>1 / 72 (1.39%) 1</p>		

Bronchitis			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	7		
Otitis media			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	2		
Respiratory tract infection			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	5		
Urosepsis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Gout			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Hyperlipidaemia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Hypertriglyceridaemia			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	7 / 72 (9.72%)		
occurrences (all)	7		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2009	Clinical Trial Protocol Amendment # 1 – Spain; Synopsis (Subsection Study Design), Section 8.7 and Section 18.7.2 were updated
07 January 2010	Global Protocol Amendment # 1; Synopsis (Sub-Section Criteria for Evaluation: Safety), Section 9.2, Section 9.2.3.5, Section 9.6.2, Section 9.6.2, Section 9.6.3, Section 9.6.5, Section 9.6.6, Section 9.6.7, Section 11.1.1 and Section 18.7.1 were updated
27 January 2010	Clinical Trial Protocol Amendment # 1 – Germany; Synopsis (Sub-Section Exclusion Criteria), Section 7.2.2, Section 7.2.3, Section 7.5.2 and Section 15.6 were updated
21 June 2011	Global Protocol Amendment # 2; Synopsis Section Inclusion Criteria, and Section 7.2.1 Inclusion Criteria and Section 7.3.1 Screening Failures were updated
17 November 2011	Protocol Changes for (Asia) Amendment No. 1; Section 9.3.1, Section 9.4.2, Section 14.2 and Section 7.6 were updated
21 November 2011	Protocol Changes for South Korea Amendment No. 1; Section 7.6, Section 8.1, Section 9.3.1, Section 9.4.2, Section 14.2 were updated, Administrative revisions were done as well

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported