Clinical trial results:
EFFECTS OF ESLICARBAZEPINE ACETATE (BIA 2-093) ON COGNITIVE FUNCTION IN CHILDREN WITH PARTIAL ONSET SEIZURES: AN ADD-ON, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER CLINICAL TRIAL

Summary

EudraCT number	2008-005606-39
Trial protocol	NL PL IT
Global end of trial date	27 May 2013

Results information

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

Trial information

Trial identification

Sponsor protocol code	BIA-2093-208

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01527513
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BIAL - Portela & Ca SA
Sponsor organisation address	À Av. Siderurgia Nacional, Coronado, Portugal, 4745-457
Public contact	André Garrido, BIAL - Portela & Cª, S.A., 00351 229866100, andre.garrido@bial.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000696-PIP02-10
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2012
Global end of trial reached?	Yes
Global end of trial date	27 May 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary: To evaluate the effects of ESL on cognition in comparison with placebo as adjunctive therapy in children aged 6 to 16 years old with refractory partial-onset
seizures over a 12-week DB 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 throughout the trial and subject was followed by 28 days after the completion of the study.

Background therapy:

Concomitant AED therapy (1 or 2 AEDs). Concomitant AED therapy will be kept stable during the whole study.

Evidence for comparator:

-

Actual start date of recruitment	10 August 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Poland: 18
Country: Number of subjects enrolled	Russian Federation: 47
Country: Number of subjects enrolled	Ukraine: 40
Worldwide total number of subjects	123
EEA total number of subjects	36

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)	54
Adolescents (12-17 years)	69
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled in 27 sites in Italy, Poland, Russia and the Ukraine.

Pre-assignment

Screening details:

Subjects who met all the inclusion criteria and none of the exclusion criteria. 133 subjects were enrolled to the trial and 10 subjects were screening failures.

Pre-assignment period milestones

Number of subjects started	133[1]
Number of subjects completed	123

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not meet the inclusion/exclusion criteria: 10

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	Part I
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	Part I - ESL

Arm description:

Eslicarbazepine acetate (BIA 2-093): ESL 10-30 mg/kg/day QD (maximum 1200 mg/day).

Arm type	Experimental
Investigational medicinal product name	Eslicarbazepine acetate (BIA 2-093)
Investigational medicinal product code	
Other name	Eslicarbazepine acetate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosages were as follows:
• During the 4-week titration period, ESL 10 mg/kg/day for 2 weeks followed by 20 mg/kg/day for 2 weeks, to a maximum dose of 1200 mg/day.
• During the 8-week maintenance period, ESL 30 mg/kg/day to a maximum dose of 1200 mg/day.
• During the tapering-off period, patients were tapered off in 10 mg/kg/day steps every 2 weeks. The duration of this period depended on the dose that the patient was taking at the end of the maintenance period (30, 20, or 10 mg/kg/day).
ESL was provided as 200 mg tablets. Doses were rounded to the nearest 100 mg unit. Half tablets could be used for dosage adjustment, if necessary (tablets were scored).

Arm title	Part I - Placebo

Arm description:

Placebo Once-Daily (QD)

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:

Dosages were as follows:
• During the 4-week titration period, Placebo 10 mg/kg/day for 2 weeks followed by 20 mg/kg/day for 2 weeks, to a maximum dose of 1200 mg/day.
• During the 8-week maintenance period, Placebo 30 mg/kg/day to a maximum dose of 1200 mg/day.
• During the tapering-off period, patients were tapered off in 10 mg/kg/day steps every 2 weeks. The duration of this period depended on the dose that the patient was taking at the end of the maintenance period (30, 20, or 10 mg/kg/day).
Placebo was provided as 200 mg tablets. Doses were rounded to the nearest 100 mg unit. Half tablets could be used for dosage adjustment, if necessary (tablets were scored).

Number of subjects in period 1	Part I - ESL	Part I - Placebo
Started	83	40
Completed	75	37
Not completed	8	3
Adverse event, serious fatal	1	-
Consent withdrawn by subject	2	1
Adverse event, non-fatal	4	-
Other	-	1
Non-Compliance of Patient	1	1

Period 2

Period 2 title	Part II
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part II - ESL

Arm description:

Eslicarbazepine acetate (BIA 2-093): ESL 10-30 mg/kg/day QD (maximum 1200 mg/day).

Arm type	Experimental
Investigational medicinal product name	Eslicarbazepine acetate (BIA 2-093)
Investigational medicinal product code	
Other name	Eslicarbazepine acetate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosages were as follows:
All patients who entered Period II initially received a dose of 10 mg/kg/day ESL, but this dose was

titrated by the investigator according to clinical response, with a dose range from 10 to 30 mg/kg/day (maximum allowed dose of 1200 mg QD). Doses were rounded to the nearest 100 mg unit. Half tablets could be used for dosage adjustment, if necessary (tablets were scored). Down-titration was allowed according to clinical response or in case of intolerable AEs, as often as needed.

Number of subjects in period 2	Part II - ESL
Started	112
Completed	95
Not completed	17
Consent withdrawn by subject	12
Physician decision	1
Other	2
Non-Compliance of Patient	1
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	Part I - ESL
Reporting group description:	
Eslicarbazepine acetate (BIA 2-093): ESL 10-30 mg/kg/day QD (maximum 1200 mg/day).	
Reporting group title	Part I - Placebo
Reporting group description:	
Placebo Once-Daily (QD)	

Reporting group values	Part I - ESL	Part I - Placebo	Total
Number of subjects	83	40	123
Age Categorical			
Age Categorical Characteristic			
Units: Subjects			
In Utero	0	0	0
Preterm newborn- gestational age < 37 wk	0	0	0
Newborns (0-27days)	0	0	0
Infants and toddlers (28days – 23months)	0	0	0
Children (2-11 years)	36	18	54
Adolescents (12-17 year)	47	22	69
From 18 - 64 years	0	0	0
From 65 – 84 years	0	0	0
Over 85 years	0	0	0
Age Continuous			
Age Continuous Characteristic			
Units: Years			
arithmetic mean	11.8	11.6	
standard deviation	± 3.14	± 2.79	-
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	36	14	50
Male	47	26	73

End points

End points reporting groups

Reporting group title	Part I - ESL
Reporting group description:	
Eslicarbazepine acetate (BIA 2-093): ESL 10-30 mg/kg/day QD (maximum 1200 mg/day).	
Reporting group title	Part I - Placebo
Reporting group description:	
Placebo Once-Daily (QD)	
Reporting group title	Part II - ESL
Reporting group description:	
Eslicarbazepine acetate (BIA 2-093): ESL 10-30 mg/kg/day QD (maximum 1200 mg/day).	
Subject analysis set title	Part I - ESL x Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized patients who received at least one dose of study treatment after randomization.	
Subject analysis set title	Part I - Placebo x Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized patients who received at least one dose of study treatment after randomization.	
Subject analysis set title	Part II - ESL x Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who entered Part II and who received at least one dose of study treatment.	
Subject analysis set title	Part I - ESL x Modified Cognitive ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients who received at least one dose of study treatment after randomization and had at least one post-baseline assessment of cognition.	
Subject analysis set title	Part I - Placebo x Modified Cognitive ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients who received at least one dose of study treatment after randomization and had at least one post-baseline assessment of cognition.	
Subject analysis set title	Part I - ESL x Cognitive PP
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients in the Modified Cognitive ITT population who completed the 8-week maintenance period and were not IPDs with respect to the primary cognitive endpoint.	
Subject analysis set title	Part I - Placebo x Cognitive PP
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients in the Modified Cognitive ITT population who completed the 8-week maintenance period and were not IPDs with respect to the primary cognitive endpoint.	
Subject analysis set title	Part I - ESL x Modified Efficacy ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients who received at least one dose of study treatment after randomization and had at least one post-baseline seizure	

frequency assessment.

Subject analysis set title	Part I - Placebo x Modified Efficacy ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients who received at least one
dose of study treatment after randomization and had at least one post-baseline seizure
frequency assessment.

Subject analysis set title	Part II - ESL x Modified Efficacy ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who entered Part II,
who received at least one dose of study treatment and had at least one post-baseline
seizure frequency assessment during Part II

Primary: Change from baseline to the end of the Part I (DB period) in the composite Power of Attention measure, in order to assess information processing speed and attention/psychomotor speed.

End point title	Change from baseline to the end of the Part I (DB period) in the composite Power of Attention measure, in order to assess information processing speed and attention/psychomotor speed.

End point description:

Change from baseline to the end of the Part I (DB period) in the composite Power of Attention measure, in order to assess information processing speed and attention/psychomotor speed by treatment group for the Modified Cognitive ITT

End point type	Primary

End point timeframe:

From baseline to the end of the Part I

End point values	Part I - ESL x Modified Cognitive ITT	Part I - Placebo x Modified Cognitive ITT	Part I - ESL x Cognitive PP	Part I - Placebo x Cognitive PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	73	37	59	33
Units: Power of Attention measure				
arithmetic mean (standard deviation)				
Baseline(V2)	1733.976 (± 582.46)	1724.103 (± 443.4066)	1699.186 (± 531.0453)	1759.848 (± 456.0726)
End of Part I	1818.474 (± 605.688)	1824.383 (± 568.5121)	1759.485 (± 544.0179)	1868.03 (± 584.2275)
Change from Baseline at End of Part I	84.013 (± 403.3595)	101.937 (± 422.4147)	59.122 (± 403.4904)	111.085 (± 445.6327)

Statistical analyses

Statistical analysis title	Non-Inferiority: ESL vs Placebo Mod. Cognitive ITT

Statistical analysis description:

Analysis of change from baseline at end of double-blind period based on an ANCOVA model including treatment and country as fixed effects, baseline Power of Attention (ms) score and sex as covariates.

Comparison groups	Part I - ESL x Modified Cognitive ITT v Part I - Placebo x Modified Cognitive ITT

Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.977
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.2085
Confidence interval	
level	95 %
sides	2-sided
lower limit	-154.451
upper limit	150.034

Statistical analysis title	Non-Inferiority: ESL vs Placebo Cognitive PP

Statistical analysis description:

Change from baseline to the end of the Part I (DB period) in the composite Power of Attention measure, in order to assess information processing speed and attention/psychomotor speed.

Comparison groups	Part I - ESL x Cognitive PP v Part I - Placebo x Cognitive PP
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	33.2001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-137.593
upper limit	203.993

Secondary: Change From Baseline in Standardized Seizure Frequency- Part I

End point title	Change From Baseline in Standardized Seizure Frequency- Part I

End point description:

Standardized seizure frequency change from baseline in Part I by treatment group for the Modified Efficacy ITT

End point type	Secondary

End point timeframe:

Baseline, Maintenance Period

End point values	Part I - ESL x Modified Efficacy ITT	Part I - Placebo x Modified Efficacy ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	40		
Units: Number of seizures				
arithmetic mean (standard deviation)				
Number of seizures	-31.03 (± 87.963)	-9.13 (± 75.602)		

Statistical analyses

Statistical analysis title	Equivalence: ESL vs Placebo Mod. Efficacy ITT
Statistical analysis description:	
Results from the non-parametric analysis are based on an ANCOVA model on ranked data with ranked baseline, age group and sex as covariates and treatment and country as fixed effects.	
Comparison groups	Part I - ESL x Modified Efficacy ITT v Part I - Placebo x Modified Efficacy ITT
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	ANCOVA

Secondary: Change From Baseline in Seizure Frequency During OL period

End point title	Change From Baseline in Seizure Frequency During OL period
End point description:	
Standardized seizure frequency change from baseline during OL period for the Modified Efficacy ITT	
End point type	Secondary
End point timeframe:	
Weeks 1 to ≥ 41 weeks	

End point values	Part II - ESL x Modified Efficacy ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	112			
Units: Number of seizures				
arithmetic mean (standard deviation)				
Number of seizures	-3.03 (± 31.37)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of study treatment up to 28 days after the completion of the study.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1
Reporting groups	
Reporting group title	Part I - ESL x Safety
Reporting group description: Subject in the Safety Set treated with ESL in Part I	
Reporting group title	Part I - Placebo x Safety
Reporting group description: Subject in the Safety Set treated with Palcebo in Part I	
Reporting group title	Part II - ESL x Safety
Reporting group description: Subject in the Safety Set treated with ESL in Part II	

Serious adverse events	Part I - ESL x Safety	Part I - Placebo x Safety	Part II - ESL x Safety
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 83 (3.61%)	2 / 40 (5.00%)	8 / 112 (7.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Mitral valve incompetence			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (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

Nervous system disorders			
Complex partial seizures			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	0 / 112 (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
Convulsion			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	3 / 112 (2.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	0 / 112 (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
Hepatitis infectious mononucleosis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			

subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (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

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

Non-serious adverse events	Part I - ESL x Safety	Part I - Placebo x Safety	Part II - ESL x Safety
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 83 (39.76%)	19 / 40 (47.50%)	41 / 112 (36.61%)
Vascular disorders			
Pallor			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Feeling abnormal			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Irritability			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	1 / 83 (1.20%)	2 / 40 (5.00%)	4 / 112 (3.57%)
occurrences (all)	1	2	6
Reproductive system and breast disorders			
Hypomenorrhoea			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	0	1	0
Cough			

subjects affected / exposed	0 / 83 (0.00%)	2 / 40 (5.00%)	2 / 112 (1.79%)
occurrences (all)	0	2	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	0	1	0
Apathy			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	1 / 83 (1.20%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	1	2	0
Nervousness			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	0	1	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Excoriation			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	0	1	0

Face injury			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	0	1	0
Head injury			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	2 / 112 (1.79%)
occurrences (all)	0	0	2
Skin laceration			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Thermal burn			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	1	0	1
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Convulsion			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	3 / 83 (3.61%)	1 / 40 (2.50%)	2 / 112 (1.79%)
occurrences (all)	3	1	2
Headache			
subjects affected / exposed	8 / 83 (9.64%)	6 / 40 (15.00%)	6 / 112 (5.36%)
occurrences (all)	8	8	7
Hemianopia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Mental retardation			
subjects affected / exposed	2 / 83 (2.41%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	2	1	0
Somnolence			

subjects affected / exposed	5 / 83 (6.02%)	2 / 40 (5.00%)	0 / 112 (0.00%)
occurrences (all)	5	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Monocytosis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Thrombocytopenia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	3 / 112 (2.68%)
occurrences (all)	0	0	3
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	1 / 112 (0.89%)
occurrences (all)	0	1	1
Conjunctivitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Diplopia			
subjects affected / exposed	3 / 83 (3.61%)	0 / 40 (0.00%)	2 / 112 (1.79%)
occurrences (all)	4	0	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 83 (2.41%)	1 / 40 (2.50%)	1 / 112 (0.89%)
occurrences (all)	5	1	1
Diarrhoea			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Dyspepsia			

subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 83 (2.41%)	2 / 40 (5.00%)	2 / 112 (1.79%)
occurrences (all)	2	2	4
Vomiting			
subjects affected / exposed	5 / 83 (6.02%)	1 / 40 (2.50%)	4 / 112 (3.57%)
occurrences (all)	6	2	5
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Dermatitis allergic			
subjects affected / exposed	4 / 83 (4.82%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	5	0	1
Ecchymosis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	1 / 112 (0.89%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	1 / 83 (1.20%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	1	1	0
Rash pruritic			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Endocrine disorders			

Autoimmune thyroiditis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Hypothalamo-pituitary disorder			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Hypothyroidism			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	2 / 112 (1.79%)
occurrences (all)	0	0	3
Bronchitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	3 / 112 (2.68%)
occurrences (all)	1	0	3
Chronic tonsillitis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	2 / 112 (1.79%)
occurrences (all)	2	0	2
Gastroenteritis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Gastrointestinal viral infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	1	0	1
Herpes simplex			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Influenza			

subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	3 / 112 (2.68%)
occurrences (all)	1	0	3
Nasopharyngitis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	3 / 112 (2.68%)
occurrences (all)	0	0	3
Pharyngitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	1 / 112 (0.89%)
occurrences (all)	0	1	1
Pharyngotonsillitis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	4 / 83 (4.82%)	2 / 40 (5.00%)	3 / 112 (2.68%)
occurrences (all)	4	3	3
Respiratory tract infection viral			
subjects affected / exposed	3 / 83 (3.61%)	0 / 40 (0.00%)	5 / 112 (4.46%)
occurrences (all)	3	0	5
Rhinitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 40 (2.50%)	1 / 112 (0.89%)
occurrences (all)	0	1	1
Rubella			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Scarlet fever			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Varicella			
subjects affected / exposed	1 / 83 (1.20%)	1 / 40 (2.50%)	0 / 112 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	0 / 83 (0.00%)	0 / 40 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Obesity			
subjects affected / exposed	1 / 83 (1.20%)	0 / 40 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2010	Amendment 1: •The list of participating countries were changed. •The list of Inclusion/exclusion criterion was updated. •Some wording and definitions in the protocol was changed •A few tests were added to the applicable study visits. •A few analyses were clarified/ updated/ added.
24 March 2011	Amendment 2: •The list of Inclusion/exclusion criterion was updated. •Some therapy was deleted/added. •Clarification for some procedures, IMP dosing and concomitant medication use were added. •Changed subject(s) to patient(s) throughout the protocol except in the Introduction.
03 October 2011	Amendment 3: •Added an additional two-year, OL treatment extension (Part III) with ESL. •Added changes arising from the inclusion of Part III. • Criteria for patient withdrawal/Statistical analysis/Informed Consent and Assent were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported