Clinical trial results:
Long-Term Eslicarbazepine Acetate Extension Study

Summary

EudraCT number	2010-019000-22
Trial protocol	CZ ES PL BG
Global end of trial date	15 April 2017

Results information

Result version number	v1
This version publication date	29 April 2018
First version publication date	29 April 2018

Trial information

Trial identification

Sponsor protocol code	093-050

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00910247
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sunovion Pharmaceuticals Inc.
Sponsor organisation address	84 Waterford Drive, Marlboro, United States, 01752
Public contact	CNS Medical Director, Sunovion Pharmaceuticals Inc., 1 866-503-6351, clinicaltrialsdisclosure@sunovion.com
Scientific contact	CNS Medical Direcctor, Sunovion Pharmaceuticals Inc., 1 866-503-6351, clinicaltrialsdisclosure@sunovion.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	15 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2017
Global end of trial reached?	Yes
Global end of trial date	15 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the 1-year and post-1-year safety and tolerability of eslicarbazepine acetate flexible dosing within the range of 800 mg to 2400 mg in subjects with partial epilepsy who have participated in an 18-week double-blind eslicarbazepine acetate monotherapy study (Protocols 093-045 or 093-046).

Protection of trial subjects:

This study was conducted according to the protocol, ICH Good Clinical Practice (GCP), ICH guidelines and the ethical principles that have their origin in the Declaration of Helsinki

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2009
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	Bulgaria: 18
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	United States: 167
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Ukraine: 57
Worldwide total number of subjects	274
EEA total number of subjects	45

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)	12

Adults (18-64 years)	258
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who participated in either study 093-045 or study 093-046 were eligible to participate in study 093-050

Pre-assignment

Screening details:

Subjects who completed the 18-week treatment period or exited the study per protocol may be eligible to participate. Subjects who discontinued for reasons other than reaching the exit criteria may be eligible if there is no safety concern, however, subjects must have completed at least the first 3 weeks of the 18-week doubleblind treatment

Period 1

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

Arms

Arm title	eslicarbazepine acetate

Arm description:

Open-label treatment with eslicarbazepine acetate will be at doses between 800 and 2400 mg QD eslicarbazepine acetate: 800 to 2400 mg once daily (QD)

Arm type	Experimental
Investigational medicinal product name	eslicarbazepine acetate
Investigational medicinal product code	
Other name	DRP-0002093, BIA 2-093
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

800 to 2400 mg once daily (QD)

Number of subjects in period 1	eslicarbazepine acetate
Started	274
Completed	205
Not completed	69
Adverse event, serious fatal	2
Physician decision	3
Consent withdrawn by subject	25
Adverse event, non-fatal	15
Not Collected	4
Lost to follow-up	10
Protocol deviation	10

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	274	274	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	12	12	
Adults (18-64 years)	258	258	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	37.9		
standard deviation	± 12.70	-	
Gender categorical Units: Subjects			
Female	134	134	
Male	140	140	

End points

End points reporting groups

Reporting group title	eslicarbazepine acetate

Reporting group description:

Open-label treatment with eslicarbazepine acetate will be at doses between 800 and 2400 mg QD
eslicarbazepine acetate: 800 to 2400 mg once daily (QD)

Primary: Number and percent of subjects with treatment emergent adverse events

End point title	Number and percent of subjects with treatment emergent adverse events[1]

End point description:

Number and percent of subjects with treatment emergent adverse events

End point type	Primary

End point timeframe:

One year

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: a statistical analysis is not applicable to this endpoint

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: subjects	220			

Statistical analyses

No statistical analyses for this end point

Secondary: Number and percentage of subjects with potentially clinically significant clinical laboratory evaluations

End point title	Number and percentage of subjects with potentially clinically significant clinical laboratory evaluations

End point description:

End point type	Secondary

End point timeframe:

One Year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: subjects	186			

Statistical analyses

No statistical analyses for this end point

Secondary: Number and percent of subjects with normal baseline sodium reaching blood sodium ≤135 mmol/L, ≤130 mmol/L, and ≤125 mmol/L

End point title	Number and percent of subjects with normal baseline sodium reaching blood sodium ≤135 mmol/L, ≤130 mmol/L, and ≤125 mmol/L

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: subjects				
≤135 mmol/L	48			
≤130 mmol/L	22			
≤125 mmol/L	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion (%) of subjects with increase of body weight ≥7%

End point title	Proportion (%) of subjects with increase of body weight ≥7%

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: percentage of participants	27			

Statistical analyses

No statistical analyses for this end point

Secondary: Number and percentage of subjects with orthostatic effects

End point title	Number and percentage of subjects with orthostatic effects

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: subjects	67			

Statistical analyses

No statistical analyses for this end point

Secondary: Number and percentage of subjects with QTc-F changes (in categories) from baseline.

End point title	Number and percentage of subjects with QTc-F changes (in categories) from baseline.

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: subjects				
>500ms at any postbaseline not present at baseline	0			
>450ms at any postbaseline not present at baseline	9			
>480ms at any postbaseline not present at baseline	1			
CFB >=60 ms for at least one post-baseline	0			
CFB>=30ms for at least one &<60ms for all PBL	42			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion (%) of events in each classification of the Columbia Suicide Severity Rating Scale (C SSRS)

End point title	Proportion (%) of events in each classification of the Columbia Suicide Severity Rating Scale (C SSRS)

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: percentage of events				
Any Suicidality	4			
Any suicidal behavior	0			
any suicidal ideation	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Time on eslicarbazepine acetate monotherapy

End point title	Time on eslicarbazepine acetate monotherapy

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	238			
Units: subjects				
discontinued	70			
censored	168			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in seizure frequency from baseline

End point title	Change in seizure frequency from baseline

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: Change in seizure frequency				
arithmetic mean (standard deviation)	-48.2 (± 58.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Responder rate (proportion [%] of subjects with a ≥50% reduction of seizure frequency from baseline)

End point title	Responder rate (proportion [%] of subjects with a ≥50% reduction of seizure frequency from baseline)

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: percentage of participants	62			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion (%) of subjects that are seizure-free during study

End point title	Proportion (%) of subjects that are seizure-free during study

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: percentage of participants	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Completion rate (% of subjects completing the one year treatment)

End point title	Completion rate (% of subjects completing the one year treatment)

End point description:

End point type	Secondary

End point timeframe:

One Year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: percentage of participants	74			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment retention time (time to withdrawal due to lack of efficacy or adverse events)

End point title	Treatment retention time (time to withdrawal due to lack of efficacy or adverse events)

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	255			
Units: subjects				
discontinued	52			
censored	203			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in total score from baseline in 31-Item Quality of Life in Epilepsy (QOLIE-31)

End point title	Change in total score from baseline in 31-Item Quality of Life in Epilepsy (QOLIE-31)

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: change in score				
arithmetic mean (standard deviation)	6.6 (± 15.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in total score from baseline in Montgomery-Asberg Depression Rating Scale (MADRS)

End point title	Change in total score from baseline in Montgomery-Asberg Depression Rating Scale (MADRS)

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: change in score				
arithmetic mean (standard deviation)	-1.5 (± 6.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in total score from baseline in MADRS in those subjects with a MADRS score of ≥14 at screening

End point title	Change in total score from baseline in MADRS in those subjects with a MADRS score of ≥14 at screening

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	274			
Units: change in score				
arithmetic mean (standard deviation)	-9.4 (± 5.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Completion rate (% of subjects completing each visit post-one year)

End point title	Completion rate (% of subjects completing each visit post-one year)

End point description:

End point type	Secondary

End point timeframe:

One year

End point values	eslicarbazepine acetate			
Subject group type	Reporting group			
Number of subjects analysed	198			
Units: percentage of participants	67			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

One year

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	eslicarbazepine acetate

Reporting group description:

Open-label treatment with eslicarbazepine acetate will be at doses between 800 and 2400 mg QD
Eslicarbazepine acetate: 800 to 2400 mg once daily (QD)

Serious adverse events	eslicarbazepine acetate		
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 274 (11.68%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
fallopian tube cancer			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
non-small cel lung cancer metastatic			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
ovarian cancer			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
accelerated hypertensionaccelerated hypertension			

subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
irritability			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
non-cardiac chest pain			
subjects affected / exposed	3 / 274 (1.09%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
sudden unexplained death in epilepsy			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
emphysema			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
depression			
subjects affected / exposed	2 / 274 (0.73%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
suicidal ideation			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
electroencephalogram			

subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
accidental overdose			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
collapse of lung			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
fall			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
post concussion syndrome			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Therapeutic agent toxicity			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
sinus tachycardia			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
akathisia			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

complex partial seizures				
subjects affected / exposed	3 / 274 (1.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
grand mal convulsion				
subjects affected / exposed	1 / 274 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
partial seizures with secondary generalisation				
subjects affected / exposed	7 / 274 (2.55%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 0			
postictal paralysis				
subjects affected / exposed	1 / 274 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
simple partial seizures				
subjects affected / exposed	2 / 274 (0.73%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
status epilepticus				
subjects affected / exposed	1 / 274 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
vertigo				
subjects affected / exposed	1 / 274 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
abdominal pain upper				
subjects affected / exposed	1 / 274 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

colitis			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
pancreatitis			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
vomiting			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
cholelithiasis obstructive			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
histoplasmosis			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
pneumonia			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
tooth infection			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
nephrolithiasis			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
arthritis			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
muscle twitching			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
chronic sinusitis			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
failure to thrive			
subjects affected / exposed	1 / 274 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	eslicarbazepine acetate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 274 (60.95%)		
Injury, poisoning and procedural complications			
fall			
subjects affected / exposed	20 / 274 (7.30%)		
occurrences (all)	33		
Nervous system disorders			

complex partial seizures subjects affected / exposed occurrences (all)	14 / 274 (5.11%) 18		
dizziness subjects affected / exposed occurrences (all)	46 / 274 (16.79%) 81		
headache subjects affected / exposed occurrences (all)	64 / 274 (23.36%) 114		
General disorders and administration site conditions fatigue subjects affected / exposed occurrences (all)	23 / 274 (8.39%) 25		
Gastrointestinal disorders diarrhoea subjects affected / exposed occurrences (all)	15 / 274 (5.47%) 19		
nausea subjects affected / exposed occurrences (all)	24 / 274 (8.76%) 31		
vomiting subjects affected / exposed occurrences (all)	16 / 274 (5.84%) 20		
Psychiatric disorders depression subjects affected / exposed occurrences (all)	18 / 274 (6.57%) 19		
insomnia subjects affected / exposed occurrences (all)	15 / 274 (5.47%) 18		
Musculoskeletal and connective tissue disorders back pain subjects affected / exposed occurrences (all)	16 / 274 (5.84%) 16		
Infections and infestations			

influenza subjects affected / exposed occurrences (all)	14 / 274 (5.11%) 15		
nasopharyngitis subjects affected / exposed occurrences (all)	24 / 274 (8.76%) 35		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported