Clinical trial results:
Double-Blind, Randomized, Historical Control Study of the Safety and Efficacy of Eslicarbazepine Acetate Monotherapy in Subjects with Partial Epilepsy Not Well Controlled by Current Antiepileptic Drugs

Summary

EudraCT number	2010-018684-42
Trial protocol	CZ ES BG
Global end of trial date	27 November 2012

Results information

Result version number	v1 (current)
This version publication date	01 October 2016
First version publication date	01 October 2016

Trial information

Trial identification

Sponsor protocol code	093-046

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01091662
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sunovion Pharmaceuticals Inc.
Sponsor organisation address	84 Waterford Drive, Marlborough, United States, 01752
Public contact	Director, Sunovion Phamaceuticals Inc., 001 866-503-6351, clinicaltrialsdisclosure@sunovion.com
Scientific contact	Director, Sunovion Phamaceuticals Inc., 001 866-503-6351 , 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	02 August 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 November 2012
Global end of trial reached?	Yes
Global end of trial date	27 November 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is an 18-week, double-blind, multicenter study with gradual conversion from previous antiepileptic therapy to eslicarbazepine acetate monotherapy in subjects with partial epilepsy.

Protection of trial subjects:

The study was conducted according to the protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), ICH guidelines, and the ethical principles that have their origin in the Declaration of Helsinki. The study was conducted in accordance with applicable local law(s) and regulation(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 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	Czech Republic: 33
Country: Number of subjects enrolled	United States: 43
Country: Number of subjects enrolled	Ukraine: 68
Country: Number of subjects enrolled	Bulgaria: 25
Country: Number of subjects enrolled	Serbia: 3
Worldwide total number of subjects	172
EEA total number of subjects	58

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)	7

Adults (18-64 years)	165
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

50 investigational sites (25 sites in US/25 sites non-US which included Bulgaria, Czech Republic, Serbia, Ukraine) screened subjects. 41 sites randomized subjects into the study which began on 30June2010

Pre-assignment

Screening details:

A total of 274 subjects were screened during the study of which 172 subjects were randomized (43 US subjects and 129 non-US subjects) into two dose groups: 1600 mg ESL (114 subjects) and 1200 mg ESL (58 subjects).

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ESL 1200 mg

Arm description:

Subjects randomized to 1200 mg QD eslicarbazepine acetate will titrate from 400 mg (Week 1) to 800 mg (Week 2) to 1200 mg (Weeks 3-18) QD and taper down from 1200 mg to 600 mg QD 3 days after the end of Week 18..

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

Dosage and administration details:

administered once daily

Arm title	ESL1600 mg

Arm description:

Subjects randomized to 1600 mg QD of eslicarbazepine acetate will titrate from 600 mg (Week 1) to 1200 mg (Week 2) to 1600 mg (Weeks 3-18) QD and taper down from 1600 mg to 800 mg QD 3 days after the end of Week 18.

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

Dosage and administration details:

administered once daily

Number of subjects in period 1	ESL 1200 mg	ESL1600 mg
Started	58	114
Completed	41	80
Not completed	17	34
met exclusion criteria	1	-
Physician decision	1	1
Consent withdrawn by subject	7	6
Adverse event, non-fatal	1	9
Pregnancy	-	1
unable to swallow capsule	-	1
met exit criteria	7	13
Lost to follow-up	-	1
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	ESL 1200 mg
Reporting group description:	
Subjects randomized to 1200 mg QD eslicarbazepine acetate will titrate from 400 mg (Week 1) to 800 mg (Week 2) to 1200 mg (Weeks 3-18) QD and taper down from 1200 mg to 600 mg QD 3 days after the end of Week 18..	
Reporting group title	ESL1600 mg
Reporting group description:	
Subjects randomized to 1600 mg QD of eslicarbazepine acetate will titrate from 600 mg (Week 1) to 1200 mg (Week 2) to 1600 mg (Weeks 3-18) QD and taper down from 1600 mg to 800 mg QD 3 days after the end of Week 18.	

Reporting group values	ESL 1200 mg	ESL1600 mg	Total
Number of subjects	58	114	172
Age Categorical Units: participants			
<=18 years	3	4	7
Between 18 and 65 years	55	110	165
>=65 years	0	0	0
Age continuous Units:			
	3 ± 55	4 ± 110	-
Gender, Male/Female Units: participants			
Female	27	62	89
Male	31	52	83
Age, Customized Units: Subjects			
<18 years	3	4	7
18-39 years	32	59	91
40-65 years	23	51	74
>65 years	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	7	8
Not Hispanic or Latino	57	107	164
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Czech Republic	11	22	33
United States	15	28	43
Ukraine	26	42	68
Bulgaria	6	19	25
Serbia	0	3	3

Subject analysis sets	
Subject analysis set title	ESL1200 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects randomized to 1200 mg QD eslicarbazepine acetate will titrate from 400 mg (Week 1) to 800 mg (Week 2) to 1200 mg (Weeks 3-18) QD and taper down from 1200 mg to 600 mg QD 3 days after the end of Week 18..

Subject analysis set title	ESL 1600 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects randomized to 1600 mg QD of eslicarbazepine acetate will titrate from 600 mg (Week 1) to 1200 mg (Week 2) to 1600 mg (Weeks 3-18) QD and taper down from 1600 mg to 800 mg QD 3 days after the end of Week 18.

Reporting group values	ESL1200 mg	ESL 1600 mg	
Number of subjects	58	114	
Age Categorical Units: participants			
<=18 years	3	4	
Between 18 and 65 years	55	110	
>=65 years	0	0	
Age continuous Units:			
	3 ± 55	4 ± 110	
Gender, Male/Female Units: participants			
Female	27	62	
Male	31	52	
Age, Customized Units: Subjects			
<18 years	3	4	
18-39 years	32	59	
40-65 years	23	51	
>65 years	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	7	
Not Hispanic or Latino	57	107	
Unknown or Not Reported	0	0	
Region of Enrollment Units: Subjects			
Czech Republic	11	22	
United States	15	28	
Ukraine	26	42	
Bulgaria	6	19	
Serbia	0	3	

End points

End points reporting groups

Reporting group title	ESL 1200 mg
Reporting group description:	
Subjects randomized to 1200 mg QD eslicarbazepine acetate will titrate from 400 mg (Week 1) to 800 mg (Week 2) to 1200 mg (Weeks 3-18) QD and taper down from 1200 mg to 600 mg QD 3 days after the end of Week 18..	
Reporting group title	ESL1600 mg
Reporting group description:	
Subjects randomized to 1600 mg QD of eslicarbazepine acetate will titrate from 600 mg (Week 1) to 1200 mg (Week 2) to 1600 mg (Weeks 3-18) QD and taper down from 1600 mg to 800 mg QD 3 days after the end of Week 18.	
Subject analysis set title	ESL1200 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects randomized to 1200 mg QD eslicarbazepine acetate will titrate from 400 mg (Week 1) to 800 mg (Week 2) to 1200 mg (Weeks 3-18) QD and taper down from 1200 mg to 600 mg QD 3 days after the end of Week 18..	
Subject analysis set title	ESL 1600 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects randomized to 1600 mg QD of eslicarbazepine acetate will titrate from 600 mg (Week 1) to 1200 mg (Week 2) to 1600 mg (Weeks 3-18) QD and taper down from 1600 mg to 800 mg QD 3 days after the end of Week 18.	

Primary: Cumulative 112-day exit rate as estimated by Kaplan-Meier method

End point title	Cumulative 112-day exit rate as estimated by Kaplan-Meier method
End point description:	
Cumulative exit rate was defined as the proportion of subjects meeting at least one of the following five exit criteria over a 16-week study period (from start of AED taper/con. period (Wk 3) to end of double blind monotherapy period (Wk 18)).1.One episode of status epilepticus.2.One secondary gen. partial seizure (in subjects who did not have gen.seizures during 6 mo. prior to screening).3.A two fold increase in any consecutive 28 day seizure rate compared to the highest consecutive 28 day seizure rate during the 8 week baseline period. 4.A two fold increase in any consecutive 2 day seizure rate compared to the highest consecutive 2 day seizure rate during the 8 week baseline period. If the highest number of seizures in any consecutive 2 day period during the 8 week baseline was 1 then 3 seizures in a consecutive 2 day period was required to exit. 5.Worsening of seizures or increase in seizure frequency considered serious or requiring intervention as judged by the investigator	
End point type	Primary
End point timeframe:	
From beginning of Week 3 to end of Week 18	

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	100	54	100
Units: proportion of participants				
number (confidence interval 95%)	0.156 (0.081 to 0.2874)	0.128 (0.075 to 0.2152)	0.156 (0.081 to 0.2874)	0.128 (0.075 to 0.2152)

Statistical analyses

Statistical analysis title	Cumulative 112-day exit rate as estimated by Kapla
Statistical analysis description: Cumulative 112-day exit rate as estimated by Kaplan-Meier method	
Comparison groups	ESL1200 mg v ESL 1600 mg
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	number
Point estimate	0.156
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.081
upper limit	0.2874
Variability estimate	Standard deviation

Statistical analysis title	Cumulative 112-day exit rate as estimated by Kapla
Statistical analysis description: Cumulative 112-day exit rate as estimated by Kaplan-Meier method	
Comparison groups	ESL 1600 mg v ESL1200 mg
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	number
Point estimate	0.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.075
upper limit	0.2152

Secondary: Proportion (%) of subjects that are seizure-free during the 10-week double-blind monotherapy treatment period.

End point title	Proportion (%) of subjects that are seizure-free during the 10-week double-blind monotherapy treatment period.

End point description:

Seizure-free subjects during the monotherapy period were determined as subjects who had seizure assessments during the monotherapy period, and did not have any seizures in the 10 weeks between Visits 6 and 9 (Weeks 9 through 18). Subjects who discontinued during this period were considered not

seizure-free even if they were seizure-free at the time of discontinuation, i.e., to be considered seizure-free, subjects must complete the 10-week period without any seizures.

End point type	Secondary

End point timeframe:

Week 9 through 18

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	100	54	100
Units: percentage of participants				
number (confidence interval 95%)	7.4 (2.1 to 17.9)	10 (4.9 to 17.6)	7.4 (2.1 to 17.9)	10 (4.9 to 17.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects seizure-free during the last 4 weeks on eslicarbazepine acetate monotherapy.

End point title	Percentage of subjects seizure-free during the last 4 weeks on eslicarbazepine acetate monotherapy.

End point description:

Percentage of participants that were Seizure-free during the last four weeks of monotherapy were determined as subjects who had seizure assessments during the 4 weeks between Visits 8 and 9 (Weeks 15 through 18), and did not have any seizures.

End point type	Secondary

End point timeframe:

Week 15 through 18

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	100	54	100
Units: percentage of participants				
number (confidence interval 95%)	16.7 (7.9 to 29.3)	17 (10.2 to 25.8)	16.7 (7.9 to 29.3)	17 (10.2 to 25.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Completion rate (% of subjects completing the 18 weeks of double-blind treatment).

End point title	Completion rate (% of subjects completing the 18 weeks of

	double-blind treatment).

End point description:

Subjects completing the study were determined as subjects who completed the 18 weeks of double-blind treatment.

End point type	Secondary

End point timeframe:

18 weeks

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	100	54	100
Units: percentage of participants				
number (confidence interval 95%)	75.9 (62.4 to 86.5)	80 (70.8 to 87.3)	75.9 (62.4 to 86.5)	80 (70.8 to 87.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Completion rate during the 10 weeks of monotherapy (% of subjects entering the monotherapy period who complete).

End point title	Completion rate during the 10 weeks of monotherapy (% of subjects entering the monotherapy period who complete).

End point description:

Monotherapy completion rate was defined as the proportion (%) of subjects entering the monotherapy period who completed the 10 weeks of monotherapy treatment.

End point type	Secondary

End point timeframe:

Week 8 through 18

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	100	54	100
Units: percentage of participants				
number (confidence interval 95%)	85.4 (72.2 to 93.9)	90.9 (82.9 to 96)	85.4 (72.2 to 93.9)	90.9 (82.9 to 96)

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:

The start of the monotherapy period was defined as the date of termination of all other AEDs while taking study monotherapy medication. Time on monotherapy was defined from the start of monotherapy period to the last dose of monotherapy treatment.

End point type	Secondary

End point timeframe:

Week 8 to Week 18

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	100	54	100
Units: days				
median (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)

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:

The relative (%) change in standardized seizure frequency was evaluated for four periods: titration (Weeks 1 to 2), AED taper/conversion (Weeks 3 to 8), monotherapy (Weeks 9 to 18), and double-blind (Weeks 1 to 18).

End point type	Secondary

End point timeframe:

18 weeks, Double-blind:weeks 1-18; Baseline: weeks -8to -1; titration: weeks 1 to 2; AED taper/conversion: weeks 3 to 8; monotherapy; weeks 9 to 18

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	98	54	98
Units: Percent change				
median (inter-quartile range (Q1-Q3))				
Relative(%) change from baseline fo DB pd n=54,98	-36.1 (-59.2 to -17.1)	-47.5 (-70.8 to -11.3)	-36.1 (-59.2 to -17.1)	-47.5 (-70.8 to -11.3)
Relative(%)chg from baseline for titrat pd n=54,98	-19.3 (-57.9 to 3.3)	-35.6 (-72.4 to -9.4)	-19.3 (-57.9 to 3.3)	-35.6 (-72.4 to -9.4)
Relative (%) chg from baseline-AED t/c pd n=54,98	-39.4 (-54 to 0)	-42.9 (-73.8 to -12.1)	-39.4 (-54 to 0)	-42.9 (-73.8 to -12.1)
Relative (%) change from baseline-mono pd n=48,87	-45.7 (-72.1 to -20.1)	-52.1 (-81.6 to -21.8)	-45.7 (-72.1 to -20.1)	-52.1 (-81.6 to -21.8)

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:

Responder rate was defined as the proportion (%) of subjects with a ≥ 50% reduction of seizure frequency from baseline. This analysis was done for the titration (Weeks 1 to 2), AED taper/conversion (Weeks 3 to 8), monotherapy (Weeks 9 to 18), and double-blind (Weeks 1 to 18) periods.

End point type	Secondary

End point timeframe:

Week 0 to Week 18, Double-blind weeks 1-18; baseline: weeks -8 to -1; Titration: weeks 1-2; AED taper/conversion; weeks 3-8; monotherapy weeks 9-18

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	100	54	100
Units: percentage of participants				
number (confidence interval 95%)				
responder rate during the DB period	38.9 (29.5 to 58.8)	46 (36 to 56.3)	35.2 (22.7 to 49.4)	46 (36 to 56.3)
responder rate during titration period	35.2 (22.7 to 49.4)	37 (27.6 to 47.2)	29.6 (18 to 43.6)	37 (27.6 to 47.2)
responder rate during the AED	29.6 (18 to 43.6)	39 (29.4 to 49.3)	29.6 (18 to 43.6)	39 (29.4 to 49.3)
responder rate during monotherapy period	29.6 (18 to 43.6)	46 (41.4 to 63)	38.9 (29.5 to 58.8)	46 (41.4 to 63)

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion (%) of subjects reaching each exit criteria

End point title	Proportion (%) of subjects reaching each exit criteria

End point description:

The proportion (%) of subjects reaching each of the 5 exit criteria-1.One episode of status epilepticus.2.One secondary gen. partial seizure (in subjects who did not have gen.seizures during 6 mo. prior to screening).3.A two fold increase in any consecutive 28 day seizure rate compared to the highest consecutive 28 day seizure rate during the 8 week baseline period. 4.A two fold increase in any consecutive 2 day seizure rate compared to the highest consecutive 2 day seizure rate during the 8

week baseline period. If the highest number of seizures in any consecutive 2 day period during the 8 week baseline was 1 then 3 seizures in a consecutive 2 day period was required to exit.
5.Worsening of seizures or increase in seizure frequency considered serious or requiring intervention as judged by the investigator

End point type	Secondary

End point timeframe:

Week 1 to Week 18, (beginning of week 1 to end of week 18)

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	100	54	100
Units: percentage of participants				
number (not applicable)				
exit criterion 1	0	0	0	0
exit criterion 2	1.9	0	1.9	0
exit criterion investigator prog. assessment)	5.6	2	5.6	2
exit criterion 3 (sponsors prog. assessment)	3.7	1	3.7	1
exit criterion 4 (investigaor prog. assessment)	1.9	5	1.9	5
exit criterion 4 (sponsor prog. assessment)	3.7	6	3.7	6
exit criterion 5	3.7	5	3.7	5

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:

The QOLIE-31 overall score was obtained by using a weighted average of multi-item scale scores. The recorded responses were converted to 0-100 point scales. The mean of the individual item scores in each subgroup were calculated, with higher converted scores reflecting better quality of life.

End point type	Secondary

End point timeframe:

Week 0 to Week 18, Baseline: Day 0: End of AED taper/conversion period: end of week 8; End of monotherapy period: end of week 18

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	100	54	100
Units: units on a scale				
arithmetic mean (standard deviation)				
chg from baseline-end of AED taper/covn.pd n=45,85	3.4 (± 12.3)	5.8 (± 11.77)	3.4 (± 12.3)	5.8 (± 11.77)
change from baseline-end of monotherapy pd n=50,96	4 (± 11.48)	4.7 (± 13.7)	4 (± 11.48)	4.7 (± 13.7)

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The total score of MADRS is defined as the sum of all individual item scores. From 0-60, high score indicates more severe

End point type	Secondary

End point timeframe:

Week 0 to Week 18,baseline day 0; end of AED taper/conversion period; end of week 8; end of monotherapy period; end of week 18

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	100	54	100
Units: units on a scale				
arithmetic mean (standard deviation)				
chg from baseline-end of AED taper/covn.pd n=48,88	-1.2 (± 3.69)	-1.8 (± 4.01)	-1.2 (± 3.69)	-1.8 (± 4.01)
chg from baseline-end of monotherapy pd n=54,98	0 (± 6.47)	-1.6 (± 4.54)	0 (± 6.47)	-1.6 (± 4.54)

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The total score of MADRS is defined as the sum of all individual item scores. From 0-60, higher score

indicates more severe

End point type	Secondary

End point timeframe:

Week 0 to Week 18, baseline:day 0;end of AED taper/conversion period; end of week 8; end of monotherapy period: end of week 18

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	100	50	100
Units: units on a scale				
arithmetic mean (standard deviation)				
chge from baseline-end of AED taper/covn.pd n=7,16	-3.9 (± 4.3)	-6.6 (± 4.15)	-3.9 (± 4.3)	-6.6 (± 4.15)
chg from baseline-end of monotherapy pd n=7,18	-6.1 (± 6.72)	-4.1 (± 7.58)	-6.1 (± 6.72)	-4.1 (± 7.58)

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion (%) of subjects with increase of body weight >= 7% from baseline

End point title	Proportion (%) of subjects with increase of body weight >= 7% from baseline

End point description:

End point type	Secondary

End point timeframe:

18 Week Double-blind treatment period

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	58	114	58	114
Units: percentage of participants				
number (not applicable)	1.8	11.7	1.8	11.7

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion (%) of subjects with normal baseline sodium reaching blood sodium ≤135 mmol/L, ≤130 mmol/L, and ≤125 mmol/L.

End point title	Proportion (%) of subjects with normal baseline sodium reaching blood sodium ≤135 mmol/L, ≤130 mmol/L, and ≤125 mmol/L.

End point description:

Proportion (%) of Subjects With Normal Baseline Sodium Reaching Blood Sodium ≤135 mmol/L, ≤130 mmol/L, and ≤125 mmol/L

End point type	Secondary

End point timeframe:

Week 0 to Week 18

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	58	114	58	114
Units: percentage of participants				
number (not applicable)				
≤ 135 and > 130 mEq/L	8.8	54.5	49.1	54.5
≤ 130 and > 125 mEq/L	0	20.9	8.8	20.9
≤ 125 mEq/L	49.1	0	0	0

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:

18 Week Double-blind treatment period

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	58	114	58	114
Units: Percent of particiants				
number (not applicable)				
Actual Attempt	3.4	0	3.4	0
Non-suicidal Self-Injurious Behavior	0	0.9	0	0.9
Interrupted Attempt	0	0	0	0
Aborted Attempt	0	0	0	0
Preparatory Attempts	0	0	0	0
Suicidal Behavior	3.4	0	3.4	0

Wish to be Dead	1.7	0.9	1.7	0.9
Non-specific Active Suicidal Thoughts	0	1	0	1
Act. Suicidal Idea. w/any method-no intent to act	0	0	0	0
Act. Suicidal Idea.w/any method-some intent to act	0	0.9	0	0.9
Act. Suicidal Idea. w/any method-Spec. Plan to act	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Standardized seizure frequency (SSF) by period

End point title	Standardized seizure frequency (SSF) by period

End point description:

Seizure frequency was evaluated by using a standardized frequency per 4 weeks (28 days). It was evaluated for five periods: baseline (Weeks -8 to -1), titration (Weeks 1 to 2), AED taper/conversion (Weeks 3 to 8), monotherapy (Weeks 9 to 18), and double-blind (Weeks 1 to 18).

End point type	Secondary

End point timeframe:

Double-blind: week to 18; Baseline: weeks -8 to -1; titration: weeks 1 to 2; AED taper/conversion weeks 3 to 8; monotherapy: weeks 9 to 18

End point values	ESL 1200 mg	ESL1600 mg	ESL1200 mg	ESL 1600 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	100	54	100
Units: seizures in 28 days				
arithmetic mean (standard deviation)				
SSF during double-blind pd n=54,100	5.5 (± 7.75)	5.2 (± 5.38)	5.5 (± 7.75)	5.2 (± 5.38)
SSF druing baseline pd n=54,98	7.4 (± 5.89)	8.7 (± 7.2)	7.4 (± 5.89)	8.7 (± 7.2)
SSF during titration pd n=54,100	6 (± 6.16)	6.4 (± 8.11)	6 (± 6.16)	6.4 (± 8.11)
SSF during AED taper/conversion pd n=54,100	6 (± 9.68)	5.1 (± 5.26)	6 (± 9.68)	5.1 (± 5.26)
SSF during monotherapy pd n=48,88	4.7 (± 6.1)	5 (± 5.62)	4.7 (± 6.1)	5 (± 5.62)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
18 week double-blind treatment period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups	
Reporting group title	ESL 1600 mg
Reporting group description:	
Titrate from 600 mg (Week 1) to 1200 mg (Week 2) to 1600 mg (Weeks 3-18) QD and taper down from 1600 mg to 800 mg QD 3 days after end of Week 18.	
Reporting group title	ESL1200 mg
Reporting group description:	
Titrate from 400 mg (Week 1) to 800 mg (Week2) to 1200 mg (Weeks 3-18) QD and taper down from 1200 mg to 600 mg QD 3 days after end of Week 18.	

Serious adverse events	ESL 1600 mg	ESL1200 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 114 (7.02%)	1 / 58 (1.72%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
ankle fracture			
subjects affected / exposed	1 / 114 (0.88%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post concussion syndrome			
subjects affected / exposed	1 / 114 (0.88%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 114 (0.88%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial flutter			
subjects affected / exposed	1 / 114 (0.88%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Complex partial seizures			
subjects affected / exposed	1 / 114 (0.88%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures with secondary generalisation			
subjects affected / exposed	1 / 114 (0.88%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synocope			
subjects affected / exposed	1 / 114 (0.88%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 114 (0.88%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash pruritic			
subjects affected / exposed	1 / 114 (0.88%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug rash with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 114 (0.88%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			

subjects affected / exposed	1 / 114 (0.88%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ESL 1600 mg	ESL1200 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 114 (56.14%)	29 / 58 (50.00%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	24 / 114 (21.05%)	6 / 58 (10.34%)	
occurrences (all)	37	7	
Headache			
subjects affected / exposed	32 / 114 (28.07%)	11 / 58 (18.97%)	
occurrences (all)	87	16	
Solmnolence			
subjects affected / exposed	10 / 114 (8.77%)	2 / 58 (3.45%)	
occurrences (all)	12	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 114 (5.26%)	4 / 58 (6.90%)	
occurrences (all)	7	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 114 (6.14%)	6 / 58 (10.34%)	
occurrences (all)	12	8	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 114 (0.88%)	3 / 58 (5.17%)	
occurrences (all)	1	4	
Insomnia			
subjects affected / exposed	3 / 114 (2.63%)	4 / 58 (6.90%)	
occurrences (all)	3	4	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	6 / 114 (5.26%)	3 / 58 (5.17%)	
occurrences (all)	7	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 114 (7.89%)	4 / 58 (6.90%)	
occurrences (all)	9	4	
Influenza			
subjects affected / exposed	1 / 114 (0.88%)	3 / 58 (5.17%)	
occurrences (all)	1	3	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: