# 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<br>Units: participants | | | |
| <=18 years | 3 | 4 | 7 |
| Between 18 and 65 years | 55 | 110 | 165 |
| >=65 years | 0 | 0 | 0 |
| Age continuous<br>Units: | | | |
| | 3<br>± 55 | 4<br>± 110 | - |
| Gender, Male/Female<br>Units: participants | | | |
| Female | 27 | 62 | 89 |
| Male | 31 | 52 | 83 |
| Age, Customized<br>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)<br>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<br>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<br>Units: participants | | | |
| <=18 years | 3 | 4 | |
| Between 18 and 65 years | 55 | 110 | |
| >=65 years | 0 | 0 | |
| Age continuous<br>Units: | | | |
| | 3<br>± 55 | 4<br>± 110 | |
| Gender, Male/Female<br>Units: participants | | | |
| Female | 27 | 62 | |
| Male | 31 | 52 | |
| Age, Customized<br>Units: Subjects | | | |
| <18 years | 3 | 4 | |
| 18-39 years | 32 | 59 | |
| 40-65 years | 23 | 51 | |
| >65 years | 0 | 0 | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | 7 | |
| Not Hispanic or Latino | 57 | 107 | |
| Unknown or Not Reported | 0 | 0 | |
| Region of Enrollment<br>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.<br>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:<br>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:<br>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 | | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 114 (0.88%) | 3 / 58 (5.17%) | |
| occurrences (all) | 1 | 3 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 114 (7.89%) | 4 / 58 (6.90%) | |
| occurrences (all) | 9 | 4 | |

## 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: