



## Clinical trial results:

### Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children (EcLiPSE) – an open label randomised controlled trial

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-002188-13 |
| Trial protocol           | GB             |
| Global end of trial date | 21 May 2018    |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 22 November 2018 |
| First version publication date | 22 November 2018 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | UoL001087 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN22567894 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |                                                                                                        |
|------------------------------|--------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Alder Hey NHS Foundation Trust                                                                         |
| Sponsor organisation address | Eaton Road, Liverpool, United Kingdom, L12 2AP                                                         |
| Public contact               | Nadia Al-Najjar, Medicines for Children Clinical Trials Unit, +44 01517958755, eclipse@liverpool.ac.uk |
| Scientific contact           | Nadia Al-Najjar, Medicines for Children Clinical Trials Unit, +44 01517958755, eclipse@liverpool.ac.uk |
| Sponsor organisation name    | University of Liverpool                                                                                |
| Sponsor organisation address | 2nd Floor Block D Waterhouse Building, 3 Brownlow Street, Liverpool, United Kingdom, L69 3GL           |
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| Scientific contact           | Nadia Al-Najjar, Medicines for Children Clinical Trials Unit, +44 01517958755, eclipse@liv.ac.uk       |

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                       | 21 May 2018 |
| Is this the analysis of the primary completion data? | Yes         |
| Primary completion date                              | 21 May 2018 |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 21 May 2018 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

1. To determine whether intravenous phenytoin or intravenous levetiracetam is the more efficacious second-line anticonvulsant for the emergency management of convulsive status epilepticus (CSE) in children.
2. To determine if intravenous levetiracetam is associated with fewer adverse effects than intravenous phenytoin

Protection of trial subjects:

Both treatments used in the EcLiPSE clinical trial (Levetiracetam and Phenytoin) are licensed for their use to treat the clinical condition investigated in the study - Convulsive Status Epilepticus. The administration of the trial treatments was done so by trained medical professionals in a hospital environment using standard, routine procedures. All those who oversaw treatment were trained on the study, which is evidenced by the collection of site training logs. Current CVs and GCP certificates were also obtained for all members of staff who had a delegated duty within the study to ensure the correct level of training had been given for them to complete the delegated tasks.

All members of site staff who approached the participant's family for consent were trained on the study, this equipped them with sufficient knowledge to answer any trial related questions. In addition, these members of staff also had the required clinical skills to provide additional support to those families that were emotionally distressed by their child's condition.

Patient information was collected at site using CRFs specifically designed for the EcLiPSE trial. All collected information was pseudo-anonymised and transferred to the Clinical Trial Research Centre (CTRC) in an agreed secure format. The management of the study was done in line with Ethical, Regulatory and CTRC policies/procedures.

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 17 July 2015 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 286 |
| Worldwide total number of subjects   | 286                 |
| EEA total number of subjects         | 286                 |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 118 |
| Children (2-11 years)                     | 155 |
| Adolescents (12-17 years)                 | 13  |
| Adults (18-64 years)                      | 0   |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Patients aged 6 months up to 18 years presenting to the ED with generalised tonic-clonic, generalised clonic or focal clonic status epilepticus that requires second-line treatment were assessed by clinical staff and randomised if they fulfilled the eligibility criteria. The study opened to recruitment on 17/07/2015, and was closed on 10/04/2018.

### Pre-assignment

Screening details:

1432 children were assessed for eligibility. 1028 (72%) were excluded: 833 children did not meet the inclusion criteria, eligibility was missing for 3 children, and 192 children were excluded for other reasons.

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Randomised              |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

### Arms

|                              |               |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes           |
| <b>Arm title</b>             | Levetiracetam |

Arm description:

Patients randomised to Levetiracetam.

|                                        |                                 |
|----------------------------------------|---------------------------------|
| Arm type                               | Experimental                    |
| Investigational medicinal product name | Levetiracetam                   |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Intravenous use                 |

Dosage and administration details:

Levetiracetam should be administered as a single dose, at a dosage of 40mg/kg (maximum dose 2500mg) of body weight (estimated according to the child's age). The treatment should be administered intravenously as an infusion over 5 minutes in a large vein.

Levetiracetam should be diluted to a maximum of 50mg/mL with sodium chloride 0.9% before administration

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Phenytoin |
|------------------|-----------|

Arm description:

Patients randomised to Phenytoin.

|                                        |                                 |
|----------------------------------------|---------------------------------|
| Arm type                               | Active comparator               |
| Investigational medicinal product name | Phenytoin                       |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Intravenous use                 |

Dosage and administration details:

Phenytoin should be administered as a single dose, at a dosage of 20mg/kg (maximum dose 2000mg) of estimated body weight (estimated according to the child's age).

The total maximum dose of phenytoin administered should be 2000mg. However, sites should confirm prior to study start if their local procedure states that the maximum phenytoin dose is less than 2000mg. If this is the case then the maximum dose for phenytoin should be as per local procedure and should be adhered to.

The treatment should be administered intravenously as an infusion in a large vein:

- Infusion time for phenytoin dose  $\leq 1000\text{mg}$ : 20 minutes
- Infusion time for phenytoin dose  $>1000\text{mg}$  and  $\leq 1500\text{mg}$ : Between 20 – 30 minutes
- Infusion time for phenytoin dose  $>1500\text{mg}$  and  $\leq 2000\text{mg}$ : Between 30 – 40 minutes

The final concentration of phenytoin in the solution for infusion should be a maximum of 10mg/ml with 0.9% sodium chloride.

| Number of subjects in period 1     | Levetiracetam | Phenytoin |
|------------------------------------|---------------|-----------|
| Started                            | 212           | 192       |
| Completed                          | 152           | 134       |
| Not completed                      | 60            | 58        |
| Unknown                            | 1             | 5         |
| Declined consent                   | 8             | 11        |
| Second-line treatment not required | 51            | 42        |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | Treated                 |
| Is this the baseline period? | Yes <sup>[1]</sup>      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

## Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | Levetiracetam |
|------------------|---------------|

Arm description:

Patients randomised to Levetiracetam and treated.

|                                        |                                 |
|----------------------------------------|---------------------------------|
| Arm type                               | Experimental                    |
| Investigational medicinal product name | Levetiracetam                   |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Intravenous use                 |

Dosage and administration details:

Levetiracetam should be administered as a single dose, at a dosage of 40mg/kg (maximum dose 2500mg) of body weight (estimated according to the child's age). The treatment should be administered intravenously as an infusion over 5 minutes in a large vein.

Levetiracetam should be diluted to a maximum of 50mg/mL with sodium chloride 0.9% before administration

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Phenytoin |
|------------------|-----------|

Arm description:

Patients randomised to Phenytoin and treated.

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|                                        |                                 |
|----------------------------------------|---------------------------------|
| Investigational medicinal product name | Phenytoin                       |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Intravenous use                 |

**Dosage and administration details:**

Phenytoin should be administered as a single dose, at a dosage of 20mg/kg (maximum dose 2000mg) of estimated body weight (estimated according to the child's age).

The total maximum dose of phenytoin administered should be 2000mg. However, sites should confirm prior to study start if their local procedure states that the maximum phenytoin dose is less than 2000mg. If this is the case then the maximum dose for phenytoin should be as per local procedure and should be adhered to.

The treatment should be administered intravenously as an infusion in a large vein:

- Infusion time for phenytoin dose  $\leq 1000\text{mg}$ : 20 minutes
- Infusion time for phenytoin dose  $> 1000\text{mg}$  and  $\leq 1500\text{mg}$ : Between 20 – 30 minutes
- Infusion time for phenytoin dose  $> 1500\text{mg}$  and  $\leq 2000\text{mg}$ : Between 30 – 40 minutes

The final concentration of phenytoin in the solution for infusion should be a maximum of 10mg/ml with 0.9% sodium chloride.

**Notes:**

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics are only reported for those patients who were randomised and treated (Period 2), as specified in the Statistical Analysis Plan version 2.0 15/05/2018.

| <b>Number of subjects in period 2</b> | Levetiracetam | Phenytoin |
|---------------------------------------|---------------|-----------|
| Started                               | 152           | 134       |
| Completed                             | 152           | 134       |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Levetiracetam |
|-----------------------|---------------|

Reporting group description:

Patients randomised to Levetiracetam and treated.

|                       |           |
|-----------------------|-----------|
| Reporting group title | Phenytoin |
|-----------------------|-----------|

Reporting group description:

Patients randomised to Phenytoin and treated.

| Reporting group values                                | Levetiracetam | Phenytoin    | Total |
|-------------------------------------------------------|---------------|--------------|-------|
| Number of subjects                                    | 152           | 134          | 286   |
| Age categorical<br>Units: Subjects                    |               |              |       |
| In utero                                              | 0             | 0            | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0             | 0            | 0     |
| Newborns (0-27 days)                                  | 0             | 0            | 0     |
| Infants and toddlers (28 days-23<br>months)           | 65            | 53           | 118   |
| Children (2-11 years)                                 | 81            | 74           | 155   |
| Adolescents (12-17 years)                             | 6             | 7            | 13    |
| Adults (18-64 years)                                  | 0             | 0            | 0     |
| From 65-84 years                                      | 0             | 0            | 0     |
| 85 years and over                                     | 0             | 0            | 0     |
| Age continuous<br>Units: years                        |               |              |       |
| median                                                | 2.73          | 2.72         |       |
| inter-quartile range (Q1-Q3)                          | 1.27 to 5.88  | 1.59 to 5.59 | -     |
| Gender categorical<br>Units: Subjects                 |               |              |       |
| Female                                                | 77            | 62           | 139   |
| Male                                                  | 75            | 72           | 147   |
| Weight<br>Units: Subjects                             |               |              |       |
| 0 to <12kg                                            | 52            | 42           | 94    |
| 12kg to 36kg                                          | 86            | 80           | 166   |
| >36kg                                                 | 14            | 12           | 26    |
| Weight<br>Units: kilogram(s)                          |               |              |       |
| median                                                | 12.10         | 12.00        |       |
| inter-quartile range (Q1-Q3)                          | 10 to 19      | 10 to 18     | -     |

## End points

### End points reporting groups

|                                                                                   |               |
|-----------------------------------------------------------------------------------|---------------|
| Reporting group title                                                             | Levetiracetam |
| Reporting group description:<br>Patients randomised to Levetiracetam.             |               |
| Reporting group title                                                             | Phenytoin     |
| Reporting group description:<br>Patients randomised to Phenytoin.                 |               |
| Reporting group title                                                             | Levetiracetam |
| Reporting group description:<br>Patients randomised to Levetiracetam and treated. |               |
| Reporting group title                                                             | Phenytoin     |
| Reporting group description:<br>Patients randomised to Phenytoin and treated.     |               |

### Primary: Time to seizure cessation

|                                                     |                           |
|-----------------------------------------------------|---------------------------|
| End point title                                     | Time to seizure cessation |
| End point description:                              |                           |
| End point type                                      | Primary                   |
| End point timeframe:<br>24 hours from randomisation |                           |

| End point values                     | Levetiracetam   | Phenytoin       |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 152             | 134             |  |  |
| Units: Seizure cessation             |                 |                 |  |  |
| Number of events (seizure cessation) | 106             | 86              |  |  |
| Number of censored times (RSI)       | 46              | 48              |  |  |

### Statistical analyses

|                                         |                           |
|-----------------------------------------|---------------------------|
| Statistical analysis title              | Time to seizure cessation |
| Comparison groups                       | Levetiracetam v Phenytoin |
| Number of subjects included in analysis | 286                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| P-value                                 | = 0.1992                  |
| Method                                  | Logrank                   |

|                                                                                                                          |                                           |
|--------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Statistical analysis title</b>                                                                                        | Time to seizure cessation adjusted Cox-PH |
| Statistical analysis description:<br>Time to seizure cessation adjusted Cox-PH: Allocation (Levetiracetam vs. Phenytoin) |                                           |
| Comparison groups                                                                                                        | Levetiracetam v Phenytoin                 |
| Number of subjects included in analysis                                                                                  | 286                                       |
| Analysis specification                                                                                                   | Pre-specified                             |
| Analysis type                                                                                                            | superiority                               |
| P-value                                                                                                                  | = 0.299 <sup>[1]</sup>                    |
| Method                                                                                                                   | Regression, Cox                           |
| Parameter estimate                                                                                                       | Hazard ratio (HR)                         |
| Point estimate                                                                                                           | 1.17                                      |
| Confidence interval                                                                                                      |                                           |
| level                                                                                                                    | 95 %                                      |
| sides                                                                                                                    | 2-sided                                   |
| lower limit                                                                                                              | 0.87                                      |
| upper limit                                                                                                              | 1.57                                      |

Notes:

[1] - This analysis was adjusted for weight, gender, whether it is a patients' first seizure, site of initial access, and whether any additional anticonvulsants were administered alongside the infusion. Site was included in the model as a random effect.

## Secondary: Need for further anticonvulsant(s) to manage the seizure after the initial agent

|                                                     |                                                                                  |
|-----------------------------------------------------|----------------------------------------------------------------------------------|
| End point title                                     | Need for further anticonvulsant(s) to manage the seizure after the initial agent |
| End point description:                              |                                                                                  |
| End point type                                      | Secondary                                                                        |
| End point timeframe:<br>24 hours from randomisation |                                                                                  |

| End point values                          | Levetiracetam   | Phenytoin       |  |  |
|-------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                        | Reporting group | Reporting group |  |  |
| Number of subjects analysed               | 152             | 134             |  |  |
| Units: Need for further anticonvulsant(s) |                 |                 |  |  |
| Yes                                       | 57              | 50              |  |  |
| No                                        | 95              | 84              |  |  |

## Statistical analyses

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | Chi-squared results       |
| Comparison groups                 | Levetiracetam v Phenytoin |

|                                         |                 |
|-----------------------------------------|-----------------|
| Number of subjects included in analysis | 286             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority     |
| P-value                                 | = 0.974         |
| Method                                  | Chi-squared     |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 1.01            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.74            |
| upper limit                             | 1.36            |

|                                         |                           |
|-----------------------------------------|---------------------------|
| <b>Statistical analysis title</b>       | Logistic regression       |
| Comparison groups                       | Levetiracetam v Phenytoin |
| Number of subjects included in analysis | 286                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| P-value                                 | = 0.75 <sup>[2]</sup>     |
| Method                                  | Regression, Logistic      |
| Parameter estimate                      | Odds ratio (OR)           |
| Point estimate                          | 1.09                      |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 0.65                      |
| upper limit                             | 1.83                      |

Notes:

[2] - This analysis was adjusted for weight, gender, whether it is a patients' first seizure, site of initial access, and whether any additional anticonvulsants were administered alongside the infusion. Site was included in the model as a random effect.

### **Secondary: Need for rapid sequence induction (RSI) with thiopentone or another agent (e.g. propofol) due to ongoing CSE**

|                             |                                                                                                              |
|-----------------------------|--------------------------------------------------------------------------------------------------------------|
| End point title             | Need for rapid sequence induction (RSI) with thiopentone or another agent (e.g. propofol) due to ongoing CSE |
| End point description:      |                                                                                                              |
|                             |                                                                                                              |
| End point type              | Secondary                                                                                                    |
| End point timeframe:        |                                                                                                              |
| 24 hours from randomisation |                                                                                                              |

| <b>End point values</b>                        | Levetiracetam   | Phenytoin       |  |  |
|------------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                             | Reporting group | Reporting group |  |  |
| Number of subjects analysed                    | 152             | 134             |  |  |
| Units: Need for rapid sequence induction (RSI) |                 |                 |  |  |
| Yes                                            | 44              | 47              |  |  |
| No                                             | 108             | 87              |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | Chi-squared results       |
|-----------------------------------------|---------------------------|
| Comparison groups                       | Levetiracetam v Phenytoin |
| Number of subjects included in analysis | 286                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| P-value                                 | = 0.267                   |
| Method                                  | Chi-squared               |
| Parameter estimate                      | Risk ratio (RR)           |
| Point estimate                          | 0.83                      |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 0.59                      |
| upper limit                             | 1.16                      |

| <b>Statistical analysis title</b>       | Logistic regression results |
|-----------------------------------------|-----------------------------|
| Comparison groups                       | Levetiracetam v Phenytoin   |
| Number of subjects included in analysis | 286                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.367                     |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 0.79                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.47                        |
| upper limit                             | 1.32                        |

## Secondary: Need to be admitted to critical care

|                        |                                      |
|------------------------|--------------------------------------|
| End point title        | Need to be admitted to critical care |
| End point description: |                                      |

|                             |           |
|-----------------------------|-----------|
| End point type              | Secondary |
| End point timeframe:        |           |
| 24 hours from randomisation |           |

| End point values                            | Levetiracetam   | Phenytoin       |  |  |
|---------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                          | Reporting group | Reporting group |  |  |
| Number of subjects analysed                 | 152             | 134             |  |  |
| Units: Need to be admitted to critical care |                 |                 |  |  |
| Yes                                         | 97              | 72              |  |  |
| No                                          | 55              | 62              |  |  |

### Statistical analyses

| Statistical analysis title              | Chi-squared results       |
|-----------------------------------------|---------------------------|
| Comparison groups                       | Levetiracetam v Phenytoin |
| Number of subjects included in analysis | 286                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| P-value                                 | = 0.084                   |
| Method                                  | Chi-squared               |
| Parameter estimate                      | Risk ratio (RR)           |
| Point estimate                          | 1.19                      |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 0.97                      |
| upper limit                             | 1.45                      |

| Statistical analysis title              | Logistic regression results |
|-----------------------------------------|-----------------------------|
| Comparison groups                       | Levetiracetam v Phenytoin   |
| Number of subjects included in analysis | 286                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.101 <sup>[3]</sup>      |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 1.52                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.92                        |
| upper limit                             | 2.5                         |

Notes:

[3] - This analysis was adjusted for weight, gender, whether it is a patients' first seizure, site of initial access, and whether any additional anticonvulsants were administered alongside the infusion. Site was included in the model as a random effect.

### Other pre-specified: Sensitivity analysis 1

|                                         |                        |
|-----------------------------------------|------------------------|
| End point title                         | Sensitivity analysis 1 |
| End point description:                  |                        |
| Time to seizure cessation from infusion |                        |
| End point type                          | Other pre-specified    |
| End point timeframe:                    |                        |
| 24 hours from randomisation             |                        |

| End point values                     | Levetiracetam   | Phenytoin       |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 152             | 134             |  |  |
| Units: Seizure cessation             |                 |                 |  |  |
| Number of events (seizure cessation) | 106             | 86              |  |  |
| Number of censored times (RSI)       | 46              | 48              |  |  |

### Statistical analyses

|                                         |                           |
|-----------------------------------------|---------------------------|
| Statistical analysis title              | Sensitivity analysis 1    |
| Comparison groups                       | Phenytoin v Levetiracetam |
| Number of subjects included in analysis | 286                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| P-value                                 | = 0.3195                  |
| Method                                  | Logrank                   |

|                                         |                                         |
|-----------------------------------------|-----------------------------------------|
| Statistical analysis title              | Sensitivity analysis 1: adjusted Cox-PH |
| Comparison groups                       | Levetiracetam v Phenytoin               |
| Number of subjects included in analysis | 286                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.512 <sup>[4]</sup>                  |
| Method                                  | Regression, Cox                         |
| Parameter estimate                      | Hazard ratio (HR)                       |
| Point estimate                          | 1.1                                     |
| Confidence interval                     |                                         |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 0.82                                    |
| upper limit                             | 1.48                                    |

Notes:

[4] - This analysis was adjusted for weight, gender, whether it is a patients' first seizure, site of initial access, and whether any additional anticonvulsants were administered alongside the infusion.

## Other pre-specified: Sensitivity analysis 2

|                 |                        |
|-----------------|------------------------|
| End point title | Sensitivity analysis 2 |
|-----------------|------------------------|

End point description:

Time to seizure cessation including non-treated patients

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

24 hours from randomisation

| End point values                     | Levetiracetam   | Phenytoin       |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 203             | 176             |  |  |
| Units: Seizure cessation             |                 |                 |  |  |
| Number of events (seizure cessation) | 106             | 86              |  |  |
| Number of censored times (RSI)       | 97              | 90              |  |  |

## Statistical analyses

|                                         |                           |
|-----------------------------------------|---------------------------|
| Statistical analysis title              | Sensitivity analysis 2    |
| Comparison groups                       | Levetiracetam v Phenytoin |
| Number of subjects included in analysis | 379                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| P-value                                 | = 0.1992                  |
| Method                                  | Logrank                   |

|                                         |                                         |
|-----------------------------------------|-----------------------------------------|
| Statistical analysis title              | Sensitivity analysis 2: adjusted Cox-PH |
| Comparison groups                       | Levetiracetam v Phenytoin               |
| Number of subjects included in analysis | 379                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.299 <sup>[5]</sup>                  |
| Method                                  | Regression, Cox                         |
| Parameter estimate                      | Hazard ratio (HR)                       |
| Point estimate                          | 1.17                                    |
| Confidence interval                     |                                         |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 0.87                                    |
| upper limit                             | 1.57                                    |

Notes:

[5] - This analysis was adjusted for weight, gender, whether it is a patients' first seizure, site of initial access, and whether any additional anticonvulsants were administered alongside the infusion. Site was included in the model as a random effect.

### Other pre-specified: Sensitivity analysis 3

|                                                                          |                        |
|--------------------------------------------------------------------------|------------------------|
| End point title                                                          | Sensitivity analysis 3 |
| End point description:                                                   |                        |
| Time to seizure cessation censoring at time of 2nd second-line treatment |                        |
| End point type                                                           | Other pre-specified    |
| End point timeframe:                                                     |                        |
| 24 hours from randomisation                                              |                        |

| End point values                           | Levetiracetam   | Phenytoin       |  |  |
|--------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                         | Reporting group | Reporting group |  |  |
| Number of subjects analysed                | 152             | 134             |  |  |
| Units: Seizure cessation                   |                 |                 |  |  |
| Number of events (seizure cessation)       | 98              | 85              |  |  |
| Number of censored times (RSI)             | 41              | 45              |  |  |
| Number of censored times (2nd second-line) | 13              | 4               |  |  |

### Statistical analyses

|                                         |                           |
|-----------------------------------------|---------------------------|
| Statistical analysis title              | Sensitivity analysis 3    |
| Comparison groups                       | Levetiracetam v Phenytoin |
| Number of subjects included in analysis | 286                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| P-value                                 | = 0.3349                  |
| Method                                  | Logrank                   |

|                                         |                                         |
|-----------------------------------------|-----------------------------------------|
| Statistical analysis title              | Sensitivity analysis 3: adjusted Cox-PH |
| Comparison groups                       | Levetiracetam v Phenytoin               |
| Number of subjects included in analysis | 286                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.415 <sup>[6]</sup>                  |
| Method                                  | Regression, Cox                         |
| Parameter estimate                      | Hazard ratio (HR)                       |
| Point estimate                          | 1.13                                    |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.84    |
| upper limit         | 1.53    |

Notes:

[6] - This analysis was adjusted for weight, gender, whether it is a patients' first seizure, site of initial access, and whether any additional anticonvulsants were administered alongside the infusion.

#### Other pre-specified: Sensitivity analysis 4

|                                                                                                 |                        |
|-------------------------------------------------------------------------------------------------|------------------------|
| End point title                                                                                 | Sensitivity analysis 4 |
| End point description:                                                                          |                        |
| Time to seizure cessation using Gray's test for competing risks where the competing risk is RSI |                        |
| End point type                                                                                  | Other pre-specified    |
| End point timeframe:                                                                            |                        |
| 24 hours from randomisation                                                                     |                        |

| End point values                     | Levetiracetam   | Phenytoin       |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 152             | 134             |  |  |
| Units: Seizure cessation             |                 |                 |  |  |
| Number of events (seizure cessation) | 106             | 86              |  |  |
| Number of competing events (RSI)     | 46              | 48              |  |  |

#### Statistical analyses

|                                         |                           |
|-----------------------------------------|---------------------------|
| <b>Statistical analysis title</b>       | Sensitivity analysis 4    |
| Comparison groups                       | Levetiracetam v Phenytoin |
| Number of subjects included in analysis | 286                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| P-value                                 | = 0.1735                  |
| Method                                  | Fine and Gray             |

|                                         |                                                |
|-----------------------------------------|------------------------------------------------|
| <b>Statistical analysis title</b>       | Sensitivity analysis 4: adjusted Fine and Gray |
| Comparison groups                       | Levetiracetam v Phenytoin                      |
| Number of subjects included in analysis | 286                                            |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | = 0.299 <sup>[7]</sup>                         |
| Method                                  | Fine and Gray model                            |
| Parameter estimate                      | Hazard ratio (HR)                              |
| Point estimate                          | 1.17                                           |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.87    |
| upper limit         | 1.57    |

Notes:

[7] - This analysis was adjusted for weight, gender, whether it is a patients' first seizure, site of initial access, and whether any additional anticonvulsants were administered alongside the infusion.

### Other pre-specified: Sensitivity analysis 5

|                                                                 |                        |
|-----------------------------------------------------------------|------------------------|
| End point title                                                 | Sensitivity analysis 5 |
| End point description:                                          |                        |
| Time to seizure cessation excluding patients with imputed times |                        |
| End point type                                                  | Other pre-specified    |
| End point timeframe:                                            |                        |
| 24 hours from randomisation                                     |                        |

| End point values                     | Levetiracetam   | Phenytoin       |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 150             | 132             |  |  |
| Units: Seizure cessation             |                 |                 |  |  |
| Number of events (seizure cessation) | 105             | 84              |  |  |
| Number of censored times (RSI)       | 45              | 48              |  |  |

### Statistical analyses

|                                         |                           |
|-----------------------------------------|---------------------------|
| <b>Statistical analysis title</b>       | Sensitivity analysis 5    |
| Comparison groups                       | Levetiracetam v Phenytoin |
| Number of subjects included in analysis | 282                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| P-value                                 | = 0.1534                  |
| Method                                  | Logrank                   |

|                                         |                                         |
|-----------------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b>       | Sensitivity analysis 5: adjusted Cox-PH |
| Comparison groups                       | Levetiracetam v Phenytoin               |
| Number of subjects included in analysis | 282                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.258 <sup>[8]</sup>                  |
| Method                                  | Regression, Cox                         |
| Parameter estimate                      | Hazard ratio (HR)                       |
| Point estimate                          | 1.19                                    |

| Confidence interval |         |
|---------------------|---------|
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.88    |
| upper limit         | 1.59    |

Notes:

[8] - This analysis was adjusted for weight, gender, whether it is a patients' first seizure, site of initial access, and whether any additional anticonvulsants were administered alongside the infusion. Site was included in the model as a random effect.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring from randomisation until 24 hours after the second-line treatment infusion has started.

Adverse event reporting additional description:

If death or organ failure is noted at the 14 day safety follow up this should be recorded on the '14 day follow up' CRF, however, no additional reporting is required unless the local investigator feels that the event(s) are related to the study medication.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 18 |
|--------------------|----|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Levetiracetam |
|-----------------------|---------------|

Reporting group description:

Patients receiving Levetiracetam.

|                       |           |
|-----------------------|-----------|
| Reporting group title | Phenytoin |
|-----------------------|-----------|

Reporting group description:

Patients receiving Phenytoin

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Levetiracetam and Phenytoin |
|-----------------------|-----------------------------|

Reporting group description:

Patients receiving Levetiracetam and Phenytoin.

| Serious adverse events                            | Levetiracetam   | Phenytoin       | Levetiracetam and Phenytoin |
|---------------------------------------------------|-----------------|-----------------|-----------------------------|
| Total subjects affected by serious adverse events |                 |                 |                             |
| subjects affected / exposed                       | 1 / 132 (0.76%) | 2 / 130 (1.54%) | 1 / 24 (4.17%)              |
| number of deaths (all causes)                     | 0               | 0               | 2                           |
| number of deaths resulting from adverse events    | 0               | 0               | 1                           |
| Vascular disorders                                |                 |                 |                             |
| Hypotension                                       |                 |                 |                             |
| subjects affected / exposed                       | 0 / 132 (0.00%) | 1 / 130 (0.77%) | 0 / 24 (0.00%)              |
| occurrences causally related to treatment / all   | 0 / 0           | 1 / 1           | 0 / 0                       |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 0                       |
| Cardiac disorders                                 |                 |                 |                             |
| Cardiac arrest                                    |                 |                 |                             |
| subjects affected / exposed                       | 1 / 132 (0.76%) | 0 / 130 (0.00%) | 0 / 24 (0.00%)              |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           | 0 / 0                       |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 0                       |
| Nervous system disorders                          |                 |                 |                             |

|                                                      |                 |                 |                |
|------------------------------------------------------|-----------------|-----------------|----------------|
| Seizure                                              |                 |                 |                |
| subjects affected / exposed                          | 0 / 132 (0.00%) | 1 / 130 (0.77%) | 0 / 24 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Intracranial pressure increased                      |                 |                 |                |
| subjects affected / exposed                          | 0 / 132 (0.00%) | 0 / 130 (0.00%) | 1 / 24 (4.17%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 1          |
| General disorders and administration site conditions |                 |                 |                |
| Device malfunction                                   |                 |                 |                |
| subjects affected / exposed                          | 0 / 132 (0.00%) | 1 / 130 (0.77%) | 0 / 24 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | Levetiracetam     | Phenytoin         | Levetiracetam and Phenytoin |
|-------------------------------------------------------|-------------------|-------------------|-----------------------------|
| Total subjects affected by non-serious adverse events |                   |                   |                             |
| subjects affected / exposed                           | 16 / 132 (12.12%) | 18 / 130 (13.85%) | 4 / 24 (16.67%)             |
| Injury, poisoning and procedural complications        |                   |                   |                             |
| Mechanical ventilation complication                   |                   |                   |                             |
| subjects affected / exposed                           | 0 / 132 (0.00%)   | 1 / 130 (0.77%)   | 0 / 24 (0.00%)              |
| occurrences (all)                                     | 0                 | 1                 | 0                           |
| Vascular disorders                                    |                   |                   |                             |
| Hypotension                                           |                   |                   |                             |
| subjects affected / exposed                           | 2 / 132 (1.52%)   | 3 / 130 (2.31%)   | 1 / 24 (4.17%)              |
| occurrences (all)                                     | 2                 | 3                 | 1                           |
| Hypertension                                          |                   |                   |                             |
| subjects affected / exposed                           | 0 / 132 (0.00%)   | 2 / 130 (1.54%)   | 0 / 24 (0.00%)              |
| occurrences (all)                                     | 0                 | 2                 | 0                           |
| Pallor                                                |                   |                   |                             |
| subjects affected / exposed                           | 0 / 132 (0.00%)   | 1 / 130 (0.77%)   | 0 / 24 (0.00%)              |
| occurrences (all)                                     | 0                 | 1                 | 0                           |
| Cardiac disorders                                     |                   |                   |                             |

|                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                          |                                                                                                          |                                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                   | 1 / 132 (0.76%)<br>1                                                                                     | 3 / 130 (2.31%)<br>3                                                                                     | 1 / 24 (4.17%)<br>1                                                                                  |
| Nervous system disorders<br>Depressed level of consciousness<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                  | 0 / 132 (0.00%)<br>0                                                                                     | 1 / 130 (0.77%)<br>1                                                                                     | 0 / 24 (0.00%)<br>0                                                                                  |
| General disorders and administration site conditions<br>Extravasation<br>subjects affected / exposed<br>occurrences (all)<br><br>Catheter site related reaction<br>subjects affected / exposed<br>occurrences (all)<br><br>Adverse reaction<br>subjects affected / exposed<br>occurrences (all)<br><br>Infusion site erythema<br>subjects affected / exposed<br>occurrences (all) | 0 / 132 (0.00%)<br>0<br><br>1 / 132 (0.76%)<br>1<br><br>0 / 132 (0.00%)<br>0<br><br>0 / 132 (0.00%)<br>0 | 4 / 130 (3.08%)<br>4<br><br>1 / 130 (0.77%)<br>1<br><br>0 / 130 (0.00%)<br>0<br><br>1 / 130 (0.77%)<br>1 | 1 / 24 (4.17%)<br>1<br><br>2 / 24 (8.33%)<br>3<br><br>1 / 24 (4.17%)<br>1<br><br>0 / 24 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                        | 0 / 132 (0.00%)<br>0                                                                                     | 1 / 130 (0.77%)<br>1                                                                                     | 0 / 24 (0.00%)<br>0                                                                                  |
| Respiratory, thoracic and mediastinal disorders<br>Stridor<br>subjects affected / exposed<br>occurrences (all)<br><br>Wheezing<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                | 0 / 132 (0.00%)<br>0<br><br>1 / 132 (0.76%)<br>1                                                         | 0 / 130 (0.00%)<br>0<br><br>0 / 130 (0.00%)<br>0                                                         | 1 / 24 (4.17%)<br>1<br><br>0 / 24 (0.00%)<br>0                                                       |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                | 2 / 132 (1.52%)<br>2                                                                                     | 1 / 130 (0.77%)<br>1                                                                                     | 0 / 24 (0.00%)<br>0                                                                                  |
| Psychiatric disorders                                                                                                                                                                                                                                                                                                                                                             |                                                                                                          |                                                                                                          |                                                                                                      |

|                             |                  |                 |                |
|-----------------------------|------------------|-----------------|----------------|
| Agitation                   |                  |                 |                |
| subjects affected / exposed | 11 / 132 (8.33%) | 4 / 130 (3.08%) | 0 / 24 (0.00%) |
| occurrences (all)           | 11               | 4               | 0              |
| Confusional state           |                  |                 |                |
| subjects affected / exposed | 1 / 132 (0.76%)  | 0 / 130 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all)           | 1                | 0               | 0              |
| Hallucination               |                  |                 |                |
| subjects affected / exposed | 1 / 132 (0.76%)  | 0 / 130 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all)           | 1                | 0               | 0              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 23 April 2015  | Protocol was updated to ensure key processes are clear within the protocol, such as screening, randomisation and consent. Patient follow up was also increased to 14 days following request of the EcLiPSE TSC. Minor typographical errors and clarifications were also made throughout to ensure consistency. Please refer to section 19.2 of the protocol to see the summary of changes.                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 17 June 2015   | Protocol updated to clarify that the concentrations are a maximum of 10mg/mL and 50mg/mL for phenytoin and levetiracetam, respectively.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 27 August 2015 | Protocol was updated to increase the maximum dose of phenytoin to 2000mg and consequentially, the infusion times for phenytoin have also been increased. The increase in the maximum dose for phenytoin aligns with the maximum dose in the adult BNF and standard practise at some sites. The following updates were also made to the consent study:<br>1) Online questionnaire now available for completion.<br>2) Clarify that both parents can complete the questionnaire.<br>3) Allow the consent study team to follow up on missing consent study questionnaires if they are contacting families for consent study follow up, providing consent has been obtained for this.<br>4) Face-to-face interviews to occur when families live in (or close to) the Merseyside area, if this is preferred by the families. |
| 05 April 2017  | <p>The protocol was updated to clarify the randomisation and consent process. This namely included additional information relating to timescales of obtaining consent and the follow up of non-treated participants. The distribution of a questionnaire to non-treated participants was added. Following this update, it was determined that participants classed as "non treated" would not be included in the trial recruitment figure.</p> <p>The protocol update provided clarification on the route of trial treatment administration and confirmation of the Levetiracetam and Phenytoin SmPC. The process for any serious breaches, protocol deviations and urgent safety measures was also added.</p>                                                                                                          |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported