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
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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:

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)	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 cloned 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
Arm title	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

Arm title	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 ≤1000mg: 20 minutes
- Infusion time for phenytoin dose >1000mg and ≤1500mg: Between 20 – 30 minutes
- Infusion time for phenytoin dose >1500mg and ≤2000mg: 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[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	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

Arm title	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 ≤1000mg: 20 minutes
- Infusion time for phenytoin dose >1000mg and ≤1500mg: Between 20 – 30 minutes
- Infusion time for phenytoin dose >1500mg and ≤2000mg: 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.

Number of subjects in period 2	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 Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 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 Units: years			
median	2.73	2.72	
inter-quartile range (Q1-Q3)	1.27 to 5.88	1.59 to 5.59	-
Gender categorical Units: Subjects			
Female	77	62	139
Male	75	72	147
Weight Units: Subjects			
0 to <12kg	52	42	94
12kg to 36kg	86	80	166
>36kg	14	12	26
Weight 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: Patients randomised to Levetiracetam.	
Reporting group title	Phenytoin
Reporting group description: Patients randomised to Phenytoin.	
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.	

Primary: Time to seizure cessation

End point title	Time to seizure cessation
End point description:	
End point type	Primary
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	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

Statistical analysis title	Time to seizure cessation adjusted Cox-PH

Statistical analysis description:

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 [1]
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:

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

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	= 0.974
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

Statistical analysis title	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 [2]
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

End point values	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

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	= 0.267
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

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	= 0.367
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 [3]
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 [4]
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 [5]
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 [6]
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

Statistical analysis title	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

Statistical analysis title	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 [7]
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

Statistical analysis title	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

Statistical analysis title	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 [8]
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 %

Non-serious adverse events	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			
subjects affected / exposed	1 / 132 (0.76%)	3 / 130 (2.31%)	1 / 24 (4.17%)
occurrences (all)	1	3	1
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Extravasation			
subjects affected / exposed	0 / 132 (0.00%)	4 / 130 (3.08%)	1 / 24 (4.17%)
occurrences (all)	0	4	1
Catheter site related reaction			
subjects affected / exposed	1 / 132 (0.76%)	1 / 130 (0.77%)	2 / 24 (8.33%)
occurrences (all)	1	1	3
Adverse reaction			
subjects affected / exposed	0 / 132 (0.00%)	0 / 130 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Infusion site erythema			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 132 (0.00%)	1 / 130 (0.77%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Stridor			
subjects affected / exposed	0 / 132 (0.00%)	0 / 130 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	1 / 132 (0.76%)	0 / 130 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 132 (1.52%)	1 / 130 (0.77%)	0 / 24 (0.00%)
occurrences (all)	2	1	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: 1) Online questionnaire now available for completion. 2) Clarify that both parents can complete the questionnaire. 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. 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	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. 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported