Emergency treatment with Levetiracetam or Phenytoin in convulsive status epilepticus in children – the EcLiPSE trial: a multi-centre, randomised, open label, superiority trial

AUTHORS
Mark D Lyttle MBChB1,2
mdlyttle77@gmail.com

Naomi EA Rainford MSc3
naomi.rainford@liverpool.ac.uk

Carrol Gamble PhD3,4 (Professor)
c.gamble@liverpool.ac.uk

Shrouk Messahel, MBChB5
shrouk.messahel@alderhey.nhs.uk

Amy Humphreys BSc3
amy.humphreys@liverpool.ac.uk

Helen Hickey PGDip3
h.hickey@liverpool.ac.uk

Kerry Woolfall PhD6
k.woolfall@liverpool.ac.uk

Louise Roper CPsychol6
louise.roper@liverpool.ac.uk

Joanne Noblet BSc (Hons)5
Joanne.noblet@alderhey.nhs.uk

Elizabeth D Lee5 BSc
Liz.lee@alderhey.nhs.uk

Sarah Potter BSc (Hons)1
Sarah.potter@uhbristol.nhs.uk

Paul Tate3
Paul.tate@liverpool.ac.uk

Anand Iyer, MD7
anand.iyer@alderhey.nhs.uk

Vicki Evans BA (Hons)
Vickievans2512@outlook.com

Richard E Appleton MA (Oxon), FRCPCH7 (Hon Professor)
richardappleton55@hotmail.co.uk

In conjunction with Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI)
Affiliations

1Bristol Royal Hospital for Children
Address: Emergency Department, Bristol Royal Hospital for Children, Upper Maudlin Street, Bristol, BS2 8BJ, United Kingdom

2University of the West of England
Address: Faculty of Health and Applied Sciences, University of the West of England, Blackberry Hill, Bristol, BS16 1XS, United Kingdom

3University of Liverpool, a member of Liverpool Health Partners.
Address: Clinical Trials Research Centre, University of Liverpool, Institute of Child Health, Alder Hey Children’s NHS Foundation Trust, Liverpool, United Kingdom

4University of Liverpool, a member of Liverpool Health Partners.
Address: Department of Biostatistics, Waterhouse Building, University of Liverpool, 1-5 Brownlow Street, Liverpool, L69 3GL, United Kingdom

5Emergency Department
Alder Hey Children’s Hospital, a member of Liverpool Health Partners.
Address: Alder Hey Children’s NHS Foundation Trust, Liverpool, Merseyside, L12 2AP, United Kingdom

6University of Liverpool, a member of Liverpool Health Partners.
Address: Institute of Population Health Sciences, Waterhouse Building, University of Liverpool, Liverpool, L69 3BX, United Kingdom

7Department of Neurology
Alder Hey Children’s Hospital, a member of Liverpool Health Partners.
Address: Alder Hey Children’s NHS Foundation Trust, Liverpool, Merseyside, L12 2AP, United Kingdom

Corresponding author
Professor Richard Appleton
The Roald Dahl EEG Unit
Department of Neurology
Alder Hey Children’s Health Park
Liverpool
L12 2AP
E-mail: richardappleton55@hotmail.co.uk
Telephone: 07976 010754
SUMMARY

Background
Phenytoin is the recommended second-line intravenous anticonvulsant to treat paediatric convulsive status epilepticus (CSE) in the UK. Some evidence suggests levetiracetam may be an effective and safer alternative. This trial compared the effectiveness and safety of these treatments in paediatric CSE.

Methods
This superiority, pragmatic, open-label randomised controlled trial was undertaken in 30 UK Emergency Departments with clinicians following national treatment algorithms. Consent was sought retrospectively (‘Research Without Prior Consent’) as CSE is a medical emergency. Participants were males and females, aged 6 months to <18 years, with CSE requiring second-line treatment, and were randomised (1:1) to receive levetiracetam (40 mg/kg over 5 minutes) or phenytoin (20 mg/kg over at least 20 minutes), stratified by centre. Primary outcome was time from randomisation to CSE-cessation. Statistical analysis adhered to a pre-specified strategy adopting the intention-to-treat principle. Trial Registration number: ISRCTN22567894.

Findings
Between 17th July 2015 and 7th April 2018, 286 participants were randomised and treated; 152 were allocated levetiracetam, and 134 phenytoin. CSE was terminated in 106 (70%) allocated levetiracetam, and 86 (64%) allocated phenytoin. Median time from randomisation to CSE-cessation was 35 minutes (IQR 20-NA) in the levetiracetam and 45 minutes (IQ 24-NA) in the phenytoin group (Hazard Ratio 1.17; 95% CI 0.87-1.57, p = 0.3). Results were robust to pre-specified sensitivity analyses including time from treatment commencement to CSE-cessation, and competing risks. One phenytoin-treated participant experienced serious adverse reactions.

Interpretation
Levetiracetam was not statistically superior to phenytoin in CSE-cessation rate, time taken to terminate CSE, or serious adverse reactions. However, the results, together with previously reported safety profiles and comparative ease of administration of levetiracetam, suggest it would be an appropriate alternative to phenytoin as the first-choice, second-line anticonvulsant in the treatment of paediatric CSE.

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INTRODUCTION

Convulsive status epilepticus (CSE) is the most common neurological emergency of childhood.\(^1\) It has an annual incidence of 20 per 100,000 children, and is the second most common reason for unplanned admissions to Paediatric Intensive Care Units (PICU) in the UK.\(^2\) Mortality is low, but morbidity including neuro-disability, learning difficulties, and de novo and drug-resistant epilepsy, may be as high as 22%.\(^3\)-\(^6\) The longer the duration of CSE, the more difficult it is to terminate, and the greater the morbidity risk.\(^1\),\(^5\)-\(^6\)

CSE is treated using an algorithm recommended by Advanced Paediatric Life Support (APLS), which incorporates 10 minute intervals between treatments.\(^7\) Second-line treatment is given when CSE persists, either after two doses of benzodiazepine, or the child’s personalised emergency (rescue) treatment. Failure of second-line treatment is followed by anaesthesia via rapid sequence induction (RSI).\(^7\) Randomised controlled trial (RCT) evidence supports the use of benzodiazepines as first-line treatment.\(^8\) There is no high quality RCT evidence to support any second-line treatment.\(^9\)

The currently recommended second-line treatment of CSE in the UK and Europe is intravenous phenytoin (fosphenytoin in the USA) based on predominantly non-RCT data; reported cessation rates vary widely between 50% and 96%.\(^10\)-\(^11\) Safety concerns are widely reported, particularly cardiovascular disturbance (hypotension and fatal arrhythmias) and Stevens Johnson syndrome.\(^12\)-\(^14\) Levetiracetam has been reported to be effective and well-tolerated in the management of serial seizures and CSE, also based on largely non-RCT data with reported CSE-cessation rates of between 44 and 94%.\(^9\),\(^11\),\(^15\)-\(^17\) Adverse reactions appear less frequent and less severe than with phenytoin.\(^18\) Levetiracetam is administered more rapidly (five to 10 minutes) than phenytoin (a minimum of 20 minutes), suggesting a more rapid termination of CSE may be possible. However findings of existing studies of second-line treatments cannot be generalised due to methodological issues, including small sample sizes and heterogeneity of primary outcomes. The management of CSE was therefore identified as one of five priority areas for research by the National Institute for Health and Care Excellence.

The Emergency treatment with Levetiracetam or Phenytoin in convulsive Status Epilepticus in children (EcLiPSE) trial aimed to determine whether intravenous levetiracetam or intravenous phenytoin is the more effective and safer second-line anticonvulsant for the emergency management of childhood CSE.
METHODS

Trial design
An open-label parallel-randomised controlled trial was undertaken in 30 UK Emergency Departments (ED), all members of Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI). These included secondary care (district general hospitals) and tertiary centres. The trial protocol was published in 2017 and is also available from the funders in full (https://www.journalslibrary.nihr.ac.uk/programmes/hta/12127134/#/).

Participants
Children of both sexes, aged 6 months to <18 years, presenting with CSE (generalised tonic-clonic, generalised clonic, or focal clonic) that required second-line treatment were eligible for inclusion. Patients were ineligible if they (i) presented with absence, myoclonic, or non-convulsive status epilepticus, or infantile spasms, (ii) were known or suspected to be pregnant, (iii) had a contraindication or allergy to levetiracetam or phenytoin, (iv) had established renal failure, (v) had received a second-line anticonvulsant during the presenting episode of CSE prior to screening, or (vi) were known to have been previously enrolled in EcLiPSE.

The trial used Research Without Prior Consent (RWPC; ‘deferred consent’) due to the time-critical management of CSE, in accordance with regulatory requirements, RWPC guidance and pre-trial research. Parents/legal representatives/patients (hereafter participants) were approached once the child’s clinical condition was stable (ideally within 24 hours of randomisation, and prior to discharge from hospital), at which point written informed consent was sought to continue data collection and use data already collected. When consent was not sought prior to discharge, participants were contacted within five working days of randomisation by a member of the research team, and informed of the participant’s involvement and trial details. Participants were sent written information, a consent form, and a covering letter stating they had four weeks from the date of the letter to confirm or decline participation. We employed an ‘opt-out’ postal approach; the covering letter explained that the participant would be included in the trial if no response was received.

Ethical approval was gained from the National Research Ethics Service (NRES), Liverpool Central, on the 3rd March 2016 (reference: 15/NW/0090); all participating centres were granted NHS permission prior to commencing recruitment.

Randomisation and masking
Participants were randomised to receive levetiracetam or phenytoin in a ratio of 1:1 using random variable block sizes of two and four. A computer generated randomisation schedule was produced.
by an independent statistician, stratified by centre. Sites were provided with randomisation packs, which were sequentially numbered, heavy duty, opaque, A4 cardboard envelopes with tamper-proof closure strips to be opened in ascending order. Each envelope contained the random treatment allocation and relevant case report form (CRF). Periodic checks ensured sites had the correct number of envelopes, that they were intact, and that the sequential numbering system was maintained.

Treating clinicians opened randomisation envelopes after confirmation of eligibility. This was undertaken following administration of the final first-line treatment to allow sufficient time to prepare and administer the allocated treatment in accordance with the APLS algorithm. Where CSE stopped prior to the administration of the randomised treatment, participants were excluded, but subsequently included if their seizure restarted and required a second-line treatment whilst in the ED. Team members were aware of the allocated drug, and the treating emergency clinician determined time of CSE cessation based on clinical examination.

**Procedures**

CSE management followed the APLS algorithm, and both study treatments were given intravenously. Levetiracetam was administered over five minutes in a dose of 40mg/kg (maximum dose 2·5 grams); phenytoin was administered over a minimum of 20 minutes in a dose of 20mg/kg (maximum dose 2 grams and with a maximum infusion rate of 1mg/kg/min). Clinicians treated subsequent ongoing CSE according to the APLS algorithm.

Data were recorded on a paper-based CRF by emergency clinicians during the CSE, including times of randomisation, commencement and completion of infusions, and cessation of CSE. These key data relating to the primary outcome were collated and highlighted on the first page of the CRF to ensure data accuracy. Additional information included participant demographics, CSE type, site of trial treatment administration, need for additional anticonvulsants, RSI, and adverse events (AE).

Following consent, information was collected on pre-existing epilepsy diagnosis, oral maintenance anti-epileptic drugs, neurological co-morbidities, concomitant medications, aetiology of CSE, patient location on admission and at 24 hours, and further seizure activity within 24 hours. Final follow-up was undertaken 14 days following enrolment by chart review (recording discharge, readmission, death, and organ failure), and a brief participant postal questionnaire (exploring current participant health, new medical problems, and new antiepileptic medications).

**Outcomes**
The primary outcome was time from randomisation to cessation of all visible signs of convulsive activity, defined as cessation of all continuous rhythmic clonic activity, as adjudged by the treating clinician. Electroencephalography (EEG) was not used.

Secondary outcomes were (i) need for further anticonvulsants to manage the CSE following administration of the trial treatment, (ii) need for RSI due to ongoing CSE, (iii) need for admission to critical care, defined as either a high-dependency unit (HDU) or a PICU, and (iv) serious adverse reactions including death, airway complications, cardiovascular instability, extravasation injury, and extreme agitation.

**Statistical analysis**

The sample size was calculated based on existing reported seizure cessation rates for phenytoin and levetiracetam.\(^{10,18}\) 140 randomised and consented participants per group, with a total of 183 events (CSE cessation) were required for a 0.05 level two-sided log-rank test for equality of survival curves to detect an increase in seizure cessation from 60% to 75% (a constant hazard ratio of 0.661) at 80% power. The sample size was increased to 308 to allow for 10% loss to follow up. The final sample size was 286 due to low attrition and completeness of primary outcome data.

All randomised and consented participants who received a second-line treatment were included in the analysis according to their allocated treatment. Children who were randomised, but whose CSE stopped without requiring second-line treatment (and did not restart in the ED) were excluded (Figure 1). The safety analysis included the same participants grouped according to treatment received. To avoid double-counting, serious adverse events are reported separately to adverse events.

A detailed statistical analysis plan was developed and is available in full (https://www.journalslibrary.nihr.ac.uk/programmes/hta/12127134/#/). The primary analysis was based on a modification to the intention-to-treat principle. Statistical tests were two-sided at a 5% significance level; results are presented with 95% confidence intervals. The primary outcome was analysed using the log-rank test and is presented with a Kaplan-Meier curve. All participants were followed up to CSE cessation, with censoring used in the event of RSI or death. Where an RSI was administered, time was censored at RSI plus 12 hours (720 minutes); in patients who died before CSE cessation, time was censored at time of death plus 48 hours (2880 minutes). Sensitivity analyses were conducted to consider the robustness of results to the analysis approach taken including (i) Gray’s test,\(^{23}\) treating RSI as a competing risk, (ii) time to CSE cessation calculated from infusion start
instead of randomisation, (iii) censoring participants at the time of an additional second-line treatment following failure to respond to the randomised treatment.

Additional analysis using a Cox Proportional Hazards model adjusted for baseline characteristics of weight, gender, and whether this was the child’s first seizure. Two covariates (site of infusion and additional anticonvulsants given in parallel) specified in the analysis plan were not included as they were measured post-randomisation. In addition, centre could not be included in the Cox model due to lack of convergence. Schoenfeld residual plots were used to check the assumption of proportionality. The binary secondary outcomes of need for further anticonvulsants, RSI, and admission to critical care were analysed using the chi-square test, and presented with relative risks. Logistic regression models were fitted as additional analyses to the primary chi-square tests, with adjustments as per the Cox Proportional Hazards model. No adjustment was made for multiplicity for the secondary outcomes. Baseline categorical data and adverse event data are summarised using numbers and percentages, and continuous data as medians and inter-quartile ranges (IQR) as appropriate.

All analyses were performed using SAS software, version 9·4. The trial was overseen by an Independent Data and Safety Monitoring Committee (IDSMC), which made recommendations to a Trial Steering Committee (TSC), which had an independent majority membership and remained blind to accumulating data until the trial end. The IDSMC and TSC met at least annually and were consulted prior to the decision to stop recruitment due to low attrition and completeness of data. The Haybittle-Peto approach was used by the IDSMC as a guide to consider stopping the trial within interim reports with 99.9% confidence intervals. The trial is registered with ISRCTN; ISRCTN22567894.

**Role of the funding source**

The trial funder monitored trial progress and approved oversight committee membership. They had no role in trial design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the trial and had final responsibility for the decision to submit for publication.

**RESULTS**

The EcLiPSE trial opened to enrolment on 17th July 2015 (protocol version 3·0, 17/06/2015) and closed on 7th April 2018. Two hundred and eighty six participants were randomised and treated; 152 (53%) with levetiracetam and 134 with (47%) phenytoin. Written consent was obtained in 250 (87%),
and the remaining (13%) were included via the ‘opt-out’ pathway. Participant flow is shown in Figure 1. Baseline characteristics were consistent across groups (Table 1).

CSE was terminated by levetiracetam in 106 (70%), and by phenytoin in 86 (64%) participants. Trial adherence data are shown in Table 2. Median time from randomisation to start of infusion was 11 minutes (IQR 8-15) for levetiracetam and 12 minutes (IQR 8-17) for phenytoin. Infusion duration was longer than expected for 27 (18%) and 34 (25%) participants allocated to levetiracetam and phenytoin respectively. All participants, except two allocated phenytoin, received a full dose of trial treatment.

For the primary outcome, median time from randomisation to seizure cessation was 35 minutes (IQR 20-NA) in the levetiracetam group, and 45 minutes (IQR 24-NA) in the phenytoin group (log-rank test p=0.20) (Figure 2). Event times were censored for 46 (30%) and 48 (36%) levetiracetam and phenytoin participants respectively that received RSI for any reason prior to seizure cessation. The unadjusted hazard ratio was 1.2 (95% CI 0.91-1.6, p=0.2) in favour of levetiracetam. The Schoenfeld residuals for the unadjusted model (p=0.72) indicated the independency of time and the validity of the proportionality assumption. The Schoenfeld residuals for the adjusted model indicated that the assumption of proportionality for weight was not met (p=0.05, p-value range from 0.27 to 0.71 for other variables). The data were sub-grouped according to weight category as per the baseline table (<12kg, 12-36kg, >36kg) and estimates from the unadjusted and adjusted models calculated. The proportionality assumption within each subgroup of data was supported by the Schoenfeld residuals. Direction of treatment effect was consistent across subgroups, confidence intervals were wide, and results were not statistically significant. The non-significant treatment effect was increased for children in the >36kg subgroup, however numbers within this group are small. The results are provided in full in the supplementary material.

Fifty-seven (38%) participants in the levetiracetam group and 50 (37%) in the phenytoin group received additional anticonvulsants (RR 1.01; 95% CI 0.7-1.4, p=0.97) (Table 3). Results were similar when restricted to the further management for the presenting episode of CSE.

Forty-four (29%) participants in the levetiracetam group and 47 (35%) in the phenytoin group were given an RSI due to ongoing CSE (RR 0.83; 95% CI 0.59-1.16, p=0.27). (Table 3).

Ninety-seven (64%) participants in the levetiracetam group and 72 (54%) in the phenytoin group were admitted to critical care (RR 1.19; 95% CI 0.97-1.45, p=0.08).
Safety data were analysed by treatment received (Table 4). One hundred and thirty two participants received levetiracetam, and 130 received phenytoin. The remaining 24 participants received both treatments sequentially; 17 received levetiracetam followed by phenytoin, and seven received phenytoin followed by levetiracetam. Twenty AEs were reported in 16 participants receiving levetiracetam, 23 AEs in 18 participants receiving phenytoin, and eight AEs in four participants receiving both treatments. Each individual AE had a prevalence of <10% (Table 4).

Only five serious adverse events (SAEs) were observed (three in two participants receiving phenytoin, one in a participant receiving levetiracetam, and one in a participant who received both interventions). Four SAEs resolved; the remaining SAE occurred in a participant who died. The cause of death was catastrophic cerebral oedema unrelated to either treatment. This participant received levetiracetam followed by phenytoin. Two of the SAEs were assessed as having a relationship to treatment with one classed as a serious adverse reaction (SAR) and the other a suspected unexpected serious adverse reaction (SUSAR). The SAR was a case of hypotension considered to be immediately life-threatening and the SUSAR was a case of increased focal seizures and decreased consciousness considered to be medically significant. Both occurred in the same participant who was allocated and given phenytoin.

Sensitivity analyses undertaken on the primary outcome confirmed the robustness of the results; these are provided in the supplementary material.

**DISCUSSION**

The EcLiPSE trial is the largest RCT to compare levetiracetam with phenytoin in the treatment of paediatric CSE unresponsive to first-line treatment. This trial, powered for superiority, did not detect a statistically significant difference in any outcome. The direction of effect favoured levetiracetam across the primary (time from randomisation to CSE cessation) and secondary outcomes (including the need for rapid sequence induction, and serious adverse reactions), other than for the secondary outcome of admission to critical care. These findings were robust in all sensitivity analyses.

CSE cessation rates for levetiracetam (70%) and phenytoin (64%) were broadly similar to previously reported observational and retrospective adult studies.\(^{10,16}\) CSE cessation rates as high as 85-95% have been reported, though these studies display significant heterogeneity in design and outcomes.\(^{11,24}\) One RCT undertaken in adults with CSE compared the efficacy of intravenous phenytoin (20 mg/kg), valproate (30 mg/kg) and levetiracetam (25 mg/kg) in 150 patients unresponsive to intravenous lorazepam.\(^{17}\) CSE stopped in 34 (68%) patients treated with phenytoin, 34 (68%) treated with valproate and 39 (78%) treated with levetiracetam (\(p = 0.44\)). A recent
paediatric RCT evaluated 100 children aged three to 12 years receiving levetiracetam (30mg/kg) or phenytoin (20mg/kg) if their CSE continued after one dose of intravenous diazepam. Efficacy was high and almost identical in both groups. A lower diastolic blood pressure was recorded in phenytoin-treated patients (p = 0.023). It is difficult to translate these findings to clinical practice due to the trial’s design, including many exclusion criteria, and primary outcome (absence of seizure activity within 24 hours). In UK practice, childhood CSE management follows the APLS algorithm, which is applicable to the vast majority of children presenting to EDs. Our study design therefore used eligibility criteria which were as inclusive as possible, and followed a treatment pathway that reflected clinical practice.

We did not detect a statistically significant difference between levetiracetam and phenytoin in time to CSE cessation. A superiority design was selected for three reasons: (i) reported CSE cessation rates for each drug, hypothesising that levetiracetam would be more effective, (ii) the absence of RCT data comparing the effectiveness of either treatment to placebo, and (iii) the shorter infusion time of levetiracetam (5 minutes compared to at least 20 minutes for phenytoin). We selected time from randomisation, and instructed sites to undertake randomisation at the latest possible point which would allow reconstitution of the allocated treatment to provide scientific and clinical rigour. As the median time to commencement of infusion exceeded ten minutes in each arm, we also undertook a sensitivity analysis using time to cessation from commencement of infusion, which supported our primary analysis findings.

Progression to RSI in CSE may be required for one or a combination of reasons including continuing CSE, respiratory depression, clinical deterioration, stability for transfer or to safely undertake investigations. However, RSI abolishes visible CSE activity, and may therefore prevent an assessment of CSE cessation directly related to trial treatment. Participants were therefore censored at the time of RSI but the censoring time was increased to allow for this to be a negative and potentially informative outcome. This may have artificially inflated the time to CSE cessation. However sensitivity analyses which censored patients at the time of RSI, and defined RSI as a competing risk, did not change our findings.

Observed safety profiles were similar across both treatments. Due to their relative infrequency in relation to the trial population size, together with good clinical management in participating sites, low rates of serious adverse events or reactions were observed in EcLiPSE. However, hypotension, cardiac arrhythmias, and severe extravasation injuries are well-recognised adverse effects of phenytoin; rarely, the cardiovascular effects may be fatal. Levetiracetam was well tolerated when administered over five minutes, a more rapid rate than previously reported. Agitation
was the most common adverse event in the levetiracetam group, as reported previously. There were no new or unexpected serious adverse reactions with levetiracetam. Sedation, somnolence and dizziness are rare side effects in adults but this may in part reflect the prior use of benzodiazepines or craniotomy in the study population.

EcLiPSE is unique for many reasons. It is the first adequately powered RCT to compare the efficacy and safety of two anticonvulsants as second-line treatment for CSE. Second, it is the first adequately-powered RCT to evaluate phenytoin as a second-line treatment for CSE, despite this drug’s place as first-choice, second-line treatment for over 50 years. Third, it incorporated a nested consent study that evaluated the process of RWPC in a paediatric emergency medicine trial. Fourth, it was the first multicentre RCT to be supported by and delivered across the then nascent Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI) collaborative.

This trial has a number of strengths. First, it evaluated a specific step (second-line treatment) in a UK clinical algorithm for the management of childhood CSE. A similar trial assessing the first-line, non-intravenous treatment of CSE in the same algorithm led to a change in national clinical practice. Second, it demonstrated RWPC is acceptable and successful, with 385 of 404 (95%) randomised participants providing consent; in those who were randomised and treated, 286 of 311 (92%) provided consent. RWPC is essential for the successful delivery of paediatric emergency care trials. The high consent rate mirrors that found in a previous trial of first-line CSE management (consent rate, 97%) and in a pilot RCT that compared fluid boluses in shock (consent rate, 100%). Third, it was a pragmatic trial, and recorded only key primary and secondary outcomes in the resuscitation room. This approach, supported by focussed data-collection materials and simple allocation and enrolment methods, facilitated successful delivery of the study across all sites as shown by low numbers of missed patients, high protocol adherence and accurate data capture for key outcomes. Finally, the trial was conducted in EDs from secondary and tertiary institutions throughout PERUKI, increasing generalisability of our findings, and facilitating rapid dissemination and knowledge translation.

This trial has some limitations. First, it was open. A double-blind design was considered too complex for most participating sites, in part because of the markedly different infusion rates of the two drugs, and within the context of the life-threatening nature of CSE. Second, there was likely subjectivity in the assessment of ‘cessation of all signs of continuous, rhythmic clonic activity’ as the clinical event for our primary outcome, rather than fixed time-points to assess CSE-cessation. Clearly, these two limitations may collectively increase the risk of bias. However, continual assessment of a child’s condition reflects ‘real life’ practice in a dynamic situation, in which clinicians constantly evaluate
and prepare for the next step in the treatment algorithm. Site training included a simulated demonstration of the endpoint to ensure an understanding of the key outcome measure for the trial. It would not have been feasible or pragmatic for each participant to undergo a video recording or an electroencephalogram (EEG) to determine CSE-cessation time more precisely. It is not possible to state definitively without EEG whether any patients developed non-convulsive status epilepticus. However treatment algorithms for non-convulsive status epilepticus would follow the same flow as CSE, and there was no difference between treatment groups in the number of additional anticonvulsants given after trial treatment. Third, the time-point of randomisation resulted in CSE terminating prior to administration of trial treatment in a number of cases; however this affected both treatment arms equally, and was essential to maintain high standards of clinical care and avoid treatment delays. Fourth, we included safety measures as key secondary outcomes due to previous reports of harm. However this trial was not powered to demonstrate difference in serious adverse reactions (a secondary outcome) between treatment groups given their low incidence rate. Finally we considered a superiority design was more appropriate for reasons given above.

Other treatment-related factors may be relevant to the interpretation of our findings. These include the widespread use of levetiracetam as maintenance therapy for many childhood epilepsies because of its broad-spectrum activity and safety profile. In EcLiPSE trial participants, it was the most commonly used oral anti-epileptic drug at the time of presentation. Anecdotally, clinicians are reluctant to give a loading dose of phenytoin in CSE to children on oral maintenance phenytoin due to potential cardiovascular toxicity. There seemed to be no similar concerns for levetiracetam and there was no observed increase in adverse events when giving 40mg/kg to children already receiving maintenance levetiracetam. A significant minority of children that present in CSE for the first time are subsequently commenced on maintenance therapy. This is more likely to be with levetiracetam than phenytoin because of the latter’s adverse safety profile and complex pharmacokinetics. One observational study in adults showed 8% of patients treated with intravenous fosphenytoin for CSE were subsequently commenced on oral phenytoin, in contrast to 78% treated with intravenous levetiracetam that were subsequently commenced on oral levetiracetam. Ease of drug preparation and administration is also a factor in the management of CSE. Throughout EcLiPSE, levetiracetam was reported by clinical teams in the participating centres to be easier to prepare and administer than phenytoin due to the latter’s calculations performed in reconstituting the drug, the number of vials required, and procedures needed for its administration, observations supported by the literature.
Treatment strategies in the management of CSE are evolving. This includes the increasing use of two or more second-line treatments in preference to the traditional practice of immediate progression to RSI after failure of the first second-line treatment. This was observed in 35 participants in EcLiPSE. Clinicians may consider the risks of RSI greater than the administration and assessment of a second second-line treatment. The shorter administration time of levetiracetam may appeal as a first choice agent, in contrast to 20 minutes (or more) for phenytoin. Finally, intravenous levetiracetam has been shown to be as effective (76%) as intravenous lorazepam (the current first choice first-line treatment of CSE) in terminating CSE in adults.\textsuperscript{25} This may justify further study.

The EcLiPSE trial did not show that levetiracetam was superior to phenytoin in the rate of CSE cessation, the time taken to terminate CSE, or adverse reactions and events. However, the results, together with previously reported safety profiles and relative ease of administration of levetiracetam, suggest it would be an appropriate alternative to phenytoin as the first-choice, second-line anticonvulsant in the treatment of paediatric CSE.
RESEARCH IN CONTEXT (PANEL)

Evidence before this trial
There are minimal RCT data for the second-line anticonvulsant treatment of paediatric CSE. Most published evidence for both phenytoin (the current recommended first choice anticonvulsant outside the USA) and levetiracetam is anecdotal and retrospective, or based on adult studies, or both. Observational data have suggested levetiracetam may be more effective than phenytoin. Two small RCTs undertaken predominantly in adults and a recent paediatric RCT, using a range of methodologies and outcomes, found no statistically significant difference in CSE-cessation or CSE-recurrence within 24 hours between these two anticonvulsants.

Added value of this trial
To our knowledge, this is the first robust and adequately powered RCT that has directly compared any anticonvulsant in the second-line treatment of paediatric CSE in an emergency setting. It is also the first RCT that has compared the efficacy and safety of levetiracetam and phenytoin in this paediatric neurological emergency. There was no statistical difference between the two anticonvulsants in any primary or secondary outcome although the direction of effect favoured levetiracetam across the primary and secondary outcomes of efficacy and safety. The safety profile was similar between treatments, in contrast to much existing observational evidence that has shown phenytoin to have a worse safety profile.

Implications of all the available evidence
Our results suggest that levetiracetam may be considered as an alternative treatment to phenytoin in the second-line management of paediatric CSE. Additional benefits for levetiracetam over phenytoin include its ease of preparation and administration, minimal interaction with anti-epileptic and non-epileptic medications, and easy conversion to oral maintenance therapy. Further RCT and meta-analysis data may help to confirm its potential role and replacement of phenytoin as the preferred first-choice, second-line anticonvulsant in children with benzodiazepine-resistant CSE.
CONTRIBUTORS
RA devised the trial concept, and was the grant holder and Chief Investigator. RA, CG, ML, AI, SM, KW, HH and JN secured the trial grant. RA, CG, ML, AI, SM designed the clinical trial and KW the consent study. JN, LL and SP contributed to the trial design, materials, and provided nursing leadership to participating sites. ML was the PERUKI lead for the trial. CG was the statistical lead and NR conducted the statistical analysis. KW led the Consent study and LR conducted the research. HH and AH provided the trial management, and PT provided data management. VE provided patient and public involvement (PPI). ML wrote the first draft of the manuscript with input from RA and CG. All authors reviewed and agreed the final manuscript.

DECLARATION OF INTERESTS
We declare no competing interests.

DATA SHARING
Data will be shared upon request to the Clinical Trials Research Centre. Requests will be checked for compatibility with participant consent and the CTRC data sharing policy will be followed. The CTRC data sharing policy requires investigator assessment and approval of the request and completion of a data sharing agreement. Anonymised data and a copy of the annotated case report forms will be shared. The protocol and statistical analysis plan are publicly available as referenced in this publication. The data will be available following their inclusion in a planned individual participant data meta-analysis.

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Independent Trial Steering Committee members
Professor Imti Choonara (Department of Child Health, University of Nottingham and Derbyshire Children's Hospital, Derby, UK); Professor Caroline Doré (The Comprehensive Clinical Trials Unit at UCL, London, UK); Michael J Barrett (Our Lady’s Children’s Hospital, Dublin, Ireland); Professor Ronan O’Sullivan (Cork University Hospital, Cork, Ireland); Gail Miller (PPI representative); Jane V Green (PPI representative); Denise L Bustany (PPI representative).

Independent Data Monitoring Committee members
Professor Steff C Lewis (Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh, UK); Julie A Ellison (Mid Cheshire Hospitals NHS Foundation Trust, UK); Professor Tony G Marson (University of Liverpool and The Walton Centre NHS Foundation Trust, Liverpool, UK).

EcLiPSE trial Nurse Leadership Group
Alder Hey Children’s Hospital NHS Foundation Trust: Joanne Noblet, Elizabeth D Lee, Rachel Greenwood-Bibby.
Bristol Royal Hospital for Children: Sarah Potter, Alice Smith, Phoebe Moulsdale, Holly R Lavigne-Smith.

Participating sites and investigators
Addenbrookes Hospital, Cambridge University NHS Trust, UK: Matthew Pereira, Susie Hardwick
Alder Hey Children’s Hospital NHS Foundation Trust, Liverpool, UK: Shrouk Messahel, Joanne Noblet, Elizabeth D Lee, Rachel Greenwood-Bibby
Arrowe Park Hospital, Wirral University Hospital NHS Trust, Liverpool, UK: Mark Buchanan, Sharon Hughes, Lucy Lewis
Birmingham Children’s Hospital, UK: Stuart Hartshorn, Louise Rogers, Juliet Hopkins
Bristol Royal Hospital for Children, UK: Mark D Lyttle, Daphin Fernandez, Sarah Potter, Holly R Lavigne-Smith, Phoebe Moulsdale, Alice Smith, Tracey Bingham
Chelsea & Westminster NHS Foundation Trust, London, UK: James Ross, Natasha Ramsey, Jo Hacking
City Hospitals Sunderland NHS Foundation Trust, Sunderland, UK: Niall Mullen, Paul P Corrigan, Sarah Prudhoe
Derbyshire Children’s Hospital, Derby, UK: Hani Faza, Gisela Robinson, Rachel C Sunley, Coral J Smith, Vanessa Unsworth
Evelina London Children’s Hospital, London, UK: John Criddle, Martin Laque, Alyce B Sheedy

Great North Children’s Hospital, Newcastle upon Tyne, UK: Mark Anderson, Kirsty Devine, Kathryn Bell

James Cook University Hospital, Middlesbrough, UK: Alex Scott, Ramesh Kumar, Sonia Armstrong

King’s College Hospital, London, UK: Emer Sutherland, Fleur Cantle, Sinead Helyar, Paul Riozzi, Hannah Cotton

Leeds General Infirmary, Leeds, UK: Alice J Downes, Helen Mollard

Leicester Hospitals, Leicester, UK: Damian Roland, Felix Hay

Nottingham University Hospitals NHS Trust, Nottingham, UK: Chris Gough, Sonya Finucane

Royal Alexandra Children’s Hospital, Brighton, UK: Catherine Bevan, Rebecca Ramsay, Emily Walton

Royal Belfast Hospital for Sick Children, Belfast, UK: Julie-Ann Maney, Elizabeth Dalzell, Muriel Millar

Royal Devon and Exeter NHS Foundation Trust, Exeter, UK: Rachel J Howells, Andy Appelboam, Jennie Small, Daisy Mackle

Royal Hospital for Children, Glasgow, UK: Vince Choudhery, Stewart MacLeod, Ashleigh Neil

Royal Hospital for Sick Children, Edinburgh, UK: Jen Browning, Thom O’Neill, Julia Grahamslaw

Royal London Hospital, London, UK: Ami Parikh, Imogen Skene, Rhys Thomas

Royal Manchester Children’s Hospital, Manchester, UK: Katherine Potier de la Morandiere, Jill L Wilson, Donna Danziger

Sheffield Children’s Hospital NHS Foundation Trust, Sheffield, UK: Derek Burke, Shammi Ramlakhan, Jayne Evans, Julie Morcombe, Stuart Gormley

Southampton Children’s Hospital, Southampton, UK: Jason M Barling, Katrina Cathie, Jane Bayreuther, Ruth Ensom

St George’s University Hospitals NHS Foundation Trust, London, UK: Yasser Iqbal, Sarah Rounding
University Hospital Crosshouse, Kilmarnock, UK: Joanne Mulligan, Claire Bell, Shona McLellan, Shona Leighton

University Hospital Lewisham, London, UK: Tina Sajjanhar, Maggie Nyirenda, Anastasia Alcock, Laura Crome, Neil Williamson

University Hospital of Wales, Cardiff, UK: Sara Edwards, Jeff Morgan, Colin VE Powell

Watford General Hospital, London, UK: Chaniyil A Ramesh, Solomon Kamal-Uddin

Western Sussex Hospitals NHS Foundation Trust, UK: Mike Linney, Katia Vamvakiti, Sharon Floyd, Gill Hobden
REFERENCES


### Table 1: Baseline demographic and seizure characteristics of the trial population

<table>
<thead>
<tr>
<th></th>
<th>Levetiracetam</th>
<th>Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=152 (53%)</td>
<td>n=134 (47%)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75 (49%)</td>
<td>72 (54%)</td>
</tr>
<tr>
<td>Female</td>
<td>77 (51%)</td>
<td>62 (46%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months - &lt;2 years</td>
<td>65 (43%)</td>
<td>53 (40%)</td>
</tr>
<tr>
<td>2-11 years</td>
<td>81 (53%)</td>
<td>74 (55%)</td>
</tr>
<tr>
<td>12-17 years</td>
<td>6 (4%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>2·7 (1·3-5·9)</td>
<td>2·7 (1·6-5·6)</td>
</tr>
<tr>
<td>Range</td>
<td>0·6-16·1</td>
<td>0·6-17·9</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 kg</td>
<td>52 (34%)</td>
<td>42 (31%)</td>
</tr>
<tr>
<td>12-36 kg</td>
<td>86 (57%)</td>
<td>80 (60%)</td>
</tr>
<tr>
<td>&gt;36 kg</td>
<td>14 (9%)</td>
<td>12 (9%)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>12·1 (10·0-19·0)</td>
<td>12·0 (10·0-18·0)</td>
</tr>
<tr>
<td>Range</td>
<td>7·5-70·0</td>
<td>6·0-66·0</td>
</tr>
<tr>
<td><strong>Participant’s first seizure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presenting seizure type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalised tonic-clonic</td>
<td>107 (70%)</td>
<td>105 (78%)</td>
</tr>
<tr>
<td>Generalised clonic</td>
<td>12 (8%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Focal clonic</td>
<td>33 (22%)</td>
<td>22 (16%)</td>
</tr>
<tr>
<td><strong>Seizure cause</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile convulsion</td>
<td>63 (41%)</td>
<td>58 (43%)</td>
</tr>
<tr>
<td>Seizure (pre-existing epilepsy)</td>
<td>46 (30%)</td>
<td>46 (34%)</td>
</tr>
<tr>
<td>First afebrile seizure</td>
<td>16 (11%)</td>
<td>12 (9%)</td>
</tr>
<tr>
<td>Central nervous system infection</td>
<td>6 (4%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Intracranial vascular event (bleed/stroke)</td>
<td>2 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Substance misuse</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>10 (7%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>27 (18%)</td>
<td>26 (19%)</td>
</tr>
<tr>
<td><strong>Maintenance anti-epileptic drugs at presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>29 (15.9%)</td>
<td>26 (19.4%)</td>
</tr>
<tr>
<td>Sodium Valproate</td>
<td>16 (10.5%)</td>
<td>19 (14.2%)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>12 (7.9%)</td>
<td>10 (7.5%)</td>
</tr>
<tr>
<td>Clobazam</td>
<td>9 (5.9%)</td>
<td>9 (6.7%)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>4 (2.6%)</td>
<td>8 (6.0%)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0 (0.0%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (7.2%)</td>
<td>18 (13.4%)</td>
</tr>
</tbody>
</table>

*categories not mutually exclusive
Table 2: Trial adherence data

<table>
<thead>
<tr>
<th></th>
<th>Levetiracetam n=152</th>
<th>Phenytoin n=134</th>
<th>Total n=286</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient given lower dose of trial treatment</td>
<td>8 (5·3%)</td>
<td>4 (3·0%)</td>
<td>12 (4·2%)</td>
</tr>
<tr>
<td>Patient given higher dose of trial treatment</td>
<td>2 (1·3%)</td>
<td>1 (0·8%)</td>
<td>3 (1·1%)</td>
</tr>
<tr>
<td>Dose administration shorter than expected</td>
<td>0 (0·0%)</td>
<td>1 (0·8%)</td>
<td>1 (0·4%)</td>
</tr>
<tr>
<td>Dose administration longer than expected</td>
<td>27 (17·8%)</td>
<td>34 (25·4%)</td>
<td>61 (21·3%)</td>
</tr>
<tr>
<td>Treatment prematurely discontinued</td>
<td>0 (0·0%)</td>
<td>2 (1·5%)</td>
<td>2 (0·7%)</td>
</tr>
<tr>
<td>Unauthorised route of administration (intraosseous)</td>
<td>6 (4·0%)</td>
<td>0 (0·0%)</td>
<td>6 (2·1%)</td>
</tr>
<tr>
<td>Received initial second-line treatment other than that allocated</td>
<td>3 (1·5%)</td>
<td>0 (0·0%)</td>
<td>3 (0·8%)</td>
</tr>
<tr>
<td>Received further second-line treatment*</td>
<td>22 (14·5%)</td>
<td>13 (9·7%)</td>
<td>35 (13·6%)</td>
</tr>
</tbody>
</table>

*Includes those who subsequently received the alternative trial treatment, or an additional dose of allocated treatment, within 24 hours
Table 3: Secondary outcomes and 14 day follow-up

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
<th>Levetiracetam N=152</th>
<th>Phenytoin N=134</th>
<th>Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for further anticonvulsants&lt;sup&gt;a&lt;/sup&gt;</td>
<td>57 (37.5%)</td>
<td>50 (37.3%)</td>
<td>1.01 (0.74-1.36)</td>
<td>0.97</td>
</tr>
<tr>
<td>Need for further anticonvulsants for the presenting CSE&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24 (15.8%)</td>
<td>20 (14.9%)</td>
<td>1.06 (0.61-1.83)</td>
<td>0.84</td>
</tr>
<tr>
<td>Need for further anticonvulsants for a subsequent seizure (within 24 hours)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>14 (9.2%)</td>
<td>17 (12.7%)</td>
<td>0.72 (0.37-1.4)</td>
<td>0.33</td>
</tr>
<tr>
<td>RSI to terminate an ongoing seizure</td>
<td>44 (30.0%)</td>
<td>47 (35.1%)</td>
<td>0.83 (0.59-1.16)</td>
<td>0.27</td>
</tr>
<tr>
<td>Admission to critical care</td>
<td>97 (63.8%)</td>
<td>72 (53.7%)</td>
<td>1.19 (0.97-1.45)</td>
<td>0.08</td>
</tr>
<tr>
<td>Serious adverse reaction</td>
<td>0</td>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>14 day follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged from hospital</td>
<td>145 (95.4%)</td>
<td>130 (97.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Readmitted to hospital</td>
<td>12 (7.9%)</td>
<td>10 (7.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient died</td>
<td>1 (0.7%)</td>
<td>1 (0.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ failure</td>
<td>1 (0.7%)</td>
<td>0 (0.0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval; RSI: Rapid Sequence Induction; CSE: Convulsive Status Epilepticus;
<sup>a</sup>Includes all instances of further anticonvulsant being given in following 24 hours, including for the presenting seizure, subsequent seizures, or for prophylaxis
<sup>b</sup>Post hoc analysis. Assessment conducted without knowledge of the allocated intervention
<sup>c</sup>Excludes 9 participants where the data were unavailable
<sup>d</sup>Two events in 1 participant one of which was a suspected unexpected serious adverse reaction (SUSAR)
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Levetiracetam N=132</th>
<th>Phenytoin N=130</th>
<th>Both drugs N=24</th>
<th>Total N=286</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agitation</strong></td>
<td>Events</td>
<td>Patients</td>
<td>Events</td>
<td>Patients</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>11 (8-3%)</td>
<td>4</td>
<td>4 (3-1%)</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>2</td>
<td>2 (1-5%)</td>
<td>3</td>
<td>3 (2-3%)</td>
</tr>
<tr>
<td><strong>Catheter related</strong></td>
<td>1</td>
<td>1 (0-8%)</td>
<td>1</td>
<td>1 (0-8%)</td>
</tr>
<tr>
<td><strong>Extravasation</strong></td>
<td>0</td>
<td>0 (0-0%)</td>
<td>4</td>
<td>4 (3-1%)</td>
</tr>
<tr>
<td><strong>Tachycardia</strong></td>
<td>1</td>
<td>1 (0-8%)</td>
<td>3</td>
<td>3 (2-3%)</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>2</td>
<td>2 (1-5%)</td>
<td>1</td>
<td>1 (0-8%)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>0</td>
<td>0 (0-0%)</td>
<td>2</td>
<td>2 (1-5%)</td>
</tr>
<tr>
<td><strong>Reaction to Ceftriaxone</strong></td>
<td>0</td>
<td>0 (0-0%)</td>
<td>0</td>
<td>0 (0-0%)</td>
</tr>
<tr>
<td><strong>Confused</strong></td>
<td>1</td>
<td>1 (0-8%)</td>
<td>0</td>
<td>0 (0-0%)</td>
</tr>
<tr>
<td><strong>Decreased consciousness</strong></td>
<td>0</td>
<td>0 (0-0%)</td>
<td>1</td>
<td>1 (0-8%)</td>
</tr>
<tr>
<td><strong>Hallucination</strong></td>
<td>1</td>
<td>1 (0-8%)</td>
<td>0</td>
<td>0 (0-0%)</td>
</tr>
<tr>
<td><strong>Infusion site erythema</strong></td>
<td>0</td>
<td>0 (0-0%)</td>
<td>1</td>
<td>1 (0-8%)</td>
</tr>
<tr>
<td><strong>Mechanical ventilation complication</strong></td>
<td>0</td>
<td>0 (0-0%)</td>
<td>1</td>
<td>1 (0-8%)</td>
</tr>
<tr>
<td><strong>Pallor</strong></td>
<td>0</td>
<td>0 (0-0%)</td>
<td>1</td>
<td>1 (0-8%)</td>
</tr>
<tr>
<td><strong>Stridor</strong></td>
<td>0</td>
<td>0 (0-0%)</td>
<td>0</td>
<td>0 (0-0%)</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>0</td>
<td>0 (0-0%)</td>
<td>1</td>
<td>1 (0-8%)</td>
</tr>
<tr>
<td><strong>Wheezing</strong></td>
<td>1</td>
<td>1 (0-8%)</td>
<td>0</td>
<td>0 (0-0%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>20</td>
<td>16 (12-1%)</td>
<td>23</td>
<td>18 (13-9%)</td>
</tr>
</tbody>
</table>