Clinical trial results:
Randomised factorial design controlled trial comparing carbamazepine, levetiracetam or active monitoring combined with or without sleep behaviour intervention in treatment naive children with rolandic epilepsy

Summary

EudraCT number	2018-003893-29
Trial protocol	GB
Global end of trial date	23 September 2020

Results information

Result version number	v1 (current)
This version publication date	04 April 2021
First version publication date	04 April 2021

Trial information

Trial identification

Sponsor protocol code	CASTLE

Additional study identifiers

ISRCTN number	ISRCTN12839803
ClinicalTrials.gov id (NCT number)	NCT04610879
WHO universal trial number (UTN)	-
Other trial identifiers	ISRCTN Number: ISRCTN12839803, IRAS number: 250324, Funder reference : RP-PG-0615-20007

Notes:

Sponsors

Sponsor organisation name	Kings College London
Sponsor organisation address	5 Cutcombe Road, London, United Kingdom, SE5 9RX
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Public contact	Professor Deb Pal, King's College Hospital NHS Foundation Trust, +44 0207 848 5762, deb.pal@kcl.ac.uk
Scientific contact	Professor Deb Pal, King's College Hospital NHS Foundation Trust, +44 0207 848 5762, deb.pal@kcl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	12 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2020
Global end of trial reached?	Yes
Global end of trial date	23 September 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to test two hypotheses:

A) To determine if Carbamazepine or Levetiracetam are superior to no AED (Anti-Epileptic Drug) with respect to time to 6-month seizure remission.

B) To determine if a Parent-Based Sleep (PBS) intervention is superior to standard care with respect to 3-month sleep problem frequency measured by Children's Sleep Habits Questionnaire (CSHQ).

The Primary economic objective is: To estimate the cost-utility of Carbamazepine, Levetiracetam and PBS

Protection of trial subjects:

A trial risk assessment was completed prior to the trial opening. The management of the study was done in line with Ethical, Regulatory and LCTC policies/procedures. Data from the trial will be collected centrally from NHS Digital (or national appropriate) from Hospital Episode Statistics (HES) who operate under a General Data Protection Regulation (GDPR) framework.
Both IMPs used in the CASTLE clinical trial (Carbamazepine and Levetiracetam) are licensed for their use to treat epilepsy. The initial prescription of the trial treatment was done so by trained medical professionals in line with routine practice. Those participants who were randomized to standard care were treated as per their local hospital's routine procedures. All those who oversaw trial activities were trained on the study, which is evidenced by the collection of site training logs and delegation 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 task. The consent and assent discussions were undertaken by delegated members of research staff who had experience of obtaining consent in a pediatric population. Children (≥7 years old) who were deemed to have capacity were asked to provide assent to the study. Separate consent and assent forms were sought from participants who wished to take part in the qualitative component of the study. Patient information was collected at site using CRFs specifically designed for the CASTLE trial. Questionnaires used in the study were approved for use in the study by their owners.
CANTAB data collected from participants using a pre-configured study iPad was pseudo-anonymised and transferred securely to an online server.
All collected information was pseudo-anonymised and transferred to the Liverpool Clinical Trials Centre (LCTC) in an agreed format.

Background therapy:

Carbamazepine is a first-generation AED, is the current NICE standard treatment for Rolandic Epilepsy (RE). Carbamazepine has never been compared against no-treatment in RE, and in view of the Anti-Epileptic Drug (AED's) known cognitive adverse effects, it is important to know whether any benefit in terms of seizure control offsets its impact on children's learning. Second-generation AEDs (levetiracetam, lamotrigine, gabapentin, but not topiramate) have fewer cognitive side-effects in healthy adult volunteers than first-generation (carbamazepine, oxcarbazepine, valproate, phenobarbital, phenytoin); and the International League Against Epilepsy judges only levetiracetam, of these second-generation AEDs, to have potential efficacy in RE.

A generic version of levetiracetam was released in 2014 with comparable treatment cost to carbamazepine. Although not licensed for monotherapy in children, it is in widespread off-label use and is judged to be efficacious and well-tolerated. Thus levetiracetam would make an ideal and potentially superior comparator and has not been assessed head-to-head with carbamazepine in childhood epilepsy.

Despite the frequency of sleep problems in children with epilepsy (and other neurodevelopmental disorders), clinicians in the UK receive little training on the subject. This lack of training, and lack of epilepsy-specific evidence-based interventions, combined with a focus on seizure control means that sleep problems are rarely addressed in routine clinical practice. Even if sleep problems were a management target, the lack of any evidence-based resources for intervention is a barrier to such implementation. The Parent-Based Sleep Intervention (PBS) intervention offers parents education about normal sleep, advice about sleep-promoting practices and targeted strategies parents can employ to help their children to ‘‘learn’’ an appropriate set of sleep behaviors/habits and/or to unlearn inappropriate sleep behaviors.

Evidence for comparator:

The national survey conducted for this study confirmed that UK pediatricians prescribed Carbamazepine as first-line choice (80%), but importantly, the survey revealed that in 40% of cases paediatricians treat RE patients conservatively, i.e. without drugs, as advocated in older textbooks.

Actual start date of recruitment	09 August 2019
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: 5
Worldwide total number of subjects	5
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	5
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

CASTLE received the green light from Liverpool Clinical Trials Center (LCTC) to open on 9/08/2019. The first patient was randomized on 25/11/2019. The last patient was randomized on 09/03/2020. CASTLE recruitment was halted on 23/03/2020 due to COVID-19 and never re-opened due to poor recruitment, resulting in only 5 patients being randomized.

Pre-assignment

Screening details:

All patients aged ≥5 and <13 years with diagnosis of RE previously untreated with AED were screened at the trial centres to identify potentially eligible participants for the trial. A 'Screening log' was maintained of all the patients who undergo screening regardless of whether they are assessed as eligible or decide to participate in the trial.

Period 1

Period 1 title	Main trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	No AED & sleep intervention

Arm description:

No Anti-Epileptic Drug (AED) and sleep behavior intervention

Arm type	No drug intervention but a sleep intervention

No investigational medicinal product assigned in this arm

Arm title	CBZ & sleep intervention

Arm description:

Carbamazepine (CBZ) & sleep behavior intervention

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

Dosage and administration details:

Oral carbamazepine prescribed in a formulation and at a dose deemed suitable by the treating physicians and guided by ranges in summary of product characteristics (SmPC).

Arm title	LEV & sleep intervention

Arm description:

Levetiracetam (LEV) and sleep behavior intervention

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

Dosage and administration details:

Levetiracetam prescribed in a formulation and at a dose deemed suitable by the treating physicians and guided by ranges in summary of product characteristics (SmPC).

Arm title	LEV & no sleep intervention

Arm description:

Levetiracetam (LEV) and no sleep behavior intervention (standard care)

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

Dosage and administration details:

Oral levetiracetam prescribed in a formulation and at a dose deemed suitable by the treating physicians and guided by ranges in summary of product characteristics (SmPC).

Number of subjects in period 1	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention
Started	1	1	2
Completed	1	1	1
Not completed	0	0	1
Consent withdrawn by subject	-	-	1

Number of subjects in period 1	LEV & no sleep intervention
Started	1
Completed	1
Not completed	0
Consent withdrawn by subject	-

Baseline characteristics

Reporting groups	
Reporting group title	No AED & sleep intervention
Reporting group description:	
No Anti-Epileptic Drug (AED) and sleep behavior intervention	
Reporting group title	CBZ & sleep intervention
Reporting group description:	
Carbamazepine (CBZ) & sleep behavior intervention	
Reporting group title	LEV & sleep intervention
Reporting group description:	
Levetiracetam (LEV) and sleep behavior intervention	
Reporting group title	LEV & no sleep intervention
Reporting group description:	
Levetiracetam (LEV) and no sleep behavior intervention (standard care)	

Reporting group values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention
Number of subjects	1	1	2
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)	0	0	0
Children (2-11 years)	1	1	2
Adolescents (12-17 years)	0	0	0
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	11	9	9
full range (min-max)	11 to 11	9 to 9	8 to 10
Gender categorical Units: Subjects			
Female	0	0	1
Male	1	1	1
Did the patient have any seizures in the first month of life? Units: Subjects			
Yes	0	0	0
No	1	1	2
Unknown	0	0	0
After the first month of life and before epilepsy, did the patient ever have seizures with fever?			
Full text is "After the first month of life and before developing epilepsy, did the patient ever have seizures or convulsions with fever?".			

Units: Subjects			
Yes	0	0	0
No	1	1	2
Unknown	0	0	0
How many seizures has the patient had in total since onset? Units: Subjects			
One	0	0	0
Two to Four	0	0	1
Five to Ten	0	1	0
More than Ten	1	0	1
Unknown	0	0	0
Has the patient ever had seizures lasting more than 10 minutes or had several seizures in a row? Units: Subjects			
Yes	0	0	1
No	1	1	1
Unknown	0	0	0
Has the patient ever had a generalised tonic-clonic seizure or convulsion? (Text continued below)			
Has the patient ever had a generalised tonic-clonic seizure or convulsion since being diagnosed with Childhood Epilepsy with Centrotemporal Spikes aka Benign Rolandic Epilepsy?			
Units: Subjects			
Yes	0	0	1
No	1	1	1
Unknown	0	0	0
Do the patient’s seizures occur at particular times of the day? Units: Subjects			
Yes	1	0	1
No	0	1	1
Unknown	0	0	0
Do seizures usually occur soon after going to sleep? Units: Subjects			
Yes	1	0	1
No	0	1	1
Unknown	0	0	0
Do seizures usually occur early in the morning? Units: Subjects			
Yes	1	0	0
No	0	1	2
Unknown	0	0	0
Do seizures usually occur during a day time nap? Units: Subjects			
Yes	0	0	0
No	1	1	2
Unknown	0	0	0
Noticeable features in a typical seizure: Drooping of one side of the face			

Units: Subjects			
Yes	1	0	1
No	0	1	1
Unknown	0	0	0
Noticeable features in a typical seizure: Gurgling noise from the throat Units: Subjects			
Yes	0	1	1
No	1	0	1
Unknown	0	0	0
Noticeable features in a typical seizure: Unable to speak Units: Subjects			
Yes	1	1	1
No	0	0	1
Unknown	0	0	0
Noticeable features in a typical seizure: Drooling a lot from the mouth Units: Subjects			
Yes	1	1	1
No	0	0	1
Unknown	0	0	0
Noticeable features in a typical seizure: Aware during the seizure Units: Subjects			
Yes	1	1	1
No	0	0	1
Unknown	0	0	0
Other noticeable features during a seizure: Tingling of tongue and lips Units: Subjects			
Yes	1	0	0
No	0	0	0
Unknown	0	1	2
Other noticeable features during a seizure: Vomiting, numb hands, pallor (white face) Units: Subjects			
Yes	0	0	1
No	0	0	0
Unknown	1	1	1
Other noticeable features during a seizure: Eye rolling, jerking of both arms Units: Subjects			
Yes	0	0	0
No	0	0	0
Unknown	1	1	2
Other noticeable features during a seizure: Facial twitches Units: Subjects			
Yes	0	1	0
No	0	0	0
Unknown	1	0	2

Height (cm)			
Patient height in centimetres.			
Units: Centimetres (cm)			
median	134.4	130.6	134.5
full range (min-max)	134.4 to 134.4	130.6 to 130.6	125.5 to 143.4
Weight (kg)			
Patient weight in kilograms.			
Units: Kilograms			
median	41.8	23.2	37.9
full range (min-max)	41.8 to 41.8	23.2 to 23.2	25.1 to 50.6
Days since first seizure			
Difference in days since first seizure from date of randomization.			
Units: Days before randomization			
median	1098	1128.5	124
full range (min-max)	1098 to 1098	1128.5 to 1128.5	80 to 168
Days since first rolandic seizure			
Difference in days since first rolandic seizure from date of randomization. For the Levetiracetam & Sleep Intervention arm, data was only available for 1/2 patients.			
Units: Days before randomization			
median	1098	1128.5	168
full range (min-max)	1098 to 1098	1128.5 to 1128.5	168 to 168
Days since most recent seizure			
Difference in days since most recent seizure from date of randomization.			
Units: Days before randomization			
median	7	7	74
full range (min-max)	7 to 7	7 to 7	3 to 145
Days since rolandic Epilepsy diagnosis			
Difference in days since rolandic Epilepsy diagnosis to date of randomization.			
Units: Days before randomization			
median	763	0	184
full range (min-max)	763 to 763	0 to 0	95 to 273

Reporting group values	LEV & no sleep intervention	Total	
Number of subjects	1	5	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	1	5	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	7		
full range (min-max)	7 to 7	-	

Gender categorical Units: Subjects			
Female	0	1	
Male	1	4	
Did the patient have any seizures in the first month of life? Units: Subjects			
Yes	0	0	
No	1	5	
Unknown	0	0	
After the first month of life and before epilepsy, did the patient ever have seizures with fever?			
Full text is "After the first month of life and before developing epilepsy, did the patient ever have seizures or convulsions with fever?".			
Units: Subjects			
Yes	0	0	
No	1	5	
Unknown	0	0	
How many seizures has the patient had in total since onset? Units: Subjects			
One	0	0	
Two to Four	0	1	
Five to Ten	0	1	
More than Ten	1	3	
Unknown	0	0	
Has the patient ever had seizures lasting more than 10 minutes or had several seizures in a row? Units: Subjects			
Yes	0	1	
No	1	4	
Unknown	0	0	
Has the patient ever had a generalised tonic-clonic seizure or convulsion? (Text continued below)			
Has the patient ever had a generalised tonic-clonic seizure or convulsion since being diagnosed with Childhood Epilepsy with Centrotemporal Spikes aka Benign Rolandic Epilepsy?			
Units: Subjects			
Yes	0	1	
No	1	4	
Unknown	0	0	
Do the patient’s seizures occur at particular times of the day? Units: Subjects			
Yes	1	3	
No	0	2	
Unknown	0	0	
Do seizures usually occur soon after going to sleep? Units: Subjects			
Yes	1	3	
No	0	2	

Unknown	0	0	
Do seizures usually occur early in the morning? Units: Subjects			
Yes	0	1	
No	1	4	
Unknown	0	0	
Do seizures usually occur during a day time nap? Units: Subjects			
Yes	0	0	
No	1	5	
Unknown	0	0	
Noticeable features in a typical seizure: Drooping of one side of the face Units: Subjects			
Yes	0	2	
No	1	3	
Unknown	0	0	
Noticeable features in a typical seizure: Gurgling noise from the throat Units: Subjects			
Yes	0	2	
No	1	3	
Unknown	0	0	
Noticeable features in a typical seizure: Unable to speak Units: Subjects			
Yes	1	4	
No	0	1	
Unknown	0	0	
Noticeable features in a typical seizure: Drooling a lot from the mouth Units: Subjects			
Yes	0	3	
No	1	2	
Unknown	0	0	
Noticeable features in a typical seizure: Aware during the seizure Units: Subjects			
Yes	0	3	
No	1	2	
Unknown	0	0	
Other noticeable features during a seizure: Tingling of tongue and lips Units: Subjects			
Yes	0	1	
No	0	0	
Unknown	1	4	
Other noticeable features during a seizure: Vomiting, numb hands, pallor (white face) Units: Subjects			
Yes	0	1	

No	0	0	
Unknown	1	4	
Other noticeable features during a seizure: Eye rolling, jerking of both arms Units: Subjects			
Yes	1	1	
No	0	0	
Unknown	0	4	
Other noticeable features during a seizure: Facial twitches Units: Subjects			
Yes	0	1	
No	0	0	
Unknown	1	4	
Height (cm)			
Patient height in centimetres.			
Units: Centimetres (cm)			
median	121		
full range (min-max)	121 to 121	-	
Weight (kg)			
Patient weight in kilograms.			
Units: Kilograms			
median	24.4		
full range (min-max)	24.4 to 24.4	-	
Days since first seizure			
Difference in days since first seizure from date of randomization.			
Units: Days before randomization			
median	105		
full range (min-max)	105 to 105	-	
Days since first rolandic seizure			
Difference in days since first rolandic seizure from date of randomization. For the Levetiracetam & Sleep Intervention arm, data was only available for 1/2 patients.			
Units: Days before randomization			
median	105		
full range (min-max)	105 to 105	-	
Days since most recent seizure			
Difference in days since most recent seizure from date of randomization.			
Units: Days before randomization			
median	4		
full range (min-max)	4 to 4	-	
Days since rolandic Epilepsy diagnosis			
Difference in days since rolandic Epilepsy diagnosis to date of randomization.			
Units: Days before randomization			
median	19		
full range (min-max)	19 to 19	-	

Subject analysis sets

Subject analysis set title	No AED & sleep intervention
Subject analysis set type	Full analysis

Subject analysis set description:

This analysis set includes all patients randomized to No AED & the sleep intervention

Subject analysis set title	CBZ & sleep intervention
Subject analysis set type	Full analysis
Subject analysis set description:	
This analysis set contains all patients randomized to Carbamazepine & sleep intervention.	
Subject analysis set title	LEV & sleep intervention
Subject analysis set type	Full analysis
Subject analysis set description:	
This analysis set contains all patients randomized to Levetiracetam & sleep intervention.	
Subject analysis set title	LEV & no sleep intervention
Subject analysis set type	Full analysis
Subject analysis set description:	
This analysis set contains all patients randomized to Levetiracetam & no sleep intervention (standard of care).	

Reporting group values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention
Number of subjects	1	1	2
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)	0	0	0
Children (2-11 years)	1	1	2
Adolescents (12-17 years)	0	0	0
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	11	9	9
full range (min-max)	11 to 11	9 to 9	8 to 10
Gender categorical Units: Subjects			
Female	0	0	1
Male	1	1	1
Did the patient have any seizures in the first month of life? Units: Subjects			
Yes	0	0	0
No	1	1	2
Unknown	0	0	0
After the first month of life and before epilepsy, did the patient ever have seizures with fever?			
Full text is "After the first month of life and before developing epilepsy, did the patient ever have seizures or convulsions with fever?".			
Units: Subjects			
Yes	0	0	0
No	1	1	2
Unknown	0	0	0
How many seizures has the patient had			

in total since onset? Units: Subjects			
One	0	0	0
Two to Four	0	0	1
Five to Ten	0	1	0
More than Ten	1	0	1
Unknown	0	0	0
Has the patient ever had seizures lasting more than 10 minutes or had several seizures in a row? Units: Subjects			
Yes	0	0	1
No	1	1	1
Unknown	0	0	0
Has the patient ever had a generalised tonic-clonic seizure or convulsion? (Text continued below)			
Has the patient ever had a generalised tonic-clonic seizure or convulsion since being diagnosed with Childhood Epilepsy with Centrotemporal Spikes aka Benign Rolandic Epilepsy?			
Units: Subjects			
Yes	0	0	1
No	1	1	1
Unknown	0	0	0
Do the patient’s seizures occur at particular times of the day? Units: Subjects			
Yes	1	0	1
No	0	1	1
Unknown	0	0	0
Do seizures usually occur soon after going to sleep? Units: Subjects			
Yes	1	0	1
No	0	1	1
Unknown	0	0	0
Do seizures usually occur early in the morning? Units: Subjects			
Yes	1	0	0
No	0	1	2
Unknown	0	0	0
Do seizures usually occur during a day time nap? Units: Subjects			
Yes	0	0	0
No	1	1	2
Unknown	0	0	0
Noticeable features in a typical seizure: Drooping of one side of the face Units: Subjects			
Yes	1	0	1
No	0	1	1
Unknown	0	0	0
Noticeable features in a typical seizure:			

Gurgling noise from the throat Units: Subjects			
Yes	0	1	1
No	1	0	1
Unknown	0	0	0
Noticeable features in a typical seizure: Unable to speak Units: Subjects			
Yes	1	1	1
No	0	0	1
Unknown	0	0	0
Noticeable features in a typical seizure: Drooling a lot from the mouth Units: Subjects			
Yes	1	1	1
No	0	0	1
Unknown	0	0	0
Noticeable features in a typical seizure: Aware during the seizure Units: Subjects			
Yes	1	1	1
No	0	0	1
Unknown	0	0	0
Other noticeable features during a seizure: Tingling of tongue and lips Units: Subjects			
Yes	1	0	0
No	0	0	0
Unknown	0	1	2
Other noticeable features during a seizure: Vomiting, numb hands, pallor (white face) Units: Subjects			
Yes	0	0	1
No	0	0	0
Unknown	1	1	1
Other noticeable features during a seizure: Eye rolling, jerking of both arms Units: Subjects			
Yes	0	0	0
No	0	0	0
Unknown	1	1	2
Other noticeable features during a seizure: Facial twitches Units: Subjects			
Yes	0	1	0
No	0	0	0
Unknown	1	0	2
Height (cm)			
Patient height in centimetres.			
Units: Centimetres (cm)			
median	134.4	130.6	134.5
full range (min-max)	134.4 to 134.4	130.6 to 130.6	125.5 to 143.4

Weight (kg)			
Patient weight in kilograms.			
Units: Kilograms			
median	41.8	23.2	37.9
full range (min-max)	41.8 to 41.8	23.2 to 23.2	25.1 to 50.6
Days since first seizure			
Difference in days since first seizure from date of randomization.			
Units: Days before randomization			
median	1098	1128.5	124
full range (min-max)	1098 to 1098	1128.5 to 1128.5	80 to 168
Days since first rolandic seizure			
Difference in days since first rolandic seizure from date of randomization. For the Levetiracetam & Sleep Intervention arm, data was only available for 1/2 patients.			
Units: Days before randomization			
median	1098	1128.5	168
full range (min-max)	1098 to 1098	1128.5 to 1128.5	168 to 168
Days since most recent seizure			
Difference in days since most recent seizure from date of randomization.			
Units: Days before randomization			
median	7	7	74
full range (min-max)	7 to 7	7 to 7	3 to 145
Days since rolandic Epilepsy diagnosis			
Difference in days since rolandic Epilepsy diagnosis to date of randomization.			
Units: Days before randomization			
median	763	0	184
full range (min-max)	763 to 763	0 to 0	95 to 273

Reporting group values	LEV & no sleep intervention		
Number of subjects	1		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	1		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
median	7		
full range (min-max)	7 to 7		
Gender categorical			
Units: Subjects			
Female	0		
Male	1		

Did the patient have any seizures in the first month of life? Units: Subjects			
Yes	0		
No	1		
Unknown	0		
After the first month of life and before epilepsy, did the patient ever have seizures with fever?			
Full text is "After the first month of life and before developing epilepsy, did the patient ever have seizures or convulsions with fever?".			
Units: Subjects			
Yes	0		
No	1		
Unknown	0		
How many seizures has the patient had in total since onset? Units: Subjects			
One	0		
Two to Four	0		
Five to Ten	0		
More than Ten	1		
Unknown	0		
Has the patient ever had seizures lasting more than 10 minutes or had several seizures in a row? Units: Subjects			
Yes	0		
No	1		
Unknown	0		
Has the patient ever had a generalised tonic-clonic seizure or convulsion? (Text continued below)			
Has the patient ever had a generalised tonic-clonic seizure or convulsion since being diagnosed with Childhood Epilepsy with Centrotemporal Spikes aka Benign Rolandic Epilepsy?			
Units: Subjects			
Yes	0		
No	1		
Unknown	0		
Do the patient’s seizures occur at particular times of the day? Units: Subjects			
Yes	1		
No	0		
Unknown	0		
Do seizures usually occur soon after going to sleep? Units: Subjects			
Yes	1		
No	0		
Unknown	0		
Do seizures usually occur early in the morning? Units: Subjects			
Yes	0		

No	1		
Unknown	0		
Do seizures usually occur during a day time nap? Units: Subjects			
Yes	0		
No	1		
Unknown	0		
Noticeable features in a typical seizure: Drooping of one side of the face Units: Subjects			
Yes	0		
No	1		
Unknown	0		
Noticeable features in a typical seizure: Gurgling noise from the throat Units: Subjects			
Yes	0		
No	1		
Unknown	0		
Noticeable features in a typical seizure: Unable to speak Units: Subjects			
Yes	1		
No	0		
Unknown	0		
Noticeable features in a typical seizure: Drooling a lot from the mouth Units: Subjects			
Yes	0		
No	1		
Unknown	0		
Noticeable features in a typical seizure: Aware during the seizure Units: Subjects			
Yes	0		
No	1		
Unknown	0		
Other noticeable features during a seizure: Tingling of tongue and lips Units: Subjects			
Yes	0		
No	0		
Unknown	1		
Other noticeable features during a seizure: Vomiting, numb hands, pallor (white face) Units: Subjects			
Yes	0		
No	0		
Unknown	1		
Other noticeable features during a seizure: Eye rolling, jerking of both arms Units: Subjects			

Yes	1		
No	0		
Unknown	0		
Other noticeable features during a seizure: Facial twitches Units: Subjects			
Yes	0		
No	0		
Unknown	1		
Height (cm)			
Patient height in centimetres.			
Units: Centimetres (cm)			
median	121		
full range (min-max)	121 to 121		
Weight (kg)			
Patient weight in kilograms.			
Units: Kilograms			
median	24.4		
full range (min-max)	24.4 to 24.4		
Days since first seizure			
Difference in days since first seizure from date of randomization.			
Units: Days before randomization			
median	105		
full range (min-max)	105 to 105		
Days since first rolandic seizure			
Difference in days since first rolandic seizure from date of randomization. For the Levetiracetam & Sleep Intervention arm, data was only available for 1/2 patients.			
Units: Days before randomization			
median	105		
full range (min-max)	105 to 105		
Days since most recent seizure			
Difference in days since most recent seizure from date of randomization.			
Units: Days before randomization			
median	4		
full range (min-max)	4 to 4		
Days since rolandic Epilepsy diagnosis			
Difference in days since rolandic Epilepsy diagnosis to date of randomization.			
Units: Days before randomization			
median	19		
full range (min-max)	19 to 19		

End points

End points reporting groups

Reporting group title	No AED & sleep intervention
Reporting group description:	
No Anti-Epileptic Drug (AED) and sleep behavior intervention	
Reporting group title	CBZ & sleep intervention
Reporting group description:	
Carbamazepine (CBZ) & sleep behavior intervention	
Reporting group title	LEV & sleep intervention
Reporting group description:	
Levetiracetam (LEV) and sleep behavior intervention	
Reporting group title	LEV & no sleep intervention
Reporting group description:	
Levetiracetam (LEV) and no sleep behavior intervention (standard care)	
Subject analysis set title	No AED & sleep intervention
Subject analysis set type	Full analysis
Subject analysis set description:	
This analysis set includes all patients randomized to No AED & the sleep intervention	
Subject analysis set title	CBZ & sleep intervention
Subject analysis set type	Full analysis
Subject analysis set description:	
This analysis set contains all patients randomized to Carbamazepine & sleep intervention.	
Subject analysis set title	LEV & sleep intervention
Subject analysis set type	Full analysis
Subject analysis set description:	
This analysis set contains all patients randomized to Levetiracetam & sleep intervention.	
Subject analysis set title	LEV & no sleep intervention
Subject analysis set type	Full analysis
Subject analysis set description:	
This analysis set contains all patients randomized to Levetiracetam & no sleep intervention (standard of care).	

Primary: Primary outcome 1: Time to 6-month seizure remission

End point title	Primary outcome 1: Time to 6-month seizure remission[1]
End point description:	
This endpoint was not reached for all 5 participants and no analysis could be performed.	
End point type	Primary
End point timeframe:	
Anytime from days since randomization until date of last follow-up.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to only 5 participants being recruited for the trial, no statistical analysis could be performed only summary statistics could be provided.

End point values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention	LEV & no sleep intervention
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	2	1
Units: Days since randomization				
median (full range (min-max))	187.0 (187.0 to 187.0)	112.0 (112.0 to 112.0)	128.5 (86.0 to 171.0)	192.0 (192.0 to 192.0)

Statistical analyses

No statistical analyses for this end point

Primary: Primary outcome 2: Total sleep problem scores as measured by the CSHQ (at 3 months)

End point title	Primary outcome 2: Total sleep problem scores as measured by the CSHQ (at 3 months)[2]

End point description:

This outcome is looking at scores and completion rates from the Child Sleep Habit Questionnaire (CSHQ).

A score of 0 represents the questionnaire not being filled in.

End point type	Primary

End point timeframe:

The sleep score questionnaire is completed at baseline and 3 month study visit.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to only 5 participants being recruited for the trial, no statistical analysis could be performed only summary statistics could be provided.

End point values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention	LEV & no sleep intervention
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1[3]	2[4]	1
Units: Sleep scores				
median (full range (min-max))				
CSHQ Score at Baseline	90 (90 to 90)	45 (45 to 45)	78.5 (78 to 79)	49 (49 to 49)
CSHQ Score at 3 Months	90 (90 to 90)	0 (0 to 0)	83 (83 to 83)	53 (53 to 53)

Notes:

[3] - The 3 month score was not completed for this patient.

[4] - This data is present for both patients at baseline, but only 1 at the 3 month time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary outcome 1: Time to treatment failure due to inadequate seizure control or unacceptable adverse reactions

End point title	Secondary outcome 1: Time to treatment failure due to inadequate seizure control or unacceptable adverse reactions

End point description:

This endpoint was not reached for any of the 5 patients on the trial, meaning no analysis could be performed and only the median(min-max) time of last patient follow-up in days is presented.

End point type	Secondary

End point timeframe:

Anytime from randomization until date of last patient follow-up.

End point values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention	LEV & no sleep intervention
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	2	1
Units: Days since randomization				
median (full range (min-max))	187.0 (187.0 to 187.0)	112.0 (112.0 to 112.0)	128.5 (86.0 to 171.0)	192.0 (192.0 to 192.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary outcome 2: Time to treatment failure due to inadequate seizure control

End point title	Secondary outcome 2: Time to treatment failure due to inadequate seizure control

End point description:

This endpoint was not reached for any of the 5 patients on the trial, meaning no analysis could be performed so only median (min-max) time to last patient follow-up is presented for this outcome.

End point type	Secondary

End point timeframe:

Anytime from randomization until date of last patient follow-up.

End point values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention	LEV & no sleep intervention
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	2	1
Units: Days since randomization				
median (full range (min-max))	187.0 (187.0 to 187.0)	112.0 (112.0 to 112.0)	128.5 (86.0 to 171.1)	192.0 (192.0 to 192.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary outcome 3: Time to treatment failure due to unacceptable adverse reactions

End point title	Secondary outcome 3: Time to treatment failure due to unacceptable adverse reactions

End point description:

This endpoint was not reached for any of the 5 patients on the trial, meaning no analysis could be performed so only the median (min-max) time to last patient follow-up is presented in days for this outcome.

End point type	Secondary

End point timeframe:

Anytime from randomization until date of last patient follow-up.

End point values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention	LEV & no sleep intervention
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	2	1
Units: Days since randomization				
median (full range (min-max))	187.0 (187.0 to 187.0)	112.0 (112.0 to 112.0)	128.5 (86.0 to 171.0)	192.0 (192.0 to 192.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary outcome 4: Time to first seizure

End point title	Secondary outcome 4: Time to first seizure

End point description:

This endpoint is the time in days until the patient has their first seizure since randomization.

Only 3 patients reported seizures after randomization.

End point type	Secondary

End point timeframe:

Anytime from randomization until last patient follow-up date.

End point values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention	LEV & no sleep intervention
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	0[5]	1
Units: Days since randomization				
median (full range (min-max))	17.0 (17.0 to 17.0)	35.0 (35.0 to 35.0)	(to)	80.0 (80.0 to 80.0)

Notes:

[5] - None of the patients in this arm had a seizure after randomization.

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary outcome 5: Time to 12-month remission from seizures

End point title	Secondary outcome 5: Time to 12-month remission from seizures

End point description:

None of the patients had 12 month seizure remission so this endpoint could not be analysed, only the median (min-max) time in days to last patient follow-up is presented.

End point type	Secondary

End point timeframe:

Anytime from randomization until last patient follow-up.

End point values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention	LEV & no sleep intervention
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	2	1
Units: Days since randomization				
median (full range (min-max))	187.0 (187.0 to 187.0)	112.0 (112.0 to 112.0)	128.5 (86.0 to 171.0)	192.0 (192.0 to 192.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary outcome 6: Total sleep problem score on CSHQ at 12 months since randomization

End point title	Secondary outcome 6: Total sleep problem score on CSHQ at 12 months since randomization

End point description:

No patients on the study met the 12-month time point before the trial was closed prematurely so this endpoint could not be analysed.

End point type	Secondary

End point timeframe:

Captured at 12 months from randomization.

End point values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention	LEV & no sleep intervention
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[6]	0[7]	0[8]	0[9]
Units: Sleep scores				
median (full range (min-max))	(to)	(to)	(to)	(to)

Notes:

[6] - No patients reached the 12-month time point in the trial prior to it being closed prematurely.

[7] - No patients reached the 12-month time point in the trial prior to it being closed prematurely.

[8] - No patients reached the 12-month time point in the trial prior to it being closed prematurely.

[9] - No patients reached the 12-month time point in the trial prior to it being closed prematurely.

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary outcome 7: Cognition (CANTAB)

End point title	Secondary outcome 7: Cognition (CANTAB)

End point description:

CANTAB total scores are provided in three chosen assessments delivered by CANTAB iPad Neuropsychological battery.
CANTAB was only completed at the 3 month visit for 1 patient, and only the Motor Screening Task (MOT) scores were provided. This was only a warm up screen test.

End point type	Secondary

End point timeframe:

This outcome is measured at baseline, 3 and 12 months post randomization.

End point values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[10]	0[11]	1[12]	
Units: CANTAB Score				
median (full range (min-max))				
MOTML score at 3 months	(to)	(to)	696.1 (696.1 to 696.1)	
MOTSDL score at 3 months	(to)	(to)	112.2 (112.2 to 112.2)	
MOTTC score at 3 months	(to)	(to)	10 (10 to 10)	
MOTTE score at 3 months	(to)	(to)	0 (0 to 0)	

Notes:

[10] - No CANTAB data was collected for this patient at 3 months.

[11] - No CANTAB data was collected for this patient at 3 months.

[12] - CANTAB data was only collected for one of the two patients in this arm at 3 months.

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary outcome 8: Health related quality of life

End point title	Secondary outcome 8: Health related quality of life

End point description:

The CHEQOL score is derived by totaling the scores provided on the Child Health-related Quality of Life CRF at each time point.

None of the patients reached the 12-month time point on the trial before it closed prematurely, so this endpoint could not be analysed.

End point type	Secondary

End point timeframe:

This is completed at baseline and 12 months post randomization.

End point values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention	LEV & no sleep intervention
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[13]	0[14]	0[15]	0[16]
Units: CHEQOL score totals				
median (full range (min-max))	(to)	(to)	(to)	(to)

Notes:

[13] - No patients reached the 12-month time point in the trial prior to it being closed prematurely.

[14] - No patients reached the 12-month time point in the trial prior to it being closed prematurely.

[15] - No patients reached the 12-month time point in the trial prior to it being closed prematurely.

[16] - No patients reached the 12-month time point in the trial prior to it being closed prematurely.

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary outcome 9: To compare measures of children’s behaviour across the different treatment groups

End point title	Secondary outcome 9: To compare measures of children’s behaviour across the different treatment groups

End point description:

Scores from the Strengths and Difficulties Questionnaire (SDQ).
The 12-month time point was not reached for any of the patients on the trial prior to the trial closing prematurely, so no analysis could be performed for this outcome.

End point type	Secondary

End point timeframe:

Completed at baseline and 12 months post randomization.

End point values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention	LEV & no sleep intervention
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[17]	0[18]	0[19]	0[20]
Units: Strengths and Difficulties score				
median (full range (min-max))	(to)	(to)	(to)	(to)

Notes:

[17] - No patients reached the 12-month time point in the trial prior to it being closed prematurely.

[18] - No patients reached the 12-month time point in the trial prior to it being closed prematurely.

[19] - No patients reached the 12-month time point in the trial prior to it being closed prematurely.

[20] - No patients reached the 12-month time point in the trial prior to it being closed prematurely.

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary outcome 10: To identify any adverse reactions

End point title	Secondary outcome 10: To identify any adverse reactions

End point description:

This is a descriptive analysis and details of adverse reactions can also be found under the "Adverse Events" section. Only adverse reactions were reported for this study., but all serious adverse events were reported also, however there were no serious adverse events on the trial.

End point type	Secondary

End point timeframe:

Anytime from randomization until last patient follow-up date.

End point values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention	LEV & no sleep intervention
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[21]	0[22]	1[23]	0[24]
Units: Number of adverse reactions				
number (not applicable)				
Number of adverse reactions			5	

Notes:

[21] - There are no adverse reactions reported for this patient.

[22] - There are no adverse reactions reported for this patient.

[23] - Only one patient in this arm reported adverse reactions.

[24] - There are no adverse reactions reported for this patient.

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary outcome 11: Sickness related school absences

End point title	Secondary outcome 11: Sickness related school absences

End point description:

This outcome reports the total number of reported sickness related school absences (days).

End point type	Secondary

End point timeframe:

Anytime from randomization until date of last patient follow-up.

End point values	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention	LEV & no sleep intervention
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1[25]	2[26]	1[27]
Units: Number of reported sickness days				
number (not applicable)				
Number of reported sick days at 3 months	0	0	0	0
Number of reported sick days at 6 months	0	0	0	0
Number of sick days missing at 3 months	0	1	1	1
Number of sick days missing at 6 months	0	0	0	0

Notes:

[25] - This patient withdrew after 3 months.

[26] - One patient in this arm withdrew after 3 months, the second only reported this data at 6 months.

[27] - The data for this participant at 3 months was missing, only the 6 month time point is provided.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Anytime from randomization until date of last patient follow-up.

Adverse event reporting additional description:

All serious adverse events were reported for CASTLE, and only adverse events related to participant's treatment with one of the CASTLE IMPs (carbamazepine or levetiracetam) were reported, assessed by PI. Collection method for all AEs was at each visit and the participant would be asked about adverse events and medical notes would also be reviewed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	No AED & sleep intervention

Reporting group description:

Patients randomized to no anti-epileptic drug and the sleep intervention.

Reporting group title	CBZ & sleep intervention

Reporting group description:

Patients randomized to Carbamazepine and the sleep intervention.

Reporting group title	LEV & sleep intervention

Reporting group description:

Patients who were randomized to Levetiracetam and the sleep intervention.

Reporting group title	LEV & no sleep intervention

Reporting group description:

Patients randomized to Levetiracetam and no sleep intervention (standard care).

Serious adverse events	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	LEV & no sleep intervention		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	No AED & sleep intervention	CBZ & sleep intervention	LEV & sleep intervention
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 2 (50.00%)
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Moody			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
worsening behaviour			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Infections and infestations			
Cold			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1

Non-serious adverse events	LEV & no sleep intervention		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Moody			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
worsening behaviour			

subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Infections and infestations Cold subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2019	Protocol version 2.0. This amendment to the protocol contained the addition of some new primary and secondary outcomes and the re-wording of some existing outcomes. The data collection processes were updated, in line with the amended outcomes. There were also updates to other study processes included in the document, such as safety/death reporting and retention/storage of data at the end of the trial. Clarification around obtaining consent and the actigraphy and qualitative interview activities was added to the protocol as part of this amendment.
18 August 2020	Protocol Version 3.0 (finalized on 18/08/2020). This amendment to the protocol detailed the processes in the event of an early trial termination, including reduced length of follow up and procedure for EEG review. There was also an update to the SmPC information included in the document, namely the update of the Carbamazepine SmPC name, following the discontinuation of the original IMP brand, and the inclusion of liquid/syrup formulations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 March 2020	The trial was halted due to the COVID-19 outbreak and all sites were closed for recruitment. The trial was never re-opened due to poor recruitment, with the global trial end date being 23/09/2020.	-

Notes:

Limitations and caveats

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

Early termination of the trial meant there were only 5 patients recruited into this trial, so many of the powered analyses specified in the protocol could not go ahead.

Notes: