Clinical trial results:
A Multicenter, Open-Label, Randomized, Active Comparator Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Lacosamide in Neonates With Repeated Electroencephalographic Neonatal Seizures

Summary

EudraCT number	2020-001066-10
Trial protocol	Outside EU/EEA
Global end of trial date	17 April 2025

Results information

Result version number	v1 (current)
This version publication date	29 October 2025
First version publication date	29 October 2025

Trial information

Trial identification

Sponsor protocol code	SP0968

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04519645
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Biopharma SRL
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, 1070
Public contact	UCB BIOSCIENCES GmbH, Clin Trial Reg & Results Disclosure, clinicaltrials@ucb.com
Scientific contact	UCB BIOSCIENCES GmbH, Clin Trial Reg & Results Disclosure, clinicaltrials@ucb.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000402-PIP03-17
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 April 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 August 2024
Global end of trial reached?	Yes
Global end of trial date	17 April 2025
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to evaluate the efficacy of lacosamide (LCM) versus an Active Comparator chosen based on standard of care (StOC) in severe and nonsevere seizure burden (defined as total minutes of electroencephalographic neonatal seizures (ENS) per hour) in neonates with seizures that are not adequately controlled with previous anti-epileptic drug (AED) treatment.

Protection of trial subjects:

During the conduct of the study all participants were closely monitored.

Background therapy: -

Evidence for comparator:

The local standard of care was employed as comparator.

Actual start date of recruitment	31 March 2021
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	Australia: 1
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	29
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)	29
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
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:

The study started enrollment in March 2021 and concluded in October 2024. The decision to end the study prematurely was made by the Sponsor in April 2025. During Enrollment Period: 11 randomized participants started and completed Active Comparator (AC) arm and 15 randomized participants started and completed lacosamide (LCM) arm.

Pre-assignment

Screening details:

Participant Flow refers to the Safety Set (based on treatment received). For the Full Analysis Set (based on treatment assignment, 1 participant randomized to LCM received AC): 10/11 participants randomized to AC and 15/15 randomized to LCM completed the treatment period. All participants from the Treatment Period entered/completed the SFU Period.

Period 1

Period 1 title	Enrollment Period (Up to 36 hours)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	No Treatment

Arm description:

Participant signed the informed consent form, successfully screened and randomized but never received any study medication during the study.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Active Comparator

Arm description:

Study participants randomized to receive Active Comparator (chosen and dosed based on standard of care (StOC) per local practice and treatment guidelines) in the Treatment Period. After the Treatment Period, study participants had the option to continue to receive randomized Active Comparator in the Extension Period (up to 28 days of postnatal age). Study participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day Safety Follow-up (SFU) Period with optional down titration.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Lacosamide

Arm description:

Study participants randomized to receive lacosamide 10 milligram per milliliter (mg/mL) 3 times a day as an intravenous infusion over 30 minutes for up to 96 hours in the Treatment Period. After the Treatment Period, study participants had the option to continue to receive randomized lacosamide in the Extension Period (up to 28 days of postnatal age), being switched to oral dosing of lacosamide as soon as medically possible. Study participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day SFU Period with optional down titration.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	No Treatment	Active Comparator	Lacosamide
Started	3	12	14
Completed	0	12	14
Not completed	3	0	0
Adverse event, non-fatal	1	-	-
Withdrawal by Parent/Guardian	1	-	-
Protocol deviation	1	-	-

Period 2

Period 2 title	Treatment Period (Up to 96 hours)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[2]

Arms

Are arms mutually exclusive?	Yes
Arm title	Active Comparator

Arm description:

Study participants randomized to receive Active Comparator (chosen and dosed based on StOC per local practice and treatment guidelines) in the Treatment Period. After the Treatment Period, study participants had the option to continue to receive randomized Active Comparator in the Extension Period (up to 28 days of postnatal age). Study participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day SFU Period with optional down titration.

Arm type	Active comparator
Investigational medicinal product name	Active Comparator
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intravenous use

Dosage and administration details:

Active Comparator treatment was chosen and dosed based on StOC (per local practice and treatment guidelines).

Arm title	Lacosamide

Arm description:

Study participants randomized to receive lacosamide 10 milligram per milliliter (mg/mL) 3 times a day as an intravenous infusion over 30 minutes for up to 96 hours in the Treatment Period. After the Treatment Period, study participants had the option to continue to receive randomized lacosamide in the Extension Period (up to 28 days of postnatal age), being switched to oral dosing of lacosamide as soon as medically possible. Study participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day SFU Period with optional down titration.

Arm type	Experimental

Investigational medicinal product name	Lacosamide
Investigational medicinal product code	
Other name	LCM
Pharmaceutical forms	Solution for infusion, Oral solution
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Participants received lacosamide 10 mg/mL as an intravenous (IV) infusion up to 96 hours of Treatment Period. Study participants who remain inpatient and who benefit from the LCM treatment may continue LCM if able to switch to oral LCM in the Extension Period (up to 28 days of postnatal age). Study participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day SFU Period with optional down titration.

Notes:

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

Justification: Data cannot be reported for 3 participants due to data protection/data privacy.

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This is an open label study however, central readers for the EEG were blinded.

Number of subjects in period 2[3]	Active Comparator	Lacosamide
Started	12	14
Safety Set (Actual Treated)	12	14
Completed	11	14
Not completed	1	0
Consent withdrawn by parent/guardian,not due to AE	1	-

Notes:

[3] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 29 participants were screened and enrolled in this study but only 26 participants were treated.

Period 3

Period 3 title	Extension Period: up to 28 Days of PNA
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[4]

Arms

Arm title	Lacosamide

Arm description:

Study participants randomized to receive lacosamide 10 mg/mL 3 times a day as an intravenous infusion over 30 minutes for up to 96 hours in the Treatment Period. After the Treatment Period, study participants had the option to continue to receive randomized lacosamide in the Extension Period (up to 28 days of postnatal age), being switched to oral dosing of lacosamide as soon as medically possible. Study participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day SFU Period with optional down titration.

Arm type	Experimental
Investigational medicinal product name	Lacosamide
Investigational medicinal product code	
Other name	LCM
Pharmaceutical forms	Solution for infusion, Oral solution
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Participants received lacosamide 10 mg/mL as an intravenous (IV) infusion up to 96 hours of Treatment Period. Study participants who remain inpatient and who benefit from the LCM treatment may continue LCM if able to switch to oral LCM in the Extension Period (up to 28 days of postnatal age). Participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day SFU Period with optional down titration.

Notes:

[4] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This is an open label study however, central readers for the EEG were blinded.

Number of subjects in period 3[5]	Lacosamide
Started	12
Completed	12

Notes:

[5] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Out of 15 randomized participants who completed the Treatment Period, 12 participants opted to continue in the Extension Period.

Baseline characteristics

Reporting groups	
Reporting group title	Active Comparator
Reporting group description:	
Study participants randomized to receive Active Comparator (chosen and dosed based on StOC per local practice and treatment guidelines) in the Treatment Period. After the Treatment Period, study participants had the option to continue to receive randomized Active Comparator in the Extension Period (up to 28 days of postnatal age). Study participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day SFU Period with optional down titration.	
Reporting group title	Lacosamide
Reporting group description:	
Study participants randomized to receive lacosamide 10 milligram per milliliter (mg/mL) 3 times a day as an intravenous infusion over 30 minutes for up to 96 hours in the Treatment Period. After the Treatment Period, study participants had the option to continue to receive randomized lacosamide in the Extension Period (up to 28 days of postnatal age), being switched to oral dosing of lacosamide as soon as medically possible. Study participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day SFU Period with optional down titration.	

Reporting group values	Active Comparator	Lacosamide	Total
Number of subjects	12	14	26
Age Categorical Units: participants			
0-<=27 days	12	14	26
Age Continuous Units: days			
arithmetic mean	3.1	4.1	
standard deviation	± 2.8	± 5.0	-
Sex: Female, Male Units: participants			
Female	7	7	14
Male	5	7	12

End points

End points reporting groups

Reporting group title	No Treatment

Reporting group description:

Participant signed the informed consent form, successfully screened and randomized but never received any study medication during the study.

Reporting group title	Active Comparator

Reporting group description:

Study participants randomized to receive Active Comparator (chosen and dosed based on standard of care (StOC) per local practice and treatment guidelines) in the Treatment Period. After the Treatment Period, study participants had the option to continue to receive randomized Active Comparator in the Extension Period (up to 28 days of postnatal age). Study participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day Safety Follow-up (SFU) Period with optional down titration.

Reporting group title	Lacosamide

Reporting group description:

Study participants randomized to receive lacosamide 10 milligram per milliliter (mg/mL) 3 times a day as an intravenous infusion over 30 minutes for up to 96 hours in the Treatment Period. After the Treatment Period, study participants had the option to continue to receive randomized lacosamide in the Extension Period (up to 28 days of postnatal age), being switched to oral dosing of lacosamide as soon as medically possible. Study participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day SFU Period with optional down titration.

Reporting group title	Active Comparator

Reporting group description:

Study participants randomized to receive Active Comparator (chosen and dosed based on StOC per local practice and treatment guidelines) in the Treatment Period. After the Treatment Period, study participants had the option to continue to receive randomized Active Comparator in the Extension Period (up to 28 days of postnatal age). Study participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day SFU Period with optional down titration.

Reporting group title	Lacosamide

Reporting group description:

Study participants randomized to receive lacosamide 10 milligram per milliliter (mg/mL) 3 times a day as an intravenous infusion over 30 minutes for up to 96 hours in the Treatment Period. After the Treatment Period, study participants had the option to continue to receive randomized lacosamide in the Extension Period (up to 28 days of postnatal age), being switched to oral dosing of lacosamide as soon as medically possible. Study participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day SFU Period with optional down titration.

Reporting group title	Lacosamide

Reporting group description:

Study participants randomized to receive lacosamide 10 mg/mL 3 times a day as an intravenous infusion over 30 minutes for up to 96 hours in the Treatment Period. After the Treatment Period, study participants had the option to continue to receive randomized lacosamide in the Extension Period (up to 28 days of postnatal age), being switched to oral dosing of lacosamide as soon as medically possible. Study participants (whether they discontinued randomized treatment during the Treatment Period, completed the Extension Period, were discharged from the hospital, or reached 28 days of postnatal age) then entered the 14-day SFU Period with optional down titration.

Subject analysis set title	Lacosamide
Subject analysis set type	Full analysis

Subject analysis set description:

Study participants randomized to receive lacosamide 10 milligram per milliliter (mg/mL) 3 times a day as an intravenous infusion over 30 minutes for up to 96 hours. The dose of LCM could be reduced based on clinical judgement of the investigator after the first dose Study participants who remain inpatient and who benefit from the LCM treatment may continue LCM if able to switch to oral LCM in the Extension Period. One participant was randomized to lacosamide but actually received Active Comparator. Therefore, based on randomization assignment, 15 participants are in the LCM arm in the full analysis

set.

Primary: Change in Seizure Burden Measured in the Evaluation Video-electroencephalogram (video-EEG) Compared with the Baseline Video-EEG

End point title	Change in Seizure Burden Measured in the Evaluation Video-electroencephalogram (video-EEG) Compared with the Baseline Video-EEG[1]

End point description:

Baseline seizure burden=seizure burden measured on continuous video-EEG (total electroencephalographic neonatal seizures (ENS) in minutes per hour) during period of up to 2 hours immediately prior to 1st administration of study drug. ENS= EEG seizure lasting for at least 10 seconds on video-EEG. Seizure burden in Evaluation Period= total duration of seizures between 1 and 3 hours after 1st dose of study medication divided by duration of interpretable video-EEG available in same period. Change in seizure burden measured in Evaluation video-EEG compared with Baseline video-EEG was analyzed such that positive value= reduction in seizure burden from baseline. Full Analysis Set (FAS) consisted of all study participants in SS who had minimum of 30 minutes of interpretable video-EEG data from both Baseline and period between 1 and 3 hours (Evaluation Period) after randomization to initial study medication treatment."N"= participants evaluable for this assessment. FAS=randomized treatment.

End point type	Primary

End point timeframe:

During 2-hour Evaluation starting 1 hour after initial treatment (up to 2 hours), compared to Baseline

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: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Active Comparator	Lacosamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	11		
Units: minute per hour (min/hour)				
arithmetic mean (standard deviation)	2.45 (± 14.83)	6.64 (± 6.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at least 80% Reduction in Seizure Burden in the Evaluation a Video-EEG Compared with the Baseline Video-EEG

End point title	Percentage of Participants With at least 80% Reduction in Seizure Burden in the Evaluation a Video-EEG Compared with the Baseline Video-EEG[2]

End point description:

A responder is defined as a study participant who achieved the following reduction in seizure burden without need for rescue medication, compared with the seizure burden measured during the Baseline Period immediately prior to investigational medicinal product (IMP) administration, evaluated for a 2-hour period starting 1 hour after the start of initial treatment: A reduction in seizure burden from Baseline of >=80% regardless of baseline seizure severity. Percentage of Participants With at least 80% Reduction in Seizure Burden in the Evaluation (starting 1 hour after treatment) of a Video-EEG Compared with the Baseline Video-EEG were reported. The FAS was used, and the population was based on randomized treatment.

End point type	Secondary

End point timeframe:

During 2-hour Evaluation starting 1 hour after initial treatment (up to 2 hours), compared to Baseline

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Active Comparator	Lacosamide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	15		
Units: percentage of participants				
number (not applicable)	44.4	60.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response Across the 48-hour Treatment Period Compared with the Baseline Video-EEG

End point title	Time to Response Across the 48-hour Treatment Period Compared with the Baseline Video-EEG[3]

End point description:

Time to response where response was defined as a reduction in seizure burden from Baseline of at least 80% in participants with non-severe seizure burden, and of at least 50% for participants with severe seizure burden. Time to response was censored at the date/time the participant received rescue medication or stopped video-EEG monitoring, or otherwise at the end of the 48-hour period. The FAS was used, and population was based on randomized treatment. Here, 99999 and -99999 refers to upper and lower limits of 95% confidence interval could not be calculated by the Kaplan-Meier model due to heavy censoring occurring before the median survival time was observed and a lack of variability in the response times (9/10 patients reported the same time to response).

End point type	Secondary

End point timeframe:

Across the first 48 hours of Treatment Period, compared to Baseline

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Active Comparator	Lacosamide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	15		
Units: hours				
median (confidence interval 95%)	3.0 (3.0 to 8.0)	3.0 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Responders in the Evaluation Video-EEG Compared with the Baseline Video-EEG

End point title	Percentage of Responders in the Evaluation Video-EEG Compared with the Baseline Video-EEG[4]

End point description:

A responder is defined as a study participant who achieved the following reduction in seizure burden without need for rescue medication, compared with the seizure burden measured during the Baseline Period immediately prior to the study medication administration, evaluated for a 2-hour period starting 1 hour after the start of initial treatment: − At least 80% reduction of seizure burden in participants who were categorized by the Investigator as having non-severe seizure burden during Baseline OR − At least 50% reduction of seizure burden in participants who were categorized by the Investigator as having severe seizure burden during Baseline. The FAS was used, and population was based on randomized treatment.

End point type	Secondary

End point timeframe:

During 2-hour Evaluation starting 1 hour after initial treatment (up to 2 hours), compared to Baseline

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Active Comparator	Lacosamide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	15		
Units: percentage of participants				
number (not applicable)	66.7	60.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Seizure Burden Across the First 48-hours of the Treatment Period Measured by Continuous Video-EEG Compared With the Baseline Video-EEG

End point title	Absolute Change in Seizure Burden Across the First 48-hours of the Treatment Period Measured by Continuous Video-EEG Compared With the Baseline Video-EEG

End point description:

Baseline seizure burden=total duration of seizures (in minutes) between -2 and 0 hours before first dose of study medication divided by total duration of interpretable video-EEG(in hours) in same period. Seizure burden for 8,16,24,32,40 and 48 hour time points= total duration of seizures in hour prior to time point divided by duration of interpretable video-EEG available in same period. If <30 minutes of interpretable video-EEG were available in 1 hour prior to time point, response=seizure burden for most recent 30 minutes of interpretable video-EEG in 2 hours(8 and 16 hour points)or 4 hours(24, 32, 40 and 48 hour points)prior to time point. 30 minutes of video-EEG did not need to be continuous.Absolute reduction in seizure burden for these time points=seizure burden in Baseline Period minus seizure burden at that time point. FAS was used, and population was based on randomized treatment."N"= participants evaluable for this assessment;n=participants evaluable at specified timepoints.

End point type	Secondary

End point timeframe:

Treatment Period: 7-8 hours, 15-16 hours, 23-24 hours, 31-32 hours, 39-40 hours, 47-48 hours,

End point values	Active Comparator	Lacosamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	11		
Units: mins/hour				
arithmetic mean (standard deviation)				
Treatment, 7 hour - 8 hour (n=6,11)	-2.74 (± 15.53)	6.30 (± 6.74)		
Treatment, 15 hour - 16 hour (n=6,10)	3.63 (± 5.28)	7.21 (± 6.33)		
Treatment, 23 hour - 24 hour (n=6,10)	5.08 (± 4.81)	8.69 (± 8.06)		
Treatment, 31 hour - 32 hour (n=5, 10)	5.71 (± 5.09)	8.93 (± 8.56)		
Treatment, 39 hour - 40 hour (n=4, 10)	4.43 (± 5.80)	8.93 (± 8.56)		
Treatment, 47 hour - 48 hour (n=4,10)	4.84 (± 5.44)	8.93 (± 8.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Seizure Freedom Across the First 48-hour Treatment Period Compared with the Baseline Video-EEG

End point title	Time to Seizure Freedom Across the First 48-hour Treatment Period Compared with the Baseline Video-EEG[5]

End point description:

Seizure freedom was defined as 0 minutes of seizures in a 1-hour period (or 2-hour period for the 3-hour time point) and was analyzed across the 48 hours. The time to seizure freedom was measured in hours, defined as the first time point when the response criterion was met minus the date and time of the first dose of randomized study medication administration. Time to seizure freedom was censored at the time of receiving rescue medication, stopping video-EEG monitoring or otherwise at 48 hours after first dose. The FAS was used, and population was based on randomized treatment. Here, 99999 and -99999 refers to upper and lower limits of 95% confidence interval could not be calculated by the Kaplan-Meier model due to heavy censoring occurring before the median survival time was observed and a lack of variability in the response times (4/6 participants [Active Comparator] and 9/10 participants [Lacosamide]) reported the same time to seizure freedom).

End point type	Secondary

End point timeframe:

Across the first 48 hours of Treatment Period, compared to Baseline

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Active Comparator	Lacosamide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	15		
Units: hours				
median (confidence interval 95%)	8.0 (3.0 to 99999)	3.0 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Seizure Burden Across the First 48-hours of the Treatment Period Measured by Continuous Video-EEG Compared with the Baseline Video-EEG

End point title	Percent Change in Seizure Burden Across the First 48-hours of the Treatment Period Measured by Continuous Video-EEG Compared with the Baseline Video-EEG

End point description:

The percent change in seizure burden for the 8, 16, 24, 32, 40 and 48 hour time points was calculated as the seizure burden at Baseline minus the seizure burden at the respective time point, divided by the seizure burden in the Baseline Period, multiplied by 100. Percent change in seizure burden was analyzed such that a positive value indicates a reduction in seizure burden from baseline. FAS was used, and population was based on randomized treatment. Here, "N" included all participants who were evaluable for this assessment and n signifies participants who were evaluable at specified timepoints.

End point type	Secondary

End point timeframe:

Treatment Period: 7-8 hours, 15-16 hours, 23-24 hours, 31-32 hours, 39-40 hours, 47-48 hours, compared to Baseline

End point values	Active Comparator	Lacosamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	11		
Units: percent change				
arithmetic mean (standard deviation)				
Treatment: 7 hour-8 hour (n=6,11)	39.85 (± 147.33)	80.92 (± 45.56)		
Treatment: 15 hour-16 hour (n=6,10)	48.22 (± 116.94)	93.19 (± 21.53)		
Treatment: 23 hour-24 hour (n=6,10)	100.00 (± 0.00)	99.03 (± 3.05)		
Treatment: 31 hour-32 hour (n=5,10)	100.00 (± 0.00)	100.00 (± 0.00)		
Treatment: 39 hour-40 hour (n=4,10)	77.13 (± 45.73)	100.00 (± 0.00)		
Treatment: 47 hour-48 hour (n=4,10)	100.00 (± 0.00)	100.00 (± 0.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Categorized Percentage of Participants With Change in Seizure Burden in the Evaluation Video-EEG Compared With the Baseline Video-EEG

End point title	Categorized Percentage of Participants With Change in Seizure Burden in the Evaluation Video-EEG Compared With the Baseline Video-EEG

End point description:

Baseline seizure burden=total duration of seizures(in mins)between -2 and 0 hours before 1st dose of study medication divided by total duration of interpretable video-EEG(in hours)in same period.Seizure burden in Evaluation Period=total duration of seizures between 1 and 3 hours after 1st dose of study medication divided by duration of interpretable video-EEG available in same period.Percent(%) change in seizure burden for Evaluation period=seizure burden at Baseline minus seizure burden at time points,divided by seizure burden in Baseline Period, multiplied by 100.Participants classified in categories based on their %reduction from Baseline to Evaluation Period: <-25%(worsening),-25%- <25%(no change),25%-<50%,50%-<80%, >=80%.% change in seizure burden was analyzed and categorized as positive value=reduction in seizure burden from baseline.FAS was used, population based on randomized treatment."N"=participants evaluable for assessment.

End point type	Secondary

End point timeframe:

During 2-hour Evaluation starting 1 hour after initial treatment (up to 2 hours), compared to Baseline

End point values	Active Comparator	Lacosamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	11		
Units: Percentage of participants				
number (not applicable)				
Evaluation:1 hour-3 hour: <-25	22.2	0.0		
Evaluation: 1 hour-3 hour: -25% to <25%	0.0	9.1		
Evaluation: 1 hour-3 hour: 25% to <50%	11.1	9.1		
Evaluation: 1 hour-3 hour: 50% to <80%	22.2	0.0		
Evaluation: 1 hour-3 hour: >=80%	44.4	81.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Responders at the end of the First 48-hours of the Treatment Period

End point title	Percentage of Responders at the end of the First 48-hours of the Treatment Period

End point description:

A responder is defined as a study participant who achieved the following reduction in seizure burden without need for rescue medication, compared with the seizure burden measured during the Baseline Period immediately prior to investigational medicinal product (IMP) administration, evaluated for a 2-hour period starting 1 hour after the start of initial treatment: At least 80% reduction of seizure burden in participants who were categorized as having nonsevere seizure burden during Baseline OR At least

50% reduction of seizure burden in participants who had at least one 30-minute period of severe seizure burden during Baseline. The denominator for the percentages was based on the number of participants with video- EEG data available at the 48 hour time point. FAS was used, and population was based on randomized treatment. Here, "N" included all participants who were evaluable for this assessment.

End point type	Secondary

End point timeframe:

Across the first 48 hours of Treatment Period

End point values	Active Comparator	Lacosamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	13		
Units: percentage of participants				
number (not applicable)	66.7	76.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Study Participants who are Seizure-free (100% Reduction in Seizure Burden from Baseline) at 24 hours After Start of the Treatment Period, Categorized by Study Participants with Non severe or Severe Seizure Burden at Baseline

End point title	Percentage of Study Participants who are Seizure-free (100% Reduction in Seizure Burden from Baseline) at 24 hours After Start of the Treatment Period, Categorized by Study Participants with Non severe or Severe Seizure Burden at Baseline

End point description:

Seizure free was defined as 100% reduction in seizure burden or having no seizures in the assessment period (23 to 24 hours after first dose) from Baseline. For the study participants with severe seizure burden at Baseline (as determined by the Investigator), the numerator was defined as the number of participants with severe seizure burden at Baseline who had no seizures between 23 and 24 hours after the start of the Treatment Period. The denominator for the percentages was based on the number of participants with video-EEG data available at the 24 hour time point. FAS was used and population was based on randomized treatment. Here, "N" included all participants who were evaluable for this assessment and "n"= participants evaluable for specified seizure burden categories.

End point type	Secondary

End point timeframe:

24 hours after the start of Treatment Period, compared to Baseline

End point values	Active Comparator	Lacosamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	14		
Units: percentage of participants				
number (not applicable)				
Severe Seizure Burden (n=3,6)	33.3	66.7		
Non-severe Seizure Burden (n=5,8)	100.0	62.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Treatment-emergent Marked Abnormalities in 12-lead Electrocardiogram (ECG)

End point title	Percentage of Participants with Treatment-emergent Marked Abnormalities in 12-lead Electrocardiogram (ECG)

End point description:

The ECG treatment-emergent marked abnormalities values are based on grade 2 toxicity based on abnormal values or clinical experience based on investigator's discretion. Participants randomized to Lacosamide and enrolled under this version of the protocol have planned assessments at Screening, 1-6 hours, 48, and 96 hours only. For participants randomized to Active Comparator treatment, only the Screening assessment was applicable. The SS consisted of all enrolled study participants who took at least 1 dose of the randomized treatment. The safety population was based on actual treatment. Here, "N" included all participants with a non-missing interpretation for this assessment.

End point type	Secondary

End point timeframe:

Active Comparator: Screening; Lacosamide: Screening, 1-6 hours, 48 and 96 hours

End point values	Active Comparator	Lacosamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: percentage of participants				
number (not applicable)				
Screening:Abnormal Clinically significant(n=8,14)	0.0	0.0		
1-6 hours:Abnormal Clinically significant(n=0,9)	0	0.0		
48 hours:Abnormal Clinically significant(n=0,13)	0	0.0		
96 hours:Abnormal Clinically significant(n=0,12)	0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Treatment-emergent Adverse Events (TEAEs) as Reported by the Investigator

End point title	Percentage of Participants with Treatment-emergent Adverse Events (TEAEs) as Reported by the Investigator

End point description:

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication. TEAEs are defined as AEs which have onset on or after the start date and time of initial study medication administration. The SS consisted of all enrolled study participants who took at least 1 dose of the randomized treatment. The safety population was based on actual treatment.

End point type	Secondary

End point timeframe:

From first administration of study treatment to the End of Safety Follow-up Period (up to Day 42)

End point values	Active Comparator	Lacosamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	14		
Units: percentage of participants				
number (not applicable)	41.7	64.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Lacosamide

End point title	Serum Concentration of Lacosamide[6]

End point description:

Serum concentrations of lacosamide were measured and concentration data were summarized. PK sparse sampling was performed. The Pharmacokinetic Per-Protocol Set (PK-PPS) consisted of all study participants who provide at least 1 measurable serum sample (with recorded sampling time) on at least 1 post-Baseline visit with documented study drug intake times. Here, overall number of participants analyzed "N" included all participants who were evaluable for this assessment, number analyzed (n) signifies participants who were evaluable at specified timepoints and 99999 refers to Geometric mean and Geometric Coefficient of Variation could not be calculated due to less number of participants.

End point type	Secondary

End point timeframe:

Day 1: 30-90 minutes and 6 - 8 hours after start of first infusion, 30 - 90 minutes and 6 - 8 hours after start of second or third infusion, Days 2, 3 and 4

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Lacosamide			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: microgram per milliliter (mcg/mL)				
geometric mean (geometric coefficient of variation)				
Day 1:30-90 mins after 1st infusion(n=11)	7.003 (± 37.6)			

Day 1:6-8 hours after 1st infusion(n=12)	5.949 (± 38.6)			
Day 1: 30–90 min after 2nd/3rd infusion (n=11)	13.27 (± 29.4)			
Day 1:6-8 hours after 2nd/ 3rd infusion(n=13)	9.607 (± 39.8)			
Day 2 (n=1)	99999 (± 99999)			
Day 3 (n=2)	99999 (± 99999)			
Day 4 (n=2)	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Enrolment: Screening (-36 hours) up to 0 hours (pre-dose); Treatment: From first administration of study treatment to the End of Safety Follow-up (up to Day 42)

Adverse event reporting additional description:

TEAEs are defined as AEs which had onset on or after the start date and time of initial study medication administration. SS was used. Eligible participants who did not undergo any treatment of lacosamide but experienced an AE, are presented in a separate group "No Treatment".

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	No Treatment

Reporting group description:

Participant signed the informed consent form, successfully screened and randomized but never received any study medication during the study.

Reporting group title	Lacosamide

Reporting group description:

Participants received lacosamide 10 milligram per milliliter (mg/mL) 3 times a day as an intravenous infusion over 30 minutes for up to 96 hours. The dose of LCM could be reduced based on clinical judgement of the investigator after the first dose.

Reporting group title	Active Comparator

Reporting group description:

Study participants randomized to receive Active Comparator chosen based on standard of care (StOC) (per local practice and treatment guidelines) in the Clinical Practice in the Treatment Period.

Serious adverse events	No Treatment	Lacosamide	Active Comparator
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	0 / 12 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Congenital, familial and genetic disorders			
Congenital central nervous system anomaly			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Cerebral infarction			

subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	No Treatment	Lacosamide	Active Comparator
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	8 / 14 (57.14%)	5 / 12 (41.67%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pulmonary hypertension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypercapnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Investigations			
Elevated Alanine Aminotransferase			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			

Right ventricular hypertrophy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Reflexes abnormal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Poor sucking reflex			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Convulsion			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Cerebral ischaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Depressed level of consciousness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Intracranial pressure increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dry eye			

subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hyperbilirubinaemia neonatal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Cholestasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Adrenal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Adrenal insufficiency			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Infections and infestations			
Neonatal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Oral candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Feeding disorder neonatal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 12 (8.33%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2020	Protocol Amendment 1 was dated 13 Oct 2022. The purpose of this substantial amendment was changes to the protocol have been made to simplify the study logistics, to update secondary objectives, to provide updated data from the pediatric PK model, and to improve consistency within the protocol. Minor grammatical, editorial, and formatting changes have also been made for clarification purposes only.
11 February 2022	Protocol Amendment 2 was dated 11 Feb 2022. The purpose of this substantial amendment was to change the protocol and made it align to the study more closely with the Neonatal Intensive Care Unit's (NICU) standard of care and practice, clarify the age criterion, clarify the Schedule of Activities, align with the current Statistical Analysis Plan (SAP), and align with the current lacosamide (LCM) clinical development program. Minor grammatical, editorial, and formatting changes have also been made for clarification purposes only.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study ended prematurely after agreed PIP modification; termination was not linked to any safety issues/reasons.

Notes: