Clinical trial results:
Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of NBI-827104 in Pediatric Subjects with Epileptic Encephalopathy with Continuous Spike-and-Wave During Sleep

Summary

EudraCT number	2020-003141-11
Trial protocol	DK FR ES DE
Global end of trial date	18 October 2022

Results information

Result version number	v1 (current)
This version publication date	28 April 2023
First version publication date	28 April 2023

Trial information

Trial identification

Sponsor protocol code	NBI-827104-CSWS2010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04625101
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Neurocrine Biosciences
Sponsor organisation address	12780 El Camino Real, San Diego, United States, 92130
Public contact	Neurocrine Medical Information, Neurocrine Biosciences, +1 877-641-3461, medinfo@neurocrine.com
Scientific contact	Neurocrine Medical Information, Neurocrine Biosciences, +1 877-641-3461, medinfo@neurocrine.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 October 2022
Global end of trial reached?	Yes
Global end of trial date	18 October 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the effect of NBI-827104 on the overnight epileptiform video electroencephalogram (video EEG) activity in pediatric participants with epileptic encephalopathy with continuous spike-wave discharges during sleep (EECSWS).

Protection of trial subjects:

The study was conducted in full compliance with International Council for Harmonisation (ICH) Technical Requirements for Pharmaceuticals for Human Use GCP guidelines and with the laws and regulations of the country in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 April 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	Spain: 3
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	24
EEA total number of subjects	6

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)	21
Adolescents (12-17 years)	3

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were enrolled at 14 clinical sites in the United States and Europe.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	NBI-827104

Arm description:

NBI-827104 administered orally daily for up to 13 weeks.

Arm type	Experimental
Investigational medicinal product name	NBI-827104
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

NBI-827104 was administered per dose and schedule specified in the arm description.

Arm title	Placebo

Arm description:

Placebo administered orally daily for up to 13 weeks.

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

Dosage and administration details:

Placebo was administered per dose and schedule specified in the arm description.

Number of subjects in period 1	NBI-827104	Placebo
Started	16	8
Completed	15	7
Not completed	1	1
Protocol deviation	1	-
Withdrawal by subject	-	1

Baseline characteristics

Reporting groups	
Reporting group title	NBI-827104
Reporting group description:	
NBI-827104 administered orally daily for up to 13 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo administered orally daily for up to 13 weeks.	

Reporting group values	NBI-827104	Placebo	Total
Number of subjects	16	8	24
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)	14	7	21
Adolescents (12-17 years)	2	1	3
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	7	3	10
Male	9	5	14
Race Units: Subjects			
White	15	7	22
Black or African American	0	1	1
Other	1	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	3	0	3
Not Hispanic or Latino	13	8	21

End points

End points reporting groups

Reporting group title	NBI-827104
Reporting group description: NBI-827104 administered orally daily for up to 13 weeks.	
Reporting group title	Placebo
Reporting group description: Placebo administered orally daily for up to 13 weeks.	

Primary: Ratio of Spike-Wave Index (SWI) During First Hour of Nonrapid Eye Movement (NREM) Sleep at Week 6

End point title	Ratio of Spike-Wave Index (SWI) During First Hour of Nonrapid Eye Movement (NREM) Sleep at Week 6
End point description: The ratio of SWI at the end of Week 6 to baseline during the first hour (60 minutes) of NREM sleep based on centralized video-EEG reading, where baseline was defined as the last value measured prior to intake of study treatment on Day 1. Full Analysis Set included all randomized participants who had at least 1 dose of study treatment and at least 1 efficacy video EEG assessment.	
End point type	Primary
End point timeframe: Baseline to Week 6	

End point values	NBI-827104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[1]	6[2]		
Units: Ratio				
least squares mean (standard error)	-0.02 (± 0.02)	0.01 (± 0.04)		

Notes:

[1] - One participant did not have a Week 6 video-EEG and was excluded from the analysis.

[2] - One participant did not have an evaluable Week 6 video-EEG and was excluded from the analysis.

Statistical analyses

Statistical analysis title	Change from Baseline to the end of Week 6
Comparison groups	NBI-827104 v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4326
Method	ANCOVA

Secondary: Ratio of SWI During First Hour of NREM Sleep at Week 12

End point title	Ratio of SWI During First Hour of NREM Sleep at Week 12

End point description:

The ratio of SWI at the end of Week 12 to baseline during the first hour (60 minutes) of NREM sleep based on centralized video-EEG reading, where baseline was defined as the last value measured prior to intake of study treatment on Day 1.
Full Analysis Set included all randomized participants who had at least 1 dose of study treatment and at least 1 efficacy video EEG assessment.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	NBI-827104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Ratio				
least squares mean (standard error)	-0.05 (± 0.02)	0.03 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Considered as Responders as Assessed by the Caregiver Global Impression of Change (CaGI-C) Score

End point title	Number of Participants Considered as Responders as Assessed by the Caregiver Global Impression of Change (CaGI-C) Score

End point description:

The CaGI-C is a 7-point scale that rates the caregiver's assessment of the overall improvement in the participants symptoms since the initiation of study treatment, ranging from 1 (very much improved) to 7 (very much worse). A responder was defined as a participant with a score of 1 (very much improved) or 2 (much improved).
Full Analysis Set included all randomized participants who had at least 1 dose of study treatment and at least 1 efficacy video EEG assessment.

End point type	Secondary

End point timeframe:

Week 6 and Week 12

End point values	NBI-827104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Count of Participants				
Week 6	1	1		
Week 12	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Considered as Responders as Assessed by the Clinician Global Impression of Change (CGI-C) Score

End point title	Number of Participants Considered as Responders as Assessed by the Clinician Global Impression of Change (CGI-C) Score

End point description:

The CGI-C is a 7-point scale that rates the clinician's assessment of overall improvement in the participant's symptoms since the initiation of study treatment, ranging from 1 (very much improved) to 7 (very much worse). A responder was defined as a participant with a score of 1 (very much improved) or 2 (much improved).
Full Analysis Set included all randomized participants who had at least 1 dose of study treatment and at least 1 efficacy video EEG assessment.

End point type	Secondary

End point timeframe:

Week 6 and Week 12

End point values	NBI-827104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Count of Participants				
Week 6	1	1		
Week 12	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Considered as Responders as Assessed by the Clinical Global Impression of Severity (CGI-S) Scores

End point title	Number of Participants Considered as Responders as Assessed by the Clinical Global Impression of Severity (CGI-S) Scores

End point description:

The CGI-S is a 7-point scale that rates the clinician's assessment of overall symptom severity, ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). A responder was defined as a participant with at least 1-point improvement in the CGI-S score from baseline.
Full Analysis Set included all randomized participants who had at least 1 dose of study treatment and at least 1 efficacy video EEG assessment.

End point type	Secondary

End point timeframe:

Baseline to Week 6 and Baseline to Week 12

End point values	NBI-827104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Count of Participants				
Week 6	3	1		
Week 12	4	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 (after dosing) to Week 17	
Adverse event reporting additional description:	
Safety analysis set included all randomized participants who had at least 1 dose of study treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	NBI-827104
Reporting group description:	
NBI-827104 administered orally daily for up to 13 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo administered orally daily for up to 13 weeks.	

Serious adverse events	NBI-827104	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	NBI-827104	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 16 (68.75%)	8 / 8 (100.00%)	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	3 / 16 (18.75%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Affect lability			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Aggression			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Depressed mood			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Irritability			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Suicidal ideation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

Terminal insomnia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	
occurrences (all)	2	2	
Blood triglycerides increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Lymphocyte count decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Protein urine present			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
White blood cell count decreased			
subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Vitamin D decreased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Face injury			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Partial seizures			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Haematochezia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Keratosis pilaris			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

Pruritus			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Endocrine disorders			
Precocious puberty			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 16 (12.50%)	2 / 8 (25.00%)	
occurrences (all)	2	2	
Infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Rash pustular			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Suspected COVID-19			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

Upper respiratory tract infection			
subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Urinary tract infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 16 (18.75%)	1 / 8 (12.50%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 May 2021	- A requirement that at least 4 days of baseline seizure diary data should be obtained prior to randomization was added. - Added permitted medications
05 August 2021	- The option for participants to enroll directly into an open-label extension study after the completion of the Week 12 study visit was added. - Updated inclusion criterion for contraception - Added prohibited medication - Reduced the total blood volume collected during the study - Added additional requirements for study treatment discontinuation

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported