Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Soticlestat as Adjunctive Therapy in Pediatric and Adult Subjects With Lennox-Gastaut Syndrome (LGS)

Summary

EudraCT number	2021-002481-40
Trial protocol	Outside EU/EEA IT FR ES LV GR NL BE PL HU DE
Global end of trial date	25 January 2024

Results information

Result version number	v1 (current)
This version publication date	10 August 2024
First version publication date	10 August 2024

Trial information

Trial identification

Sponsor protocol code	TAK-935-3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04938427
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, N/A N/A, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, N/A N/A, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000491-PIP20-21
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	25 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of the study was to assess the efficacy of soticlestat in reducing major motor drop (MMD) seizure frequency as add-on therapy to standard of care (SOC) as compared with placebo during the full treatment period (titration + maintenance) and maintenance period.

Protection of trial subjects:

Each participant signed an informed consent form (ICF) before participating in the study.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	08 November 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: 3
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	China: 40
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Japan: 34
Country: Number of subjects enrolled	Latvia: 2
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Serbia: 24
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Ukraine: 10
Country: Number of subjects enrolled	United States: 58

Worldwide total number of subjects	270
EEA total number of subjects	88

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)	129
Adolescents (12-17 years)	83
Adults (18-64 years)	58
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 84 investigative sites in Australia, Belgium, Canada, China, France, Germany, Greece, Hungary, Italy, Japan, Latvia, Netherlands, Poland, Russian Federation, Serbia, Spain, Ukraine and the United States from 08 November 2021 to 25 January 2024.

Pre-assignment

Screening details:

A total of 270 participants with a diagnosis of Lennox-Gastaut syndrome were randomized in a 1:1 ratio to receive either soticlestat or placebo.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Soticlestat placebo-matching mini-tablets or tablets, orally or via G-tube or MIC-KEY button or J-tube, BID, up to 4 weeks during titration. Participants continued to receive soticlestat placebo-matching mini-tablets or tablets for 12 weeks during maintenance. The total duration of the treatment was up to 16 weeks (Full Treatment Period). Soticlestat matching tapering was done to maintain the blind if participants decided to discontinue the treatment.

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:

Administered for 16 weeks in the treatment period.

Arm title	Soticlestat

Arm description:

Participants weighing <45 kg: Soticlestat, mini-tablets, at the dose of 40 mg to 200 mg, orally or via G-tube or MIC-KEY button or J-tube, BID based on body weight up to 4 weeks during titration. Participants continued to receive the dose that they were on at the end of the titration, for 12 weeks during maintenance. The total duration of the treatment was up to 16 weeks (Full Treatment Period) with the dose tapered down if participants decided to discontinue the treatment.

Participants weighing ≥45 kg: Soticlestat mini-tablets or tablets with a starting dose of 100 mg BID followed by 200 mg BID and, then 300 mg BID, up to 4 weeks during titration. Participants continued to receive 300 mg BID for 12 weeks during maintenance. The total duration of the treatment was up to 16 weeks (Full Treatment Period) with the dose tapered down if participants decided to discontinue the treatment.

Arm type	Experimental
Investigational medicinal product name	Soticlestat
Investigational medicinal product code	
Other name	TAK-935
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Administered for 16 weeks in the treatment period.

Number of subjects in period 1	Placebo	Soticlestat
Started	136	134
Completed	126	114
Not completed	10	20
Consent withdrawn by subject	1	-
Adverse event, non-fatal	5	19
Reason Not Specified	2	1
Withdrawal by Parent/Guardian	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Soticlestat placebo-matching mini-tablets or tablets, orally or via G-tube or MIC-KEY button or J-tube, BID, up to 4 weeks during titration. Participants continued to receive soticlestat placebo-matching mini-tablets or tablets for 12 weeks during maintenance. The total duration of the treatment was up to 16 weeks (Full Treatment Period). Soticlestat matching tapering was done to maintain the blind if participants decided to discontinue the treatment.

Reporting group title	Soticlestat

Reporting group description:

Participants weighing <45 kg: Soticlestat, mini-tablets, at the dose of 40 mg to 200 mg, orally or via G-tube or MIC-KEY button or J-tube, BID based on body weight up to 4 weeks during titration. Participants continued to receive the dose that they were on at the end of the titration, for 12 weeks during maintenance. The total duration of the treatment was up to 16 weeks (Full Treatment Period) with the dose tapered down if participants decided to discontinue the treatment.

Participants weighing ≥45 kg: Soticlestat mini-tablets or tablets with a starting dose of 100 mg BID followed by 200 mg BID and, then 300 mg BID, up to 4 weeks during titration. Participants continued to receive 300 mg BID for 12 weeks during maintenance. The total duration of the treatment was up to 16 weeks (Full Treatment Period) with the dose tapered down if participants decided to discontinue the treatment.

Reporting group values	Placebo	Soticlestat	Total
Number of subjects	136	134	270
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	12.5	13.4	
standard deviation	± 6.68	± 9.35	-
Gender categorical Units: Subjects			
Gender Female	52	55	107
Gender Male	84	79	163
Race (NIH/OMB) Units: Subjects			
Race American Indian or Alaska Native	0	0	0
Race Asian	44	42	86
Race Native Hawaiian or Other Pacific Islander	1	0	1
Race Black or African American	2	1	3
Race White	81	86	167
Race More than one race	2	0	2
Race Unknown or Not Reported	6	5	11
Ethnicity (NIH/OMB) Units: Subjects			
Ethnicity Hispanic or Latino	4	7	11
Ethnicity Not Hispanic or Latino	130	124	254
Ethnicity Unknown or Not Reported	2	3	5

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Soticlestat placebo-matching mini-tablets or tablets, orally or via G-tube or MIC-KEY button or J-tube, BID, up to 4 weeks during titration. Participants continued to receive soticlestat placebo-matching mini-tablets or tablets for 12 weeks during maintenance. The total duration of the treatment was up to 16 weeks (Full Treatment Period). Soticlestat matching tapering was done to maintain the blind if participants decided to discontinue the treatment.

Reporting group title	Soticlestat

Reporting group description:

Participants weighing <45 kg: Soticlestat, mini-tablets, at the dose of 40 mg to 200 mg, orally or via G-tube or MIC-KEY button or J-tube, BID based on body weight up to 4 weeks during titration. Participants continued to receive the dose that they were on at the end of the titration, for 12 weeks during maintenance. The total duration of the treatment was up to 16 weeks (Full Treatment Period) with the dose tapered down if participants decided to discontinue the treatment.

Participants weighing ≥45 kg: Soticlestat mini-tablets or tablets with a starting dose of 100 mg BID followed by 200 mg BID and, then 300 mg BID, up to 4 weeks during titration. Participants continued to receive 300 mg BID for 12 weeks during maintenance. The total duration of the treatment was up to 16 weeks (Full Treatment Period) with the dose tapered down if participants decided to discontinue the treatment.

Primary: Percent Change from Baseline in Major Motor Drop (MMD) Seizure Frequency Per 28 Days During the Full Treatment Period

End point title	Percent Change from Baseline in Major Motor Drop (MMD) Seizure Frequency Per 28 Days During the Full Treatment Period

End point description:

MMD seizure frequency per 28 days was defined as the total number of MMD seizures reported during the period divided by the number of days during the period seizures were assessed multiplied by 28. Percent change from Baseline was defined as (frequency of seizures per 28 days during the full Treatment Period - frequency of seizures per 28 days at Baseline) divided by the frequency of seizures per 28 days at Baseline multiplied by 100. Modified Intent-to-treat (mITT) Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period.

End point type	Primary

End point timeframe:

Baseline; Full Treatment Period: Weeks 1 to 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	134		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-6.69 (-26.41 to 24.26)	-6.11 (-38.02 to 31.99)		

Statistical analyses

Statistical analysis title	Percent Change from Baseline in Seizure Frequency
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.785 [1]
Method	ANCOVA
Parameter estimate	Hodges-Lehmann Location Shift Estimate
Point estimate	-1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.02
upper limit	9.99

Notes:

[1] - The p-value was calculated using Rank Analysis of Covariance (ANCOVA) model using treatment group, age stratum (≤6 years, >6 years), and rank of Baseline seizure frequency per 28 days as predictors.

Primary: Percent Change from Baseline in Major Motor Drop (MMD) Seizure Frequency Per 28 Days During the Maintenance Period

End point title	Percent Change from Baseline in Major Motor Drop (MMD) Seizure Frequency Per 28 Days During the Maintenance Period

End point description:

MMD seizure frequency per 28 days was defined as the total number of MMD seizures reported during the period divided by number of days during the period seizures were assessed multiplied by 28. Percent change from Baseline was defined as (frequency of seizures per 28 days during the Maintenance Period - frequency of seizures per 28 days at Baseline) divided by the frequency of seizures per 28 days at Baseline multiplied by 100. mITT Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period. Subjects analysed indicates the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Baseline; Maintenance Period: Weeks 5 to 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	124		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-9.63 (-30.15 to 23.71)	-5.24 (-41.94 to 42.29)		

Statistical analyses

Statistical analysis title	Percent Change from Baseline in Seizure Frequency
Comparison groups	Soticlestat v Placebo

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.778 [2]
Method	ANCOVA
Parameter estimate	Hodges-Lehmann Location Shift Estimate
Point estimate	2.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.86
upper limit	15.14

Notes:

[2] - The p-value was calculated using the Rank ANCOVA model using the treatment group, age stratum (≤6 years, >6 years), and rank of Baseline seizure frequency per 28 days as predictors.

Secondary: Percentage of Responders During the Maintenance Period

End point title	Percentage of Responders During the Maintenance Period

End point description:

Responders are defined as those with ≥50% reduction from Baseline in MMD seizures during the Maintenance Period. Percentages are rounded off to the nearest single decimal place. mITT Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period. Subjects analysed indicates the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Maintenance Period: Weeks 5 to 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	124		
Units: percentage of participants				
number (not applicable)	11.4	19.4		

Statistical analyses

Statistical analysis title	Percentage of Responders
Comparison groups	Soticlestat v Placebo
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	3.87

Secondary: Percentage of Responders During the Full Treatment Period

End point title	Percentage of Responders During the Full Treatment Period

End point description:

Responders are defined as those with ≥50% reduction from Baseline in MMD seizures during the Full Treatment Period. Percentages are rounded off to the nearest single decimal place. mITT Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period.

End point type	Secondary

End point timeframe:

Full Treatment Period: Weeks 1 to 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	134		
Units: percentage of participants				
number (not applicable)	9.6	16.4		

Statistical analyses

Statistical analysis title	Percentage of Responders
Comparison groups	Soticlestat v Placebo
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	4.05

Secondary: Percentage of Participants with ≤0%, >0% to ≤25%, >25% to ≤50%, >50% to ≤75%, >75% to ≤100% Reduction in MMD Seizure During the Full Treatment Period

End point title	Percentage of Participants with ≤0%, >0% to ≤25%, >25% to ≤50%, >50% to ≤75%, >75% to ≤100% Reduction in MMD Seizure During the Full Treatment Period

End point description:

Percent reduction from Baseline (%) is defined as [(Full Treatment Period MMD Seizure Frequency - Baseline MMD Seizure Frequency) divided by Baseline MMD Seizure Frequency] multiplied by 100. Data is reported as reduction of ≤0%, >0% to ≤25%, >25% to ≤50%, >50% to ≤75%, >75% to ≤100% or

more in seizures from Baseline. Percentages are rounded off to the nearest single decimal place. mITT Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period.

End point type	Secondary

End point timeframe:

Full Treatment Period: Weeks 1 to 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	134		
Units: percentage of participants				
number (not applicable)				
≤0% Reduction	43.4	43.3		
>0% to ≤ 25% Reduction	29.4	24.6		
>25% to ≤ 50% Reduction	17.6	15.7		
>50% to ≤ 75% Reduction	6.6	11.2		
>75% to ≤ 100% Reduction	2.9	5.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Caregiver Global Impression of Improvement (Care GI-I) Scale Responses as Per the Parent/Caregiver Reported Impression at Week 16

End point title	Percentage of Participants With Caregiver Global Impression of Improvement (Care GI-I) Scale Responses as Per the Parent/Caregiver Reported Impression at Week 16

End point description:

The Care GI-I is a 7-point Likert scale that the caregiver used to rate improvement in overall seizure control, behavior, safety and tolerability after the initiation of study drug relative to Baseline (before treatment with the study drug). The participant was rated as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse). The parent/caregiver completed the Care GI-I via interview. Lower scores indicate improvement. Percentages are rounded off to the nearest single decimal place. mITT Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period. Subjects analysed indicates the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	122		
Units: percentage of participants				
number (not applicable)				
Score 1: Very Much Improved	0.8	1.6		
Score 2: Much Improved	13.1	20.5		
Score 3: Minimally Improved	25.4	26.2		
Score 4: No Change	46.2	36.9		
Score 5: Minimally Worse	11.5	6.6		
Score 6: Much Worse	3.1	5.7		
Score 7: Very Much Worse	0.0	2.5		

Statistical analyses

Statistical analysis title	Percentage of Participants With Care GI-I Response
Comparison groups	Soticlestat v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	2.13

Secondary: Percentage of Participants with Clinical Global Impression of Improvement (CGI-I) Scale Responses as Per the Investigator Reported Impression at Week 16

End point title	Percentage of Participants with Clinical Global Impression of Improvement (CGI-I) Scale Responses as Per the Investigator Reported Impression at Week 16

End point description:

The CGI-I (Clinician) is a 7-point Likert scale that the investigator to rate a participant’s change (improvement) in overall seizure control, behavior, safety and tolerability after the initiation of study drug relative to Baseline (before treatment with the study drug). The participant was rated as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse). The investigator or designee will complete the CGI-I. Lower scores indicate improvement. Percentages are rounded off to the nearest single decimal place. mITT Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period. Subjects analysed indicates the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	132		
Units: percentage of participants				
number (not applicable)				
Score 1: Very Much Improved	1.5	3.0		
Score 2: Much Improved	11.3	15.9		
Score 3: Minimally Improved	17.3	24.2		
Score 4: No Change	60.2	43.2		
Score 5: Minimally Worse	5.3	7.6		
Score 6: Much Worse	4.5	4.5		
Score 7: Very Much Worse	0.0	1.5		

Statistical analyses

Statistical analysis title	Percentage of Participants with CGI-I Responses
Comparison groups	Soticlestat v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	2.21

Secondary: Percentage of Participants with CGI-I Nonseizure Symptoms Instrument Responses for Each Domain as Per the Investigator Reported Impression at Week 16

End point title	Percentage of Participants with CGI-I Nonseizure Symptoms Instrument Responses for Each Domain as Per the Investigator Reported Impression at Week 16

End point description:

The CGI-I nonseizure symptoms instrument is a series of single-item assessments that the investigator used to rate improvement in the symptoms and impacts in select nonseizure domains (alertness, communication, and disruptive behaviors) since initiating the study drug. The participant was rated by the investigator for each domain as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse). Lower scores indicate improvement. Data for percentage of participants categorized based on the responses for each domain are presented. Percentages are rounded off to the nearest single decimal place.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	132		
Units: percentage of participants				
number (not applicable)				
Alertness: Score 1: Very Much Improved	1.5	1.5		
Alertness: Score 2: Much Improved	7.5	13.6		
Alertness: Score 3: Minimally improved	12.8	16.7		
Alertness: Score 4: No Change	71.4	59.1		
Alertness: Score 5: Minimally Worse	4.5	8.3		
Alertness: Score 6: Much Worse	2.3	0.8		
Alertness: Score 7: Very Much Worse	0.0	0.0		
Communication: Score 1: Very Much Improved	1.5	2.3		
Communication: Score 2: Much Improved	7.5	10.6		
Communication: Score 3: Minimally improved	12.8	18.9		
Communication: Score 4: No Change	71.4	61.4		
Communication: Score 5: Minimally Worse	4.5	6.1		
Communication: Score 6: Much Worse	2.3	0.8		
Communication: Score 7: Very Much Worse	0.0	0.0		
Disruptive Behaviors: Score 1: Very Much Improved	0.0	1.5		
Disruptive Behaviors: Score 2: Much Improved	1.5	6.1		
Disruptive Behaviors: Score 3: Minimally improved	8.3	10.6		
Disruptive Behaviors: Score 4: No Change	79.7	75.0		
Disruptive Behaviors: Score 5: Minimally Worse	6.8	3.8		
Disruptive Behaviors: Score 6: Much Worse	3.8	2.3		
Disruptive Behaviors: Score 7: Very Much Worse	0.0	0.8		

Statistical analyses

Statistical analysis title	Alertness Domain
Comparison groups	Soticlestat v Placebo

Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	2.3

Statistical analysis title	Communication Domain
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	2.48

Statistical analysis title	Disruptive Behaviors Domain
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	3.43

Secondary: Percentage of Participants with CGI-I Seizure Intensity and Duration Instrument Responses as Per the Parent/Caregiver Reported Impression at Week 16

End point title	Percentage of Participants with CGI-I Seizure Intensity and Duration Instrument Responses as Per the Parent/Caregiver Reported Impression at Week 16

End point description:

The CGI-I seizure intensity and duration instrument was used by the parent/caregiver to rate changes in

intensity and/or duration of the most impactful seizures from the first assessment. The participant's symptoms were rated as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse). Lower scores indicate improvement. Percentages are rounded off to the nearest single decimal place. mITT Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period. Subjects analysed indicates the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	122		
Units: percentage of participants				
number (not applicable)				
Score 1: Very Much Improved	0.8	1.6		
Score 2: Much Improved	9.9	18.9		
Score 3: Minimally Improved	24.4	28.7		
Score 4: No Change	51.1	39.3		
Score 5: Minimally Worse	9.9	4.1		
Score 6: Much Worse	3.8	5.7		
Score 7: Very Much Worse	0.0	1.6		

Statistical analyses

Statistical analysis title	CGI-I Seizure Intensity and Duration
Comparison groups	Soticlestat v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	2.65

Secondary: Change From Baseline in Quality of Life Inventory-Disability (QI-Disability) Total Score at Week 16

End point title	Change From Baseline in Quality of Life Inventory-Disability (QI-Disability) Total Score at Week 16

End point description:

QI-Disability tool is parent/caregiver-reported questionnaire evaluated quality of life(QoL) in children with intellectual disabilities.It contains 32 items with 6 domains of QoL:physical health,positive &

negative emotions,social interaction,leisure,outdoors & independence.Each item is rated on Likert scale of:Never,Rarely,Sometimes,Often,& Very Often. Items were linearly transformed to scale of 0-100,higher scores=better QoL. Domain scores=average of item scores. Domain scores are summed & divided by 6 to yield total score. Total score ranges from 0-100,with higher scores=better QoL. A negative change from Baseline implies deteriorating QoL Mixed-effects model for repeated measures (MMRM) was used for analysis. mITT Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period. Subjects analysed indicates the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	107		
Units: score on a scale				
arithmetic mean (standard deviation)	-1.66 (± 10.314)	-1.17 (± 12.042)		

Statistical analyses

Statistical analysis title	QI-Disability Total Score
Comparison groups	Soticlestat v Placebo
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Square Mean Difference
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	3.24

Secondary: Percent Change From Baseline in Frequency of All Seizures per 28 Days During the Maintenance Period

End point title	Percent Change From Baseline in Frequency of All Seizures per 28 Days During the Maintenance Period

End point description:

Seizure frequency per 28 days was defined as the total number of seizures reported during the period divided by the number of days during the period seizures were assessed multiplied by 28. Percent change from Baseline was defined as (frequency of seizures per 28 days during the Maintenance Period - frequency of seizures per 28 days at Baseline) divided by the frequency of seizures per 28 days at Baseline multiplied by 100. mITT Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period. Subjects analysed indicates the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline; Maintenance Period: Weeks 5 to 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	124		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-9.92 (-30.55 to 15.55)	-16.82 (-40.93 to 20.60)		

Statistical analyses

Statistical analysis title	Percent Change From Baseline in Frequency
Comparison groups	Soticlestat v Placebo
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hodges-Lehmann Location Shift Estimate
Point estimate	-6.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.83
upper limit	4.16

Secondary: Percent Change from Baseline in Frequency of All Seizures per 28 Days During the Full Treatment Period

End point title	Percent Change from Baseline in Frequency of All Seizures per 28 Days During the Full Treatment Period

End point description:

Seizure frequency per 28 days was defined as the total number of seizures reported during the period divided by the number of days during the period seizures were assessed multiplied by 28. Percent change from Baseline was defined as (frequency of seizures per 28 days during the full Treatment Period - frequency of seizures per 28 days at Baseline) divided by the frequency of seizures per 28 days at Baseline multiplied by 100. mITT Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period.

End point type	Secondary

End point timeframe:

Baseline; Full Treatment Period: Weeks 1 to 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	134		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-6.45 (-28.11 to 16.16)	-16.71 (-39.84 to 18.53)		

Statistical analyses

Statistical analysis title	Percent Change from Baseline in Frequency
Comparison groups	Soticlestat v Placebo
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hodges-Lehmann Location Shift Estimate
Point estimate	-6.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.67
upper limit	3.12

Secondary: Change From Baseline in Percentage of MMD Seizure-free Days During the Full Treatment Period

End point title	Change From Baseline in Percentage of MMD Seizure-free Days During the Full Treatment Period

End point description:

MMD Seizure-free days was defined as the number of days the participant remained MMD seizure free after initiation of the treatment. The change from baseline in percentage of MMD seizure-free days, was defined as the percentage of seizure-free days during the Full Treatment Period minus the percentage of seizure-free days during the Baseline. A linear model with treatment group and age stratum as factors and baseline percentage as a covariate was used for analysis. mITT Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period.

End point type	Secondary

End point timeframe:

Baseline up to Week 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	134		
Units: percentage of days				
least squares mean (standard error)	5.37 (± 1.661)	7.84 (± 1.676)		

Statistical analyses

Statistical analysis title	Percentage of MMD Seizure-free Days
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	2.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.74
upper limit	6.67

Secondary: Longest MMD Seizure-free Interval During the Full Treatment Period	
End point title	Longest MMD Seizure-free Interval During the Full Treatment Period
End point description:	
Longest MMD Seizure-free Interval was defined as the longest time period that the participant remained MMD seizure-free after initiation of the treatment. A linear model with treatment group and age stratum as factors was used for analysis. mITT Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period.	
End point type	Secondary
End point timeframe:	
Full Treatment Period: Weeks 1 to 16	

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	134		
Units: days				
least squares mean (standard error)	5.5 (± 1.39)	10.9 (± 1.41)		

Statistical analyses

Statistical analysis title	Longest MMD Seizure-free Interval
Comparison groups	Soticlestat v Placebo

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	8.9

Secondary: Number of Days When Rescue Antiseizure Medication (ASM) is Used During the Full Treatment Period

End point title	Number of Days When Rescue Antiseizure Medication (ASM) is Used During the Full Treatment Period

End point description:

Use of rescue ASM was recorded in the case report form (CRF) along with start and end date of medication. Based on the start and end dates for all rescue ASMs taken by a participant, the number of days during the Full Treatment Period when rescue ASM was used was derived. mITT Analysis Set included all randomised participants who had received at least 1 dose of study drug and had been assessed for seizures for at least 1 day in the Full Treatment Period.

End point type	Secondary

End point timeframe:

Full Treatment Period: Weeks 1 to 16

End point values	Placebo	Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	134		
Units: days				
least squares mean (standard error)	3.4 (± 1.12)	2.5 (± 1.14)		

Statistical analyses

Statistical analysis title	Number of Days Rescue ASM is used
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose up to Week 19

Adverse event reporting additional description:

Safety Analysis Set included all participants who took at least 1 dose of the study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Soticlestat placebo-matching mini-tablets or tablets, orally or via G-tube or MIC-KEY button or J-tube, BID, up to 4 weeks during titration. Participants continued to receive soticlestat placebo-matching mini-tablets or tablets for 12 weeks during maintenance. The total duration of the treatment was up to 16 weeks (Full Treatment Period). Soticlestat matching tapering was done to maintain the blind if participants decided to discontinue the treatment.

Reporting group title	Soticlestat

Reporting group description:

Participants weighing <45 kg: Soticlestat, mini-tablets, at the dose of 40 mg to 200 mg, orally or via G-tube or MIC-KEY button or J-tube, BID based on body weight up to 4 weeks during titration. Participants continued to receive the dose that they were on at the end of the titration, for 12 weeks during maintenance. The total duration of the treatment was up to 16 weeks (Full Treatment Period) with the dose tapered down if participants decided to discontinue the treatment.

Participants weighing ≥45 kg: Soticlestat mini-tablets or tablets with a starting dose of 100 mg BID followed by 200 mg BID and, then 300 mg BID, up to 4 weeks during titration. Participants continued to receive 300 mg BID for 12 weeks during maintenance. The total duration of the treatment was up to 16 weeks (Full Treatment Period) with the dose tapered down if participants decided to discontinue the treatment.

Serious adverse events	Placebo	Soticlestat	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 136 (7.35%)	11 / 134 (8.21%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			

subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue injury			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	1 / 136 (0.74%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Change in seizure presentation			
subjects affected / exposed	0 / 136 (0.00%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Negative pressure pulmonary oedema			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 136 (0.00%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 136 (0.74%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchitis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (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: 5 %

Non-serious adverse events	Placebo	Soticlestat	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 136 (37.50%)	69 / 134 (51.49%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 136 (3.68%)	7 / 134 (5.22%)	
occurrences (all)	6	8	
Nervous system disorders			
Somnolence			
subjects affected / exposed	10 / 136 (7.35%)	19 / 134 (14.18%)	
occurrences (all)	10	22	
Change in seizure presentation			
subjects affected / exposed	7 / 136 (5.15%)	17 / 134 (12.69%)	
occurrences (all)	10	19	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 136 (3.68%)	8 / 134 (5.97%)	
occurrences (all)	5	9	
Pyrexia			
subjects affected / exposed	11 / 136 (8.09%)	10 / 134 (7.46%)	
occurrences (all)	14	10	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 136 (2.21%)	7 / 134 (5.22%)	
occurrences (all)	3	7	
Infections and infestations			
COVID-19			
subjects affected / exposed	3 / 136 (2.21%)	8 / 134 (5.97%)	
occurrences (all)	3	15	
Upper respiratory tract infection			
subjects affected / exposed	7 / 136 (5.15%)	11 / 134 (8.21%)	
occurrences (all)	12	13	
Nasopharyngitis			

subjects affected / exposed occurrences (all)	11 / 136 (8.09%) 13	10 / 134 (7.46%) 11	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 3 / 136 (2.21%) 3	 8 / 134 (5.97%) 10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2022	The following changes were made as per Amendment 2: 1) Changed the number of estimated sites from 65 to 100. 2) Increased maximum age to 55 years. 3) Required prior treatment failure of 1 ASM rather than 2 for enrolment in the study. 5) Changed MMD seizures to the most impactful seizure.

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.

Not Specified

Notes: