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 Young Adult Subjects With Dravet Syndrome (DS)

Summary

EudraCT number	2021-002480-22
Trial protocol	Outside EU/EEA IT FR ES LV GR NL BE PL HU DE
Global end of trial date	11 April 2024

Results information

Result version number	v1 (current)
This version publication date	26 December 2024
First version publication date	26 December 2024

Trial information

Trial identification

Sponsor protocol code	TAK-935-3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04940624
WHO universal trial number (UTN)	-
Other trial identifiers	jRCT: jRCT2051210074

Notes:

Sponsors

Sponsor organisation name	Takeda Development Center Americas, Inc.
Sponsor organisation address	95 Hayden Avenue, Lexington, MA, United States, 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, 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-002572-PIP02-19
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	11 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of soticlestat in reducing convulsive seizure frequency as add-on therapy to Standard of Care (SOC) compared with placebo during the maintenance period only.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy:

NA

Evidence for comparator: -

Actual start date of recruitment	28 October 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: 2
Country: Number of subjects enrolled	Brazil: 11
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	China: 30
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Japan: 18
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Ukraine: 4
Country: Number of subjects enrolled	United States: 17
Worldwide total number of subjects	144
EEA total number of subjects	48

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)	95
Adolescents (12-17 years)	32
Adults (18-64 years)	17
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 144 participants participated in the study at multiple investigative sites globally from 28 October 2021 to 11 April 2024.

Pre-assignment

Screening details:

A total of 144 participants with a diagnosis of Dravet Syndrome (DS) 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, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Soticlestat placebo-matching mini-tablets or tablets, orally or via gastrostomy tube (G-tube) or low-profile gastric tube (MIC-KEY) button or jejunostomy tube (J-tube),twice daily (BID), up to 4 weeks during titration. Participants continued to receive the 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	Placebo
Other name	
Pharmaceutical forms	Film-coated 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 the 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 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 dose tapered down if participants decided to discontinue the treatment.

Arm type	Experimental
Investigational medicinal product name	Soticlestat
Investigational medicinal product code	TAK-935
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Gastroenteral use, Oral use

Dosage and administration details:
Administered for 16 weeks in the Treatment Period.

Number of subjects in period 1	Placebo	Soticlestat
Started	71	73
Completed	63	60
Not completed	8	13
Physician decision	1	-
Adverse event, non-fatal	4	11
Reason Not Specified	1	-
Withdrawal by Parent/Guardian	1	2
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Soticlestat placebo-matching mini-tablets or tablets, orally or via gastrostomy tube (G-tube) or low-profile gastric tube (MIC-KEY) button or jejunostomy tube (J-tube),twice daily (BID), up to 4 weeks during titration. Participants continued to receive the 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 the 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 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 dose tapered down if participants decided to discontinue the treatment.

Reporting group values	Placebo	Soticlestat	Total
Number of subjects	71	73	144
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	10.5	10.1	
standard deviation	± 5.06	± 5.04	-
Gender categorical Units: Subjects			
Male	36	36	72
Female	35	37	72
Ethnicity categorical Units: Subjects			
Hispanic or Latino	6	5	11
Not Hispanic or Latino	62	68	130
Unknown or Not Reported	3	0	3
Race categorical Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	24	27	51
Black or African American	0	3	3
Native Hawaiian or Other Pacific Islander	0	0	0
White	43	39	82
Multiple	0	1	1
Not Reported	4	2	6

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Soticlestat placebo-matching mini-tablets or tablets, orally or via gastrostomy tube (G-tube) or low-profile gastric tube (MIC-KEY) button or jejunostomy tube (J-tube),twice daily (BID), up to 4 weeks during titration. Participants continued to receive the 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 the 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 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 dose tapered down if participants decided to discontinue the treatment.

Primary: Percent Change From Baseline in Convulsive Seizure Frequency per 28 days During the Full Treatment Period

End point title	Percent Change From Baseline in Convulsive Seizure Frequency per 28 days During the Full Treatment Period

End point description:

Convulsive seizure frequency per 28 days was defined as total number of convulsive 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 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 one dose of study drug and had been assessed for seizures for at least one 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	71	73		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-8.64 (-30.13 to 14.83)	-22.16 (-53.64 to 22.73)		

Statistical analyses

Statistical analysis title	Full Treatment Period
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061 [1]
Method	ANCOVA
Parameter estimate	Hodges-Lehmann Location Shift Estimate
Point estimate	-15.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.3
upper limit	0.24

Notes:

[1] - The p-value was computed 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 Convulsive Seizure Frequency per 28 days During the Maintenance Period

End point title	Percent Change From Baseline in Convulsive Seizure Frequency per 28 days During the Maintenance Period

End point description:

Convulsive seizure frequency per 28 days was defined as total number of convulsive 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 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 one dose of study drug and had been assessed for seizures for at least one day in the Full Treatment Period. Overall number of participants 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	68	69		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-11.99 (-31.93 to 9.75)	-23.29 (-56.92 to 14.15)		

Statistical analyses

Statistical analysis title	Maintenance Period
Comparison groups	Placebo v Soticlestat

Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.089 [2]
Method	ANCOVA
Parameter estimate	Hodges-Lehmann Location Shift Estimate
Point estimate	-14.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.51
upper limit	1.53

Notes:

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

Secondary: Percentage of Responders During Maintenance Period

End point title	Percentage of Responders During Maintenance Period

End point description:

Responders were defined as those with ≥50% reduction from Baseline in convulsive seizures during the Maintenance Period. Percentages were rounded off to the nearest single decimal place. mITT Analysis Set included all randomised participants who had received at least one dose of study drug and had been assessed for seizures for at least one day in the Full Treatment Period. Overall number of participants 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	68	69		
Units: percentage of participants				
number (not applicable)	11.8	30.4		

Statistical analyses

Statistical analysis title	Maintenance Period
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	7.96

Notes:

[3] - The p-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by age stratum (≤6 years, >6 years).

Secondary: Percentage of Responders During the Full Treatment Period

End point title	Percentage of Responders During the Full Treatment Period

End point description:

Responders were defined as those with ≥50% reduction from Baseline in convulsive seizures during the Full Treatment Period. Percentages were rounded off to the nearest single decimal place. mITT Analysis Set included all randomised participants who had received at least one dose of study drug and had been assessed for seizures for at least one 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	71	73		
Units: percentage of participants				
number (not applicable)	9.9	27.4		

Statistical analyses

Statistical analysis title	Full Treatment Period
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.36
upper limit	9.49

Notes:

[4] - The p-value was based on CMH test stratified by age stratum (<=6 years, >6 years).

Secondary: Percentage of Participants with ≤0%, >0% to ≤25%, >25% to ≤50%, >50% to ≤75%, and >75% to ≤100% Reduction in Convulsive Seizures During the

Full Treatment Period

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

End point description:

Percent reduction from Baseline (%) was defined as [(Full Treatment Period Convulsive Seizure Frequency - Baseline Convulsive Seizure Frequency) divided by Baseline Convulsive Seizure Frequency] multiplied by 100. Data was reported as reduction of ≤0%, >0% to ≤25%, >25% to ≤50%, >50% to ≤75%, >75% to ≤100% or more in seizures from Baseline. Percentages were rounded off to the nearest single decimal place. mITT Analysis Set included all randomised participants who had received at least one dose of study drug and had been assessed for seizures for at least one 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	71	73		
Units: percentage of participants				
number (not applicable)				
≤0% Reduction	39.4	31.5		
>0% to ≤25% Reduction	32.4	20.5		
>25% to ≤50% Reduction	18.3	20.5		
>50% to ≤75% Reduction	8.5	13.7		
>75% to ≤100% Reduction	1.4	13.7		

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 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 will completed the Care GI-I via interview. Higher score indicates worse symptoms. Percentages were rounded off to the nearest single decimal place. mITT Analysis Set included all randomised participants who had received at least one dose of study drug and had been assessed for seizures for at least one day in the Full Treatment Period. Overall number of participants 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	68	66		
Units: percentage of participants				
number (not applicable)				
Score 1: Very Much Improved	1.5	4.5		
Score 2: Much Improved	11.8	27.3		
Score 3: Minimally Improved	22.1	28.8		
Score 4: No Change	47.1	27.3		
Score 5: Minimally Worse	10.3	7.6		
Score 6: Much Worse	5.9	3.0		
Score 7: Very Much Worse	1.5	1.5		

Statistical analyses

Statistical analysis title	Care GI-I Scale Responses
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [5]
Method	Cumulative Logit Model
Parameter estimate	Odds ratio (OR)
Point estimate	2.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	4.72

Notes:

[5] - P-value was computed using Cumulative Logit model including treatment and age group as factors.

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 used 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 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 completed the CGI-I. Higher score indicates worse symptoms. Percentages were rounded off to the nearest single decimal place. mITT Analysis Set included all randomised participants who had received at least one dose of study drug and had been assessed for seizures for at least one day in the Full Treatment Period. Overall number of participants 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	71	71		
Units: percentage of participants				
number (not applicable)				
Score 1: Very Much Improved	2.8	7.0		
Score 2: Much Improved	8.5	25.4		
Score 3: Minimally Improved	15.5	19.7		
Score 4: No Change	59.2	38.0		
Score 5: Minimally Worse	5.6	8.5		
Score 6: Much Worse	8.5	1.4		
Score 7: Very Much Worse	0.0	0.0		

Statistical analyses

Statistical analysis title	CGI-I Scale Responses
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [6]
Method	Cumulative Logit Model
Parameter estimate	Odds ratio (OR)
Point estimate	2.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.37
upper limit	4.87

Notes:

[6] - P-value was computed using Cumulative Logit model including treatment and age group as factors.

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). Higher score

indicates worse symptoms. Percentages were rounded off to the nearest single decimal place. mITT Analysis Set included all randomised participants who had received at least one dose of study drug and had been assessed for seizures for at least one day in the Full Treatment Period. Overall number of participants 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	71	71		
Units: percentage of participants				
number (not applicable)				
Alertness: Score 1: Very Much Improved	2.8	7.0		
Alertness: Score 2: Much Improved	8.5	4.2		
Alertness: Score 3: Minimally Improved	14.1	14.1		
Alertness: Score 4: No Change	67.6	70.4		
Alertness: Score 5: Minimally Worse	5.6	4.2		
Alertness: Score 6: Much Worse	1.4	0.0		
Alertness: Score 7: Very Much Worse	0.0	0.0		
Communication: Score 1: Very Much Improved	1.4	4.2		
Communication: Score 2: Much Improved	11.3	5.6		
Communication: Score 3: Minimally Improved	18.3	22.5		
Communication: Score 4: No Change	62.0	62.0		
Communication: Score 5: Minimally Worse	4.2	4.2		
Communication: Score 6: Much Worse	2.8	1.4		
Communication: Score 7: Very Much Worse	0.0	0.0		
Disruptive Behaviors: Score 1: Very Much Improved	1.4	1.4		
Disruptive Behaviors: Score 2: Much Improved	4.2	5.6		
Disruptive Behaviors: Score 3: Minimally Improved	14.1	16.9		
Disruptive Behaviors: Score 4: No Change	69.0	64.8		
Disruptive Behaviors: Score 5: Minimally Worse	11.3	8.5		
Disruptive Behaviors: Score 6: Much Worse	0.0	1.4		
Disruptive Behaviors: Score 7: Very Much Worse	0.0	1.4		

Statistical analyses

Statistical analysis title	CGI-I Nonseizure Symptoms Alertness Domain
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.741 [7]
Method	Cumulative Logit Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	2.26

Notes:

[7] - P-value was computed using Cumulative Logit model including treatment and age group as factors.

Statistical analysis title	CGI-I Nonseizure Symptoms Behaviors Domain
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.693 [8]
Method	Cumulative Logit Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	2.28

Notes:

[8] - P-value was computed using Cumulative Logit model including treatment and age group as factors.

Statistical analysis title	CGI-I Nonseizure Symptoms Communication Domain
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.901 [9]
Method	Cumulative Logit Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	2.02

Notes:

[9] - P-value was computed using Cumulative Logit model including treatment and age group as factors.

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 on 7-point scale 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). Higher score indicates worse symptoms. Percentages were rounded off to the nearest single decimal place. mITT Analysis Set included all randomised participants who had received at least one dose of study drug and had been assessed for seizures for at least one day in the Full Treatment Period. Overall number of participants 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	69	65		
Units: percentage of participants				
number (not applicable)				
Score 1: Very Much Improved	4.3	10.8		
Score 2: Much Improved	4.3	24.6		
Score 3: Minimally Improved	15.9	23.1		
Score 4: No Change	59.4	33.8		
Score 5: Minimally Worse	5.8	1.5		
Score 6: Much Worse	8.7	6.2		
Score 7: Very Much Worse	1.4	0.0		

Statistical analyses

Statistical analysis title	CGI-I Seizure Intensity and Duration
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	Cumulative Logit Model
Parameter estimate	Odds ratio (OR)
Point estimate	3.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.87
upper limit	7.13

Notes:

[10] - P-value was computed using Cumulative Logit model including treatment and age group as factors.

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:

The QI-Disability tool is a parent/caregiver-reported questionnaire that evaluated the quality of life in children with intellectual disabilities. It contains 32 items covering 6 domains of quality of life: physical health, positive emotions, negative emotions, social interaction, leisure and the outdoors, and independence. Each QI-Disability item is rated on a Likert scale of: Never, Rarely, Sometimes, Often, and Very Often. Items were linearly transformed to a scale of 0 to 100, with higher scores representing better quality of life. Domain scores are calculated by averaging item scores. The domain scores are summed and divided by 6 to yield a total score. The total score ranges from 0 to 100, with higher scores indicating a better quality of life. A negative change from Baseline implies deteriorating quality of life. Mixed-effects model for repeated measures (MMRM) was used for analysis.

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	53	56		
Units: score on a scale				
arithmetic mean (standard deviation)	2.81 (± 10.119)	-1.23 (± 15.438)		

Statistical analyses

Statistical analysis title	Change From Baseline in QI-Disability Total Score
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.189 [11]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-3.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.59
upper limit	1.52

Notes:

[11] - P-value was based on MMRM analysis with change from baseline as outcome and baseline score as fixed continuous effect; treatment group, age stratum, analysis visit, and analysis visit by treatment group interaction as fixed categorical effects.

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 is defined as total number of seizures reported during the period divided by number of days during the period seizures were assessed multiplied by 28. Percent change from Baseline is defined as (frequency of seizures per 28 days during 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 one dose of study drug and had been assessed for seizures for at least one day in the Full Treatment Period. Overall number of participants 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	68	69		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-11.89 (-33.78 to 10.50)	-17.24 (-56.83 to 23.70)		

Statistical analyses

Statistical analysis title	Maintenance Period
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.565 [12]
Method	ANCOVA
Parameter estimate	Hodges-Lehmann Location Shift Estimate
Point estimate	-9.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.01
upper limit	7.87

Notes:

[12] - The p-value was computed using rank ANCOVA model using treatment group, age stratum (<=6 years, >6 years), and rank of Baseline seizure frequency per 28 days as predictors.

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 is defined as total number of seizures reported during the period divided by number of days during the period seizures were assessed multiplied by 28. Percent change from Baseline is defined as (frequency of seizures per 28 days during 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 one dose of study drug and had been assessed for seizures for at least one 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	71	73		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-7.46 (-32.37 to 14.83)	-9.27 (-54.11 to 30.00)		

Statistical analyses

Statistical analysis title	Full Treatment Period
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.637 [13]
Method	ANCOVA
Parameter estimate	Hodges-Lehmann Location Shift Estimate
Point estimate	-8.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.31
upper limit	10.13

Notes:

[13] - The p-value was computed using rank ANCOVA model using treatment group, age stratum (<=6 years, >6 years), and rank of Baseline seizure frequency per 28 days as predictors.

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

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

End point description:

Convulsive seizure-free days was defined as number of days a participant remained convulsive seizure free after initiation of the treatment. The percentage of convulsive seizure-free days during a period was defined as the number of non-missing seizure diary days when no convulsive seizures occurred during the period divided by the number of non-missing diary days during the period. The change from baseline was defined as the percentage of convulsive seizure -free days during the period minus the percentage

of convulsive seizure-free days during the Baseline Period. 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 one dose of study drug and had been assessed for seizures for at least one 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	71	73		
Units: percentage of days				
least squares mean (standard error)	2.74 (± 1.784)	3.54 (± 1.719)		

Statistical analyses

Statistical analysis title	Full Treatment Period
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.81
upper limit	5.4

Secondary: Longest Convulsive Seizure-free Interval During the Full Treatment Period

End point title	Longest Convulsive Seizure-free Interval During the Full Treatment Period

End point description:

Longest convulsive seizure-free interval was defined as the longest time period that the participant remained convulsive 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 one dose of study drug and had been assessed for seizures for at least one 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	71	73		
Units: days				
least squares mean (standard error)	16.7 (± 2.15)	22.3 (± 2.08)		

Statistical analyses

Statistical analysis title	Full Treatment Period
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	11.2

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 randomized participants who had received at least one dose of study drug and had been assessed for seizures for at least one 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	71	73		
Units: days				
least squares mean (standard error)	4.0 (± 0.81)	2.9 (± 0.78)		

Statistical analyses

Statistical analysis title	Number of Days Rescue ASM is Used
Comparison groups	Placebo v Soticlestat
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	1

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 had taken at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

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 the 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 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 dose tapered down if participants decided to discontinue the treatment.

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 the 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.

Serious adverse events	Soticlestat	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 73 (9.59%)	10 / 71 (14.08%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	2 / 73 (2.74%)	4 / 71 (5.63%)	
occurrences causally related to treatment / all	1 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure cluster			
subjects affected / exposed	2 / 73 (2.74%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden unexplained death in epilepsy			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (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 / 73 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory tract infection			
subjects affected / exposed	1 / 73 (1.37%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Soticlestat	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 73 (54.79%)	37 / 71 (52.11%)	
Nervous system disorders			
Change in seizure presentation			
subjects affected / exposed	10 / 73 (13.70%)	9 / 71 (12.68%)	
occurrences (all)	10	10	
Somnolence			
subjects affected / exposed	10 / 73 (13.70%)	8 / 71 (11.27%)	
occurrences (all)	11	11	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 73 (2.74%)	4 / 71 (5.63%)	
occurrences (all)	2	4	
Pyrexia			
subjects affected / exposed	8 / 73 (10.96%)	9 / 71 (12.68%)	
occurrences (all)	8	13	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 73 (8.22%)	0 / 71 (0.00%)	
occurrences (all)	6	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 73 (8.22%)	1 / 71 (1.41%)	
occurrences (all)	6	1	

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 9 / 73 (12.33%) 12 6 / 73 (8.22%) 7	 9 / 71 (12.68%) 12 8 / 71 (11.27%) 9	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 5 / 73 (6.85%) 6	 4 / 71 (5.63%) 4	

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. Removed ophthalmological evaluations from safety endpoints. 3. Changed "convulsive seizures" to the "most impactful seizures", increased the number of convulsive seizures from ≥4 to ≥12 over 12 weeks before screening. 4. Broadened option to have virtual visits to allow more flexibility for participants/parents or caregivers who may have difficulties with travel for clinic visits, such as coronavirus disease 2019 (COVID-19) restrictions or other extenuating circumstances. 5. Updated the inclusion/exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported