



## 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)                          | EMA-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:

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**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      |
| <b>Arm title</b>             | 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.

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | 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     |

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Dosage and administration details:

Administered for 16 weeks in the treatment period.

| <b>Number of subjects in period 1</b> | 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



|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[1]</sup>                            |
| 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 ( $\leq 6$  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

|                                       |                         |                         |  |  |
|---------------------------------------|-------------------------|-------------------------|--|--|
| <b>End point values</b>               | 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

|                                   |                                                   |
|-----------------------------------|---------------------------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[2]</sup>                 |
| 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 ( $\leq 6$  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 $\geq 50\%$ 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

|                                         |                          |
|-----------------------------------------|--------------------------|
| <b>Statistical analysis title</b>       | 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                     |

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**Secondary: Percentage of Responders During the Full Treatment Period**

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|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| End point title | Percentage of Responders During the Full Treatment Period |
|-----------------|-----------------------------------------------------------|

End point description:

Responders are defined as those with  $\geq 50\%$  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

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| 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                     |

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

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|                 |                                                                                                                                                                                                          |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants with $\leq 0\%$ , $>0\%$ to $\leq 25\%$ , $>25\%$ to $\leq 50\%$ , $>50\%$ to $\leq 75\%$ , $>75\%$ to $\leq 100\%$ 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  $\leq 0\%$ ,  $>0\%$  to  $\leq 25\%$ ,  $>25\%$  to  $\leq 50\%$ ,  $>50\%$  to  $\leq 75\%$ ,  $>75\%$  to  $\leq 100\%$  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

| <b>End point values</b>                           | 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

|                                   |                       |
|-----------------------------------|-----------------------|
| <b>Statistical analysis title</b> | 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             |

|                                         |                       |
|-----------------------------------------|-----------------------|
| <b>Statistical analysis title</b>       | 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                  |

|                                         |                             |
|-----------------------------------------|-----------------------------|
| <b>Statistical analysis title</b>       | 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 ( $\pm$ 1.661) | 7.84 ( $\pm$ 1.676) |  |  |

## Statistical analyses

|                                         |                                     |
|-----------------------------------------|-------------------------------------|
| <b>Statistical analysis title</b>       | 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                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                    |

|                                     |                   |                    |  |  |
|-------------------------------------|-------------------|--------------------|--|--|
| <b>End point values</b>             | Placebo           | Soticlestat        |  |  |
| Subject group type                  | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed         | 136               | 134                |  |  |
| Units: days                         |                   |                    |  |  |
| least squares mean (standard error) | 5.5 ( $\pm$ 1.39) | 10.9 ( $\pm$ 1.41) |  |  |

## Statistical analyses

|                                   |                                   |
|-----------------------------------|-----------------------------------|
| <b>Statistical analysis title</b> | 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 %

| <b>Non-serious adverse events</b>                     | 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<br>occurrences (all)                                                             | 11 / 136 (8.09%)<br>13 | 10 / 134 (7.46%)<br>11 |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 3 / 136 (2.21%)<br>3   | 8 / 134 (5.97%)<br>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:

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### 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: