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RESEARCH ARTICLE

A phase 3, randomized clinical trial of soticlestat as adjunctive therapy for Lennox–Gastaut syndrome

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Abstract

Objective: There remains a need for new treatments for Lennox–Gastaut syndrome (LGS), a developmental and epileptic encephalopathy with a heterogenous patient population that often requires polytherapy. The phase 3, randomized SKYWAY study (NCT04938427) investigated the efficacy and safety of the cholesterol 24-hydroxylase inhibitor soticlestat (TAK-935) in participants with LGS.

Methods: This global, double-blind, placebo-controlled trial enrolled participants aged 2–55 years with LGS (adjudicated by the Epilepsy Study Consortium). Participants were randomized 1:1 to stable background medication plus either soticlestat (≤300 mg twice daily, weight-adjusted) or placebo over 16 weeks

(4-week titration plus 12-week maintenance). The primary endpoint was percentage change from baseline in major motor drop (MMD) seizure frequency per 28 days.

Results: SKYWAY enrolled 270 participants (placebo, $n = 136$; soticlestat, $n = 134$); mean age was 12.9 years; 95% were receiving ≥2 antiseizure medications. The difference in median change from baseline in MMD seizure frequency for soticlestat versus placebo was −1.17% ($p = .785$) during the full treatment period and 2.43% ($p = .778$) during maintenance. No meaningful difference was observed between soticlestat and placebo for most key secondary endpoints; numerical trends for small effects favoring soticlestat were seen in the proportions of participants showing improvement in the Clinical Global Impression of Improvement (CGI-I) Non-seizure Symptoms Disruptive Behaviors domain (odds ratio = 1.91, nominal $p = .032$) and CGI-I Seizure Intensity and Duration (odds ratio = 1.67, nominal $p = .029$). Treatment-related adverse events (TEAEs; mostly mild or moderate) were reported in 68.4% of placebo-treated and 74.6% of soticlestat-treated participants; the most frequent treatment-related TEAE with soticlestat was somnolence. Serious treatment-related TEAEs occurred in one placebo-treated and three soticlestat-treated participants.

Significance: Soticlestat did not demonstrate efficacy versus placebo in reducing MMD seizure frequency; the safety findings were consistent with those of previous studies. These data suggest that targeting cholesterol 24-hydroxylase is not a suitable pharmacotherapeutic strategy for LGS.

KEYWORDS

cholesterol 24-hydroxylase, Lennox–Gastaut syndrome, soticlestat, TAK-935

1 | INTRODUCTION

Lennox–Gastaut syndrome (LGS) is a rare developmental and epileptic encephalopathy (DEE), with highly heterogeneous etiologies and multiple seizure types, that constitutes approximately 1%–6% of all epilepsies and approximately 4%–8% of childhood epilepsies.[1–6] DEEs are characterized by developmental delay or impairment in cognitive and behavioral function, and frequent epileptic activity that may be associated with further neurodevelopmental stagnation or decline.[2,3,7] Age at onset of LGS is usually between 18 months and 8 years and is most common at ages 3–5 years.[2,8] LGS has three key features.[2,9–11] These include at least two types of treatment-resistant seizures, one of which must be tonic, associated with atonic seizures, typical absence seizures, or both.[12] The other two key features are neurodevelopmental (cognitive and, frequently, behavioral) impairments that may manifest before or after seizure onset and electroencephalographic recordings that show both generalized slow spike-and-wave complexes and paroxysmal fast activity.[10] LGS typically persists into adulthood, with seizures remaining resistant to treatment.[2]

Seizure activity in LGS commonly requires simultaneous use of multiple (two to four[11–13]) antiseizure medications (ASMs; known as polytherapy),[11–13] but seizures often remain uncontrolled. Polytherapy may increase the risk of adverse events (AEs), which may include seizure worsening, behavioral problems, and sedation,[13–15] and in addition, treatments need to be changed over time. Thus, there remains a need for new treatments that are efficacious with a favorable safety profile.

Soticlestat (TAK-935) is an investigational, first-in-class, selective inhibitor of cholesterol 24-hydroxylase (CH24H; also known as CYP46A1).[16,17] CH24H metabolizes brain cholesterol into 24*S*-hydroxycholesterol (24HC), a positive allosteric modulator of N-methyl-D-aspartate receptor; interaction between 24HC and

Key points

- LGS is a rare childhood onset epilepsy that is resistant to ASMs.
- This phase 3 trial explored adjunctive therapy with the CH24H inhibitor soticlestat versus placebo in children and adults with LGS.
- Soticlestat and placebo did not differ for the primary endpoint of MMD seizure frequency change nor multiple secondary efficacy endpoints.
- TEAE incidences were similar between treatment groups, and TEAEs were generally mild to moderate in severity.
- Targeting CH24H may not be a suitable pharmacotherapeutic strategy for LGS.

N-methyl-D-aspartate receptor can enhance glutamatergic transmission, resulting in seizures.[16,18] Preclinical studies showed that soticlestat reduced seizurelike behaviors and seizure frequency in mice.[16,18] In a phase 1/2 study in adults with DEE (27.8% with LGS) and the phase 2, randomized, double-blind ELEKTRA study in children with LGS or Dravet syndrome (also a DEE), soticlestat reduced the median frequency of seizures.[17,19] Additionally, a higher proportion of participants who received soticlestat had a ≥50% reduction in seizure frequency and improvement in global functioning, as assessed via the Caregiver Global Impression of Improvement (Care GI-I) and Clinical Global Impression of Improvement (CGI-I) questionnaires, versus placebo (phase 2).[17]

Analysis of the phase 2 study's LGS subgroup showed a placebo-adjusted median reduction in drop seizures over the maintenance (17.08%, $p = .1160$) and full treatment periods (14.81%, $p = .1279$).[17] However, an additional post hoc analysis of seizures that led to a fall or would have resulted in a fall (drop seizures) showed a larger signal for efficacy (placebo-adjusted median change from baseline of −30.6%, 95% confidence interval [CI] = −82.18 to 14.44). Based on these data, a phase 3 study was designed, and the primary endpoint was changed to reduction in major motor drop (MMD) seizures.

With regard to safety, phase 1 studies in healthy volunteers showed that soticlestat was generally well tolerated, with treatment-emergent AEs (TEAEs) mostly mild in intensity.[20,21] These findings were confirmed by the phase 1/2 studies in people with LGS,[17,19] supporting the further investigation of soticlestat as a potential treatment for seizures associated with LGS.

Here, we report efficacy and safety results from SKYWAY, a global, phase 3 clinical trial of soticlestat as adjunctive therapy in children and adults with LGS.

2 | MATERIALS AND METHODS

2.1 | Trial design

This was a phase 3, global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study (ClinicalTrials.gov: NCT04938427; EudraCT number: 2021-002481-40). The study consisted of a screening/baseline period (4–6 weeks) followed by a 16-week treatment period comprising a 4-week titration period plus a 12-week maintenance period. After the treatment period, participants completed the study or rolled over to an open-label extension (Figure S1). Participants who discontinued the study drug during the treatment period and those who did not enroll in the open-label extension underwent a 1-week taper period followed by a 2-week safety follow-up visit or phone call.

Participants aged 2–55 years and with body weight≥10 kg at screening were included in the study if they had a documented clinical diagnosis of LGS that was supported by various combinations of typical clinical features (onset of seizures between ages 1 and 8 years; presence of multiple seizure types; history of abnormal electroencephalography; developmental delay or intellectual disability consistent with LGS); had ≥8 MMD seizures per month during the 3 months preceding screening; and had ≥8 MMD seizures per 28 days during the prospective baseline period (4–6 weeks in duration).

Key exclusion criteria included current enrollment in a clinical trial of a different investigational drug; participation in a clinical trial of a different study drug in the past 30 days before screening; prior receipt of soticlestat; and admission to a medical facility and intubation for treatment of status epilepticus twice or more in the 3 months before screening. Use of strong CYP3A inducers, except ASMs (e.g., carbamazepine, phenobarbital, phenytoin) and topical preparations, and herbal preparations as ASMs were not permitted. Additional information can be found in Methods S1.

The study was approved by the institutional review board or ethics committee at each site and was performed in accordance with the protocol, the Declaration of Helsinki, the International Council on Harmonization E6 Good Clinical Practice: Consolidated Guideline, and applicable local or regional regulatory requirements. All participants and/or their guardian/caregiver provided written informed consent.

2.2 | Randomization and treatments

Using an interactive web response system, participants were randomized 1:1 to receive stable background medication plus either soticlestat or placebo as adjunctive therapy (Figure S1). Stratification factors were age group (≤6 years and >6 years) and country (China, Japan, and the rest of the world). The sample size (see Methods S1) and dose selection were based on the phase 2 study and other data.[17,19]

Soticlestat or placebo were administered orally or via gastrostomy tube/low-profile gastric tube twice daily with or without food. Study treatments were administered as 20-mg minitablets for participants weighing <45 kg or as 20-mg minitablets or 100 mg for participants weighing ≥45 kg. During the titration period, for participants weighing ≥45 kg, doses were titrated up from 100 mg to a maximum of 300 mg; weight-based dosing was used for participants weighing <45 kg (Table S1). The final dose that participants tolerated at the end of the 4-week titration period was maintained until the end of the 12-week maintenance period. Further details related to dosing can be found in Methods S1.

All study treatment doses were administered blinded. Soticlestat or placebo were administered according to the titration scheme with the same number and type of tablets, which were indistinguishable.

2.3 | Endpoints

The primary endpoint was percentage change from baseline in frequency of MMD seizures per 28 days during the full 16-week treatment period (titration plus maintenance) and during the 12-week maintenance period (for European Medicines Agency registration).

An MMD seizure was defined as a seizure that either resulted in a fall or was likely to result in a fall if not prevented by body position, due to involvement of major body areas (e.g., lower extremities or trunk; Table S2). Isolated head drops or seizures involving only the face and arms were not considered MMD seizures.[22]

Key secondary endpoints were the proportion of treatment responders, defined as participants with ≥50% reduction from baseline in MMD seizures during the full treatment period and the maintenance period only; effect on the Care GI-I; effect on the CGI-I[23]; effect on the CGI-I Non-seizure Symptoms[24] completed by a clinician with input from the caregiver; effect on Quality of Life Inventory–Disability (QI-Disability; Table S3)[25]; and effect on CGI-I Seizure Intensity and Duration. See the Methods S1 for descriptions of instruments used for caregiver- and clinician-reported assessment.

Additional secondary endpoints included percentage change from baseline in frequency of all seizures per 28 days during the full treatment and maintenance periods; responder analysis of the proportion of participants with ≤0%, >0% to ≤25%, >25% to ≤50%, >50% to ≤75%, and >75% to ≤100% reduction from baseline in MMD seizures; change from baseline in proportion of MMD seizure-free days; and longest MMD seizure-free interval during the full treatment period.

Seizure frequency data were collected using an electronic daily seizure and medication diary provided to participants and/or their caregiver. The electronic diary allowed a 7-day window for data entry or correction. Backup paper diaries were also used to ensure compliance and reduce the number of missed entries. All entries were reviewed by the investigator with the participant/caregiver at each study visit (clinical or virtual) to ensure proper recording. Seizure classification at screening, as well as new seizures occurring after randomization, were reviewed and confirmed by the Epilepsy Study Consortium.

Safety endpoints included the incidence of TEAEs and incidence of abnormal clinical laboratory values.

Baseline and postdose plasma 24HC levels, a pharmacodynamic biomarker related to the mechanism of action of soticlestat, were measured at screening, Day 57 and Day 113 (Visits 1, 9, and 11) to estimate the average 24HC reduction during a dosing interval in each participant.

2.4 | Statistical analysis

Percentage change from baseline in MMD seizure frequency per 28 days was analyzed in the modified intent-to-treat population, which comprised all randomized participants who received at least one dose of study treatment and were assessed for seizures for ≥1 day during the treatment period. Seizure frequency was calculated using data collected during the baseline and treatment periods, with frequency per 28 days calculated as follows: (number of seizures during period) / (number of nonmissing diary days in the period) × 28. A rank analysis of covariance model was used to analyze the percentage change from baseline in MMD seizure frequency. The outcome variable in the model was rank of percentage change from baseline in MMD seizure frequency; treatment group, age stratum, and rank of baseline seizure frequency were included as fixed effects. Treatment effect was estimated using the Hodges–Lehmann method.

To control for global type I error, the primary and key secondary endpoints were hierarchically tested in

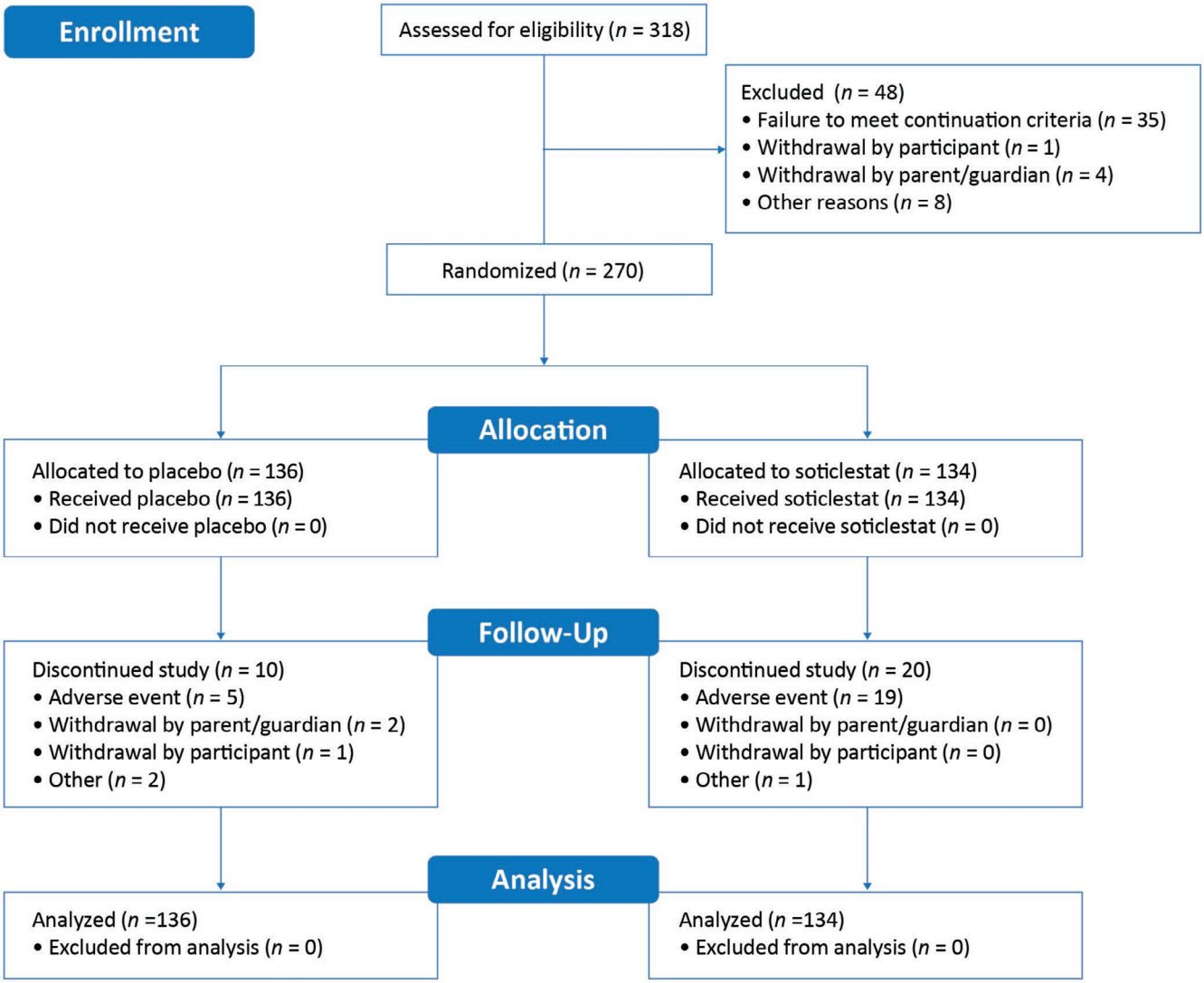

FIGURE 1 CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

the following order: the primary endpoint, responder rate, Care GI-I, CGI-I, CGI-I Non-seizure Symptoms, QI-Disability, and CGI-I Seizure Intensity and Duration. All statistical tests were two-sided at a significance level of .05.

A Cochran–Mantel–Haenszel test, stratified by age group, was used to analyze the proportion of responders. Analyses of caregiver- and clinician-reported outcome scores were based on responses at each participant's last visit at which these instruments were used. Assessments on the CGI-I Non-seizure Symptoms analyzed, in order of testing, the following three domains: alertness, communication, and disruptive behaviors. A mixed model for repeated measures was used to analyze QI-Disability scores; ordinal logistic regression was used for the other scores.

Descriptive statistics were used to summarize baseline demographics, seizure frequencies, rates of treatment response, caregiver- and clinician-reported outcomes, and safety endpoints. The safety analysis population included all participants who took at least one dose of the study drug.

3 | RESULTS

3.1 | Study population

Between November 2021 and January 2024, 270 participants were randomized to treatment with placebo (136 participants) or soticlestat (134 participants; Figure 1) at 84 study sites in 18 countries.

Baseline characteristics were balanced between the treatment groups. Overall, there were more male than female participants, and more than half were White. Between the start of screening and initial dosing in the trial, the proportions of participants who were taking at least two ASMs were 94.9% in the placebo group and

TABLE 1 Baseline demographics.

Characteristic	Placebo, *n* = 136	Soticlestat, *n* = 134
Age, years		
Mean (SD)	12.5 (6.68)	13.4 (9.35)
Median	12.0	11.5
Range	2–35	2–51
Male, *n* (%)	84 (61.8)	79 (59.0)
Female, *n* (%)	52 (38.2)	55 (41.0)
Race, *n* (%)		
Asian	44 (32.4)	42 (31.3)
Black or African American	2 (1.5)	1 (0.7)
Native Hawaiian or other Pacific Islander	1 (0.7)	0 (0.0)
White	81 (59.6)	86 (64.2)
Multiple	2 (1.5)	0 (0.0)
Not reported	6 (4.4)	5 (3.7)
Ethnicity, *n* (%)		
Hispanic or Latino	4 (2.9)	7 (5.2)
Not Hispanic or Latino	130 (95.6)	124 (92.5)
Not reported	2 (1.5)	2 (1.5)
Unknown	0 (0.0)	1 (0.7)
Years since diagnosis		
Mean (SD)	6.6 (5.5)	7.8 (8.7)
Range	0.02–25.7	0.0–46.0
Ketogenic/modified Atkins diet, *n* (%)	4 (2.9)	7 (5.2)
Vagus nerve stimulation, *n* (%)	26 (19.1)	27 (20.1)
Number of ASMs at baseline, *n* (%)[a]		
0	1 (0.7)	0 (0.0)
1	6 (4.4)	6 (4.5)
2	41 (30.1)	26 (19.4)
3	88 (64.7)	102 (76.1)
≥4	0 (0.0)	0 (0.0)
All-seizure frequency per 28 days during baseline period, median (IQR)	118.8 (59.1–238.3)	146.3 (54.1–282.3)

Abbreviations: ASM, antiseizure medicine; IQR, interquartile range.

[a]ASMs that were taken between start of screening and initial dosing.

95.5% in the soticlestat group; all participants had received at least two ASMs in the period prior to screening and up to initial dosing. Proportions of participants who were not on a ketogenic/modified Atkins diet were 97.1% (placebo) and 94.8% (soticlestat; Table 1). Mean (SD) treatment compliance was 99.6% (2.8) for the placebo group and 98.9% (6.9) for the soticlestat group.

3.2 | Effect on MMD seizure frequency

The difference for soticlestat versus placebo in placebo-adjusted median change from baseline in MMD seizure frequency was −1.17% (95% CI = −13.02 to 9.99, $p = .785$) during the full treatment period and 2.43% (95% CI = −10.86 to 15.14, $p = .778$) during the maintenance period (Figure 2). This indicates no difference in outcome between treatments.

3.3 | Secondary endpoints

Given the prespecified hierarchical testing, the absence of statistical significance for the primary endpoint restricts interpretation of secondary endpoints to numerical comparisons, and any associated *p*-values are nominal (not adjusted for multiplicity). All key secondary endpoints showed numerical trends favoring soticlestat (Table 2, Figure 3). In particular, for the CGI-I Non-seizure Symptoms Disruptive Behaviors domain (odds ratio = 1.91, 95% CI = 1.06–3.43; $p = .032$) and CGI-I Seizure Intensity and Duration (odds ratio = 1.67, 95% CI = 1.06–2.65; $p = .029$), soticlestat showed a potential benefit over placebo.

Results from the additional secondary endpoints are reported in Figures S2 and S3 and Table S4. Seven participants in the soticlestat group and four participants in the placebo group experienced a >75% reduction in MMD seizure frequency during the full treatment period (Table S4).

3.4 | Plasma 24HC levels

A decrease in plasma 24HC levels was observed for all soticlestat-treated participants (by approximately 80% vs. 3% with placebo; Figure S4). This confirmed the pharmacological effect of soticlestat and treatment adherence.

3.5 | Safety evaluation

A total of 193 participants (placebo group, 68.4%; soticlestat group, 74.6%) reported TEAEs during the study. Most TEAEs were considered not related to the study drug and were mild or moderate in severity (Table 3). There were no reported deaths in the study. TEAEs considered related to the study drug were experienced by 20.6% of participants in the placebo group and 39.6% of participants in the soticlestat group; only one participant in the placebo group and three in the soticlestat

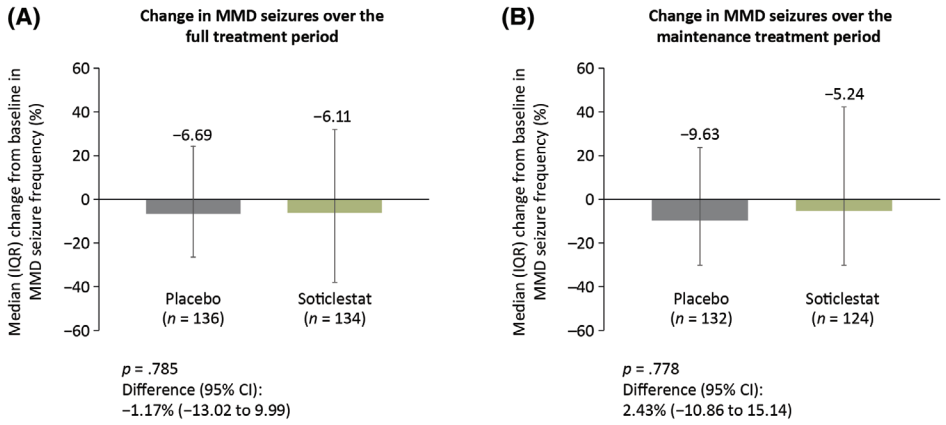

FIGURE 2 Median change from baseline in major motor drop (MMD) seizure frequency over the full (A) and maintenance (B) treatment periods. A rank analysis of covariance model was used to compute the *p*-values. The outcome variable in the model was rank of percentage change from baseline in MMD seizure frequency; treatment group, age stratum, and rank of baseline seizure frequency were included as fixed effects. The Hodges–Lehmann method was used to compute the difference and 95% confidence interval (CI). IQR, interquartile range.

TABLE 2 Secondary CGI endpoint outcomes over the full treatment period.[a]

Endpoint	Proportion of participants showing improvement		Odds ratio (95% CI)	Nominal *p*-value
	Placebo	Soticlestat		
Care CI-I	*n* = 130 39.2	*n* = 122 48.4	1.35 (0.86–2.13)	.189
CGI-I	*n* = 133 30.1	*n* = 132 43.2	1.40 (0.89–2.21)	.144
CGI-I Seizure Intensity and Duration	*n* = 131 35.1	*n* = 122 49.2	1.67 (1.06–2.65)	.029
CGI-I Non-seizure Symptoms	*n* = 133	*n* = 132		
Alertness improvement	21.8	31.8	1.40 (0.85–2.30)	.183
Communication improvement	21.8	31.8	1.50 (0.91–2.48)	.115
Disruptive behavior improvement	9.8	18.2	1.91 (1.06–3.43)	.032

Abbreviations: Care GI-I, Caregiver Global Impression of Improvement; CGI-I, Clinical Global Impression of Improvement; CI, confidence interval.

[a]Odds ratios and nominal *p*-values were computed using a cumulative logit model that adjusted for age stratum and used all seven categories of the scale. Improvement is defined as a response of minimally improved, much improved, or very much improved.

group experienced a serious treatment-related TEAE (tongue injury, change in seizure presentation [*n* = 2], and oxygen saturation decreased). TEAEs leading to study treatment discontinuation reported by more than one participant in the soticlestat group were change in seizure presentation, fatigue, and aggression. The most frequent treatment-related TEAE in the soticlestat group was somnolence (Table 3). Nothing of clinical relevance was observed for other safety outcomes.

4 | DISCUSSION

In this LGS treatment study, the addition of soticlestat resulted in a similar reduction in MMD seizure frequency to that of placebo across both the full treatment period and the maintenance period. Although numerical benefits for soticlestat compared with placebo were observed for secondary endpoints, the majority of these effects were small, and the data should be interpreted

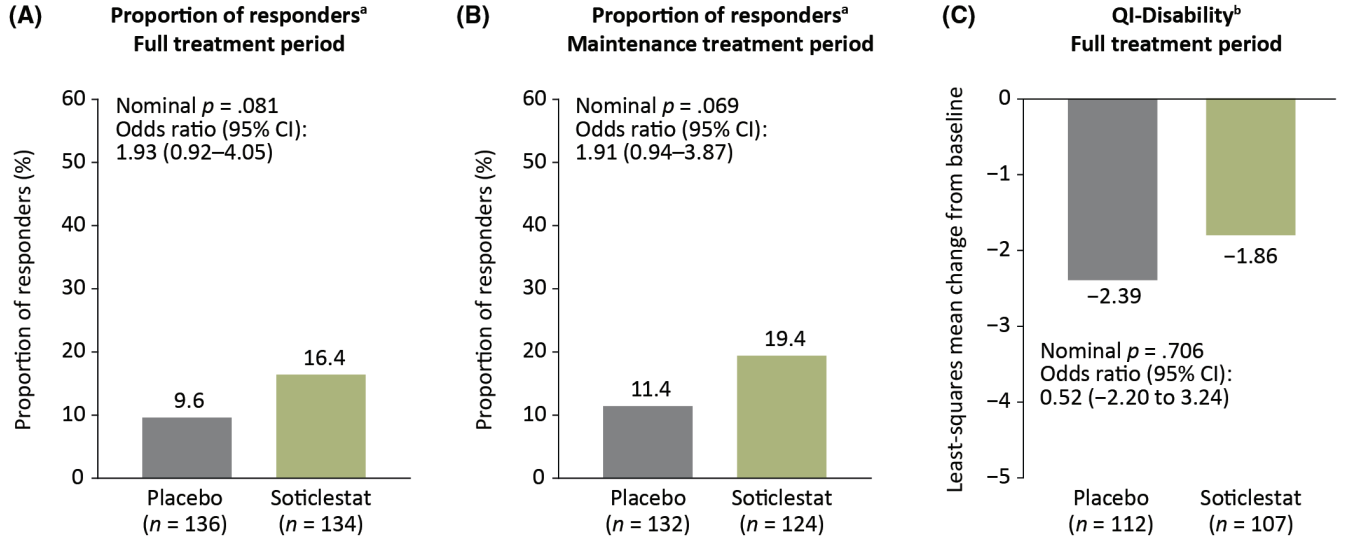

FIGURE 3 Proportion of participants with ≥50% reduction from baseline in major motor drop seizures during (A) the full treatment period and (B) the maintenance period; and (C) mean change in Quality of Life Inventory–Disability (QI-Disability) score during the full treatment period. [a]Analyzed using a Cochran–Mantel–Haenszel test stratified by age stratum. [b]Analyzed using a mixed model for repeated measures. CI, confidence interval.

with caution. The TEAEs observed in the study were generally mild to moderate in severity, occurred at similar incidences between the treatment groups, and were in line with previously published studies involving soticlestat.[17,19–21]

LGS is a very treatment-resistant DEE with highly heterogeneous etiologies and multiple seizure types.[2,5,6] Patients with LGS often require polytherapy[5] as shown in our trial, with 95% of patients receiving at least two concomitant ASMs at baseline. The therapeutic landscape for LGS is evolving, with standard of care having changed in some countries due to the introduction or approval of new ASMs.[26,27] However, despite the exposure of patients to multiple ASMs, seizures in LGS continue to be poorly controlled, with trials of established or potential ASMs frequently showing limited benefit in the difficult-to-treat LGS population.[28–30] Due to the combination of pharmacoresistance, polytherapy, and unknown factors perhaps in part related to the mechanism of action, treatments such as soticlestat, even as adjunctive therapy, may not be effective.

SKYWAY was a well-designed study, and the data are clearly interpretable. Sample size and dose selection were based on previous data and should have been sufficient to detect a treatment response. Levels of 24HC were reduced with soticlestat compared with placebo by ~80%, demonstrating sufficient dosing of soticlestat for effective inhibition of the catabolism of cholesterol to 24HC.

Several potential reasons for the lack of replication of the phase 2 findings in the present study were considered and rejected. For instance, we think it is unlikely that the lack of positive results was due to a high placebo response, as clinical trials of other approved drugs for the treatment of LGS had higher responses than seen in our study.[31–33] Compliance was also not the cause of this study not meeting its primary endpoint, as compliance with the study drug was acceptable.

Differences between the phase 2 and 3 findings should not be due to any errors in how MMD was defined, how seizure types were ascertained, or how seizure frequency was captured, as it was a refinement of the endpoint used in the previous phase 2 study. The aim of this modification to the endpoint was to further reduce variability, based on the assumption that seizure counts by caregivers are more likely to differ when there is no clearly identifiable motor component.

In addition to the primary endpoint, there were other key differences between the phase 2 and 3 studies. The phase 2 study was conducted over a longer period (20 weeks with an 8-week titration)[17] than the phase 3 study (16 weeks and 4-week titration). However, because we did not observe an increase in treatment response over time, trial duration is unlikely to be the cause of the different findings. The upper age limit was 17 years in the phase 2 study but was extended to 55 years in the phase 3 study, and the baseline age was younger in the phase 2 study (mean [SD] age = 10.0 [4.2] years in the soticlestat group and 9.8 [3.6] years in the placebo group) compared with the phase 3 study (mean [SD] age = 12.9 [8.11] years). Because data suggest that children have higher levels of 24HC than adults,[34] a substantial reduction of 24HC in this younger population may have a differential impact on seizure frequency reduction. Compared with adults,

TABLE 3 Summary of TEAEs.

	Category, *n* (%)	
	Placebo, *n* = 136	**Soticlestat, *n* = 134**
Participants with any TEAE	93 (68.4)	100 (74.6)
Mild	51 (37.5)	42 (31.3)
Moderate	35 (25.7)	43 (32.1)
Severe	7 (5.1)	15 (11.2)
Participants with treatment-related TEAEs	28 (20.6)	53 (39.6)
Participants with serious TEAEs	10 (7.4)	11 (8.2)
Status epilepticus	1 (0.7)	2 (1.5)
Change in seizure presentation	0 (0.0)	2 (1.5)
Cataract	0 (0.0)	1 (0.7)
Infections and infestations	4 (2.9)	5 (3.7)
Respiratory, thoracic, and mediastinal disorders	2 (1.5)	2 (1.5)
Esophagitis	1 (0.7)	0 (0.0)
Injury, poisoning, and procedural complications	3 (2.2)	0 (0.0)
Diarrhea and vomiting	0 (0.0)	1 (0.7)
Oxygen saturation decreased	0 (0.0)	1 (0.7)
Participants with serious and treatment-related TEAEs	1 (0.7)	3 (2.2)
Tongue injury	1 (0.7)	0 (0.0)
Change in seizure presentation	0 (0.0)	2 (1.5)
Oxygen saturation decreased	0 (0.0)	1 (0.7)
Participants with TEAEs leading to study treatment discontinuation	5 (3.7)	19 (14.2)
Treatment-related TEAEs occurring in ≥5% of participants		
Somnolence	8 (5.9)	18 (13.4)
Change in seizure presentation	6 (4.4)	15 (11.2)
Decreased appetite	0 (0.0)	8 (6.0)

Abbreviation: TEAE, treatment-emergent adverse event.

younger children may also have a lower cumulative impact of treatment-resistant seizures and disease processes. However, in SKYWAY soticlestat was not associated with significantly reduced MMD frequency in either the pediatric or adult subgroups (data not shown), and so the inclusion of adult patients cannot explain the present findings.

Clinical trials in rare diseases naturally present unique methodological challenges that influence trial design and interpretation of the results, and this is no different for rare epileptic encephalopathies like LGS. Despite its infrequency, LGS is associated with a breadth of heterogeneous etiologies, multiple seizure types, and clinical presentations. This can mean that standardized, one-size-fits-all outcomes, like "change in seizure frequency" can fail to fully capture clinical benefits for all patients. Although "change in seizure frequency" is the gold standard endpoint accepted by regulatory agencies, further research would need to focus on validating other outcome measures that reflect patient and caregiver perspectives in addition.

5 | CONCLUSIONS

In conclusion, these data suggest that targeting the CH24H mechanism of action is not a suitable pharmacotherapeutic strategy for the treatment of LGS. LGS is a syndrome with a highly heterogeneous patient population, and medications that effectively treat other epilepsies have been less successful in treating LGS.[10] Results from our study showed no difference in reducing MMD seizure frequency with adjunctive soticlestat and placebo in this population of children and adults with LGS resistant to ASM. Although numerical benefits in favor of soticlestat were observed for secondary endpoints, the effects were small, making it difficult to draw meaningful and clinically relevant conclusions. TEAEs were generally mild to moderate in severity and occurred at a similar frequency for soticlestat- and placebo-treated participants. Further research into LGS and its pathophysiology are needed to meet the current unmet needs of therapy.

AUTHOR CONTRIBUTIONS

Conceptualization: Renzo Guerrini, Yasir Khan, Pranab Mitra, Sarah I. Sheikh, Philipp von Rosenstiel, Mahnaz Asgharnejad, and Venkatesha Murthy. *Methodology:* Jimmy Schiemann, Yasir Khan, Pranab Mitra, Sarah I. Sheikh, Philipp von Rosenstiel, Mahnaz Asgharnejad, and Venkatesha Murthy. *Data acquisition:* Yasir Khan, Pranab Mitra, Mahnaz Asgharnejad, and Venkatesha Murthy. All authors were involved in data analysis or interpretation and have read and agreed to the published version of the manuscript.

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R.G. has served as a consultant or received honoraria for lectures and consulting activities from Angelini Pharma, Biocodex, BioMarin, Eisai, Ethypharm, GRIN Therapeutics, Jazz Pharmaceuticals, Novartis, Rapport Therapeutics, SK Life Science, Stoke Therapeutics, Takeda, and UCB Pharma; and has been a principal investigator for clinical trials for Eisai, Loulou Foundation, Lundbeck, Marinus, Takeda, Teva, UCB Pharma, and Zogenix. E.D.M. has been a principal investigator for studies by Acadia, Epygenix, Ionis, Jazz Pharmaceuticals, and UCB; has received research funding from the International Foundation for CDKL5 Research, International Rett Syndrome Foundation, LouLou Foundation, National Institute of Child Health and Human Development, National Institute of Neurological Disorders and Stroke, and Penn Orphan Disease Center; and has served as a consultant/advisory board member for Acadia, Stoke Therapeutics, and Taysha Therapeutics. R.K. has been an investigator for clinical trials for Longboard Pharmaceuticals, Pfizer, Takeda, and UCB Pharma, and has received honoraria for lectures from AstraZeneca and BioMarin. C.D.H. is an associate editor of the *Journal of Clinical Neurophysiology* and has received consulting income from Ceribell, Holberg EEG, Takeda Development Center Americas, Inc., and UCB Biopharma. S.A. is the deputy editor for *Epilepsia*; has served as a consultant or received honoraria for lectures from Angelini Pharma, Biocodex, Eisai, Encoded, GRIN Therapeutics, Jazz Pharmaceuticals, Neuraxpharm, Nutricia, Orion, Proveca, Stoke Therapeutics, Takeda, UCB Pharma, and Xenon; and has been an investigator for clinical trials for Eisai, Marinus, Proveca, Takeda, and UCB Pharma. J.S., Y.K., P.M., S.I.S., P.v.R., M.A., and V.M. are employees of Takeda Development Center Americas, Inc, and stockholders in Takeda Pharmaceutical Company Limited. D.D. reports research salary support from the Epilepsy Study Consortium for consulting activities, scientific advisory meetings, and investigator meetings for Beacon, Biohaven, Encoded, GRIN Pharmaceuticals, Jazz Pharmaceuticals, Longboard Pharmaceuticals, Rapport Therapeutics, SK Life Sciences, Stoke Therapeutics, Takeda, and UCB. The other authors report no disclosures relevant to this article. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Takeda does not plan to share data supporting the results reported in this article.

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REFERENCES

1. Trevathan E, Murphy CC, Yeargin-Allsopp M. Prevalence and descriptive epidemiology of Lennox-Gastaut syndrome among Atlanta children. Epilepsia. 1997;38(12):1283–8. https://doi.org/10.1111/j.1528-1157.1997.tb00065.x
2. Specchio N, Wirrell EC, Scheffer IE, Nabbout R, Riney K, Samia P, et al. International league against epilepsy classification and definition of epilepsy syndromes with onset in childhood: position paper by the ILAE task force on nosology and definitions. Epilepsia. 2022;63(6):1398–442. https://doi.org/10.1111/epi.17241
3. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512–21. https://doi.org/10.1111/epi.13709
4. Strzelczyk A, Zuberi SM, Striano P, Rosenow F, Schubert-Bast S. The burden of illness in Lennox-Gastaut syndrome: a systematic literature review. Orphanet J Rare Dis. 2023;18(1):42. https://doi.org/10.1186/s13023-023-02626-4
5. Cross JH, Benitez A, Roth J, Andrews JS, Shah D, Butcher E, et al. A comprehensive systematic literature review of the burden of illness of Lennox-Gastaut syndrome on patients, caregivers, and society. Epilepsia. 2024;65(5):1224–39. https://doi.org/10.1111/epi.17932
6. Sullivan J, Benitez A, Roth J, Andrews JS, Shah D, Butcher E, et al. A systematic literature review on the global epidemiology of Dravet syndrome and Lennox-Gastaut syndrome:

prevalence, incidence, diagnosis, and mortality. Epilepsia. 2024;65(5):1240–63. https://doi.org/10.1111/epi.17866
7. Scheffer IE, French J, Valente KD, Auvin S, Cross JH, Specchio N. Operational definition of developmental and epileptic encephalopathies to underpin the design of therapeutic trials. Epilepsia. 2025;66(4):1014–23. https://doi.org/10.1111/epi.18265
8. Resnick T, Sheth RD. Early diagnosis and treatment of Lennox-Gastaut syndrome. J Child Neurol. 2017;32(11):947–55. https://doi.org/10.1177/0883073817714394
9. Chipaux M, Szurhaj W, Vercueil L, Milh M, Villeneuve N, Cances C, et al. Epilepsy diagnostic and treatment needs identified with a collaborative database involving tertiary centers in France. Epilepsia. 2016;57(5):757–69. https://doi.org/10.1111/epi.13368
10. Asadi-Pooya AA. Lennox-Gastaut syndrome: a comprehensive review. Neurol Sci. 2018;39(3):403–14. https://doi.org/10.1007/s10072-017-3188-y
11. Benitez A, Roth J, Andrews JS, Shah D, Butcher E, Cross JH, et al. Burden of illness of Lennox–Gastaut syndrome: a systematic literature review. Presented at the American Epilepsy Society Annual Meeting; December 2–6, 2022; Nashville, TN, USA.
12. Reaven NL, Funk SE, Lyons PD, Story TJ. The direct cost of seizure events in severe childhood-onset epilepsies: a retrospective claims-based analysis. Epilepsy Behav. 2019;93:65–72. https://doi.org/10.1016/j.yebeh.2019.01.045
13. Cross JH, Auvin S, Falip M, Striano P, Arzimanoglou A. Expert opinion on the management of Lennox-Gastaut syndrome: treatment algorithms and practical considerations. Front Neurol. 2017;8:505. https://doi.org/10.3389/fneur.2017.00505
14. Kerr M, Kluger G, Philip S. Evolution and management of Lennox-Gastaut syndrome through adolescence and into adulthood: are seizures always the primary issue? Epileptic Disord. 2011;13(Suppl 1):S15–S26. https://doi.org/10.1684/epd.2011.0409
15. Ostendorf AP, Ng YT. Treatment-resistant Lennox-Gastaut syndrome: therapeutic trends, challenges and future directions. Neuropsychiatr Dis Treat. 2017;13:1131–40. https://doi.org/10.2147/NDT.S115996
16. Nishi T, Kondo S, Miyamoto M, Watanabe S, Hasegawa S, Kondo S, et al. Soticlestat, a novel cholesterol 24-hydroxylase inhibitor shows a therapeutic potential for neural hyperexcitation in mice. Sci Rep. 2020;10(1):17081. https://doi.org/10.1038/s41598-020-74036-6
17. Hahn CD, Jiang Y, Villanueva V, Zolnowska M, Arkilo D, Hsiao S, et al. A phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of soticlestat as adjunctive therapy in pediatric patients with Dravet syndrome or Lennox-Gastaut syndrome (ELEKTRA). Epilepsia. 2022;63(10):2671–83. https://doi.org/10.1111/epi.17367
18. Salamone A, Terrone G, Di Sapia R, Balosso S, Ravizza T, Beltrame L, et al. Cholesterol 24-hydroxylase is a novel pharmacological target for anti-ictogenic and disease modification effects in epilepsy. Neurobiol Dis. 2022;173:105835. https://doi.org/10.1016/j.nbd.2022.105835
19. Halford JJ, Sperling MR, Arkilo D, Asgharnejad M, Zinger C, Xu R, et al. A phase 1b/2a study of soticlestat as adjunctive therapy in participants with developmental and/or epileptic encephalopathies. Epilepsy Res. 2021;174:106646. https://doi.org/10.1016/j.eplepsyres.2021.106646
20. Wang S, Chen G, Merlo Pich E, Affinito J, Cwik M, Faessel H. Safety, tolerability, pharmacokinetics, pharmacodynamics, bioavailability and food effect of single doses of soticlestat in healthy subjects. Br J Clin Pharmacol. 2021;87(11):4354–65. https://doi.org/10.1111/bcp.14854
21. Wang S, Chen G, Merlo Pich E, Affinito J, Cwik M, Faessel HM. Pharmacokinetics, pharmacodynamics and safety assessment of multiple doses of soticlestat in healthy volunteers. Br J Clin Pharmacol. 2022;88(6):2899–908. https://doi.org/10.1111/bcp.15225
22. Dlugos D, Forgacs P, Asgharnejad M, Arkilo D. Major motor drop seizures for endpoint assessments in a phase 3 trial of soticlestat in individuals with Lennox–Gastaut syndrome. Presented at the 75th Annual Meeting of the American Epilepsy Society; December 3–7, 2021; Chicago, IL, USA.
23. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007;4(7):28–37.
24. Andrews JS, Shah D, Nacson A, Symonds T, Hughes S, Asgharnejad M, et al. Development and refinement of the clinical global impression of improvement for non-seizure symptoms measure in Dravet syndrome and Lennox-Gastaut syndrome. J Patient Rep Outcomes. 2025;9(1):24. https://doi.org/10.1186/s41687-024-00829-2
25. Downs J, Jacoby P, Leonard H, Epstein A, Murphy N, Davis E, et al. Psychometric properties of the quality of life inventory-disability (QI-disability) measure. Qual Life Res. 2019;28(3):783–94. https://doi.org/10.1007/s11136-018-2057-3
26. Auvin S, Arzimanoglou A, Falip M, Striano P, Cross JH. Refining management strategies for Lennox-Gastaut syndrome: updated algorithms and practical approaches. Epilepsia Open. 2025;10(1):85–106. https://doi.org/10.1002/epi4.13075
27. Besag FMC, Vasey MJ, Brown RJ. Promising therapeutic strategies for Lennox-Gastaut syndrome: what's new? Expert Rev Neurother. 2025;25(1):15–27. https://doi.org/10.1080/14737175.2024.2439512
28. Brigo F, Jones K, Eltze C, Matricardi S. Anti-seizure medications for Lennox-Gastaut syndrome. Cochrane Database Syst Rev. 2021;4(4):CD003277. https://doi.org/10.1002/14651858.CD003277.pub4
29. Group for the Evaluation of Cinromide in the Lennox-Gastaut Syndrome. Double-blind, placebo-controlled evaluation of cinromide in patients with the Lennox-Gastaut Syndrome. Epilepsia. 1989;30(4):422–9. https://doi.org/10.1111/j.1528-1157.1989.tb05321.x
30. Jazz Pharmaceuticals plc. Jazz Pharmaceuticals provides update on cannabidiol oral solution phase 3 trial in Japan in treatment-resistant epilepsies. 2024 [cited July 2, 2025]. Available from: https://investor.jazzpharma.com/node/21156/pdf
31. Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA. OV-1012 study investigators. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology. 2011;77(15):1473–81. https://doi.org/10.1212/WNL.0b013e318232de76
32. US Food and Drug Administration. "Silver Spring (MD): US Food and Drug Administration. EPIDIOLEX

prescribing information." 2018 [cited April 2, 2025]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210365s005s006s007lbl.pdf.

33. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391(10125):1085–96. https://doi.org/10.1016/s0140-6736(18)30136-3
34. Bretillon L, Lütjohann D, Ståhle L, Widhe T, Bindl L, Eggertsen G, et al. Plasma levels of 24S-hydroxycholesterol reflect the balance between cerebral production and hepatic metabolism and are inversely related to body surface. J Lipid Res. 2000;41(5):840–5.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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