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A phase 1b/2a study of soticlestat as adjunctive therapy in participants with developmental and/or epileptic encephalopathies

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ABSTRACT

Objective: To evaluate the safety, tolerability, and pharmacokinetics of soticlestat, a first-in-class cholesterol 24-hydroxylase inhibitor, in adults with developmental and/or epileptic encephalopathies (DEE).

Methods: The study comprised a 30-day, randomized, double-blind, placebo-controlled phase (Part A), followed by a 55-day open-label phase (Part B) (ClinicalTrials.gov ID: NCT03166215) . In Part A, patients with DEE and at least one bilateral motor seizure during the 4-week prospective baseline period were randomized 4:1 to receive soticlestat or placebo, in addition to their usual antiseizure medication. In Part B, all patients received open-label soticlestat. Soticlestat doses were titrated according to tolerability to a maximum of 300 mg twice daily (BID). Safety evaluations included the incidence of treatment-emergent adverse events (TEAEs). Plasma soticlestat concentrations were measured at various times for determination of multiple-dose pharmacokinetics and 24*S*-hydroxycholesterol (24HC). Efficacy was assessed by evaluation of changes in seizure frequency from baseline.

Results: Eighteen patients (median age, 28.5 years) were enrolled and randomized, and 14 (78 %) completed the study. In Part A, TEAEs occurred in 71.4 % of soticlestat-treated patients and 100 % of placebo-treated patients. In Part B, the overall incidence of TEAEs was 68.8 %. In Part A, TEAEs that occurred in more than one patient in the soticlestat group were dysarthria (n = 3, 21.4 %), lethargy (n = 2, 14.3 %), upper respiratory tract infection (n = 2, 14.3 %), fatigue (n = 2, 14.3 %), and headache (n = 2, 14.3 %). Four patients discontinued treatment because of TEAEs, of whom two reported drug-related seizure clusters as serious TEAEs. There were no deaths. Pharmacokinetic analysis showed dose-dependent increases in systemic exposure and peak plasma soticlestat concentrations. At the end of Part B, the overall mean percent change from baseline in plasma 24HC was −80.97 %. Changes from baseline in median seizure frequency were +16.71 % and +22.16 % in the soticlestat and placebo groups, respectively, in Part A, and −36.38 % in all participants in Part B.

Conclusion: Soticlestat was well tolerated at doses of up to 300 mg BID and was associated with a reduction in median seizure frequency over the study duration. Further studies are warranted to assess the possible efficacy of soticlestat as adjunctive therapy in patients with DEEs such as Dravet syndrome and Lennox–Gastaut syndrome.

Abbreviations: 24HC, 24*S*-hydroxycholesterol; ABC-C, Aberrant Behavior Checklist-Community Edition; ASM, antiseizure medication; $AUC_{0-\tau}$, area under the plasma concentration–time curve during a dosing interval; BID, twice daily; CH24H, cholesterol 24-hydroxylase; C-SSRS, Columbia-Suicide Severity Rating Scale; C_{trough}, observed plasma concentration at the end of a dosing interval; DEE, developmental and/or epileptic encephalopathies; DS, Dravet syndrome; ECG, electrocardiogram; FAS, full analysis set; LGS, Lennox–Gastaut syndrome; PD, pharmacodynamics; PK, pharmacokinetics; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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[1] At the time the study was conducted.

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1. Introduction

1.1. Epileptic encephalopathies

The developmental and/or epileptic encephalopathies (DEE) group of rare and severe epilepsies affects approximately 100,000–200,000 people in the USA, is characterized by multiple seizure types and developmental delay or regression, and incorporates a number of orphan syndromes, including Lennox–Gastaut syndrome (LGS; estimated prevalence 1–5 per 10,000 worldwide) and Dravet syndrome (DS; estimated prevalence 1 per 15,700 individuals in the USA) (Scheffer et al., 2017; Steward et al., 2019; Trevathan et al., 1997; Wu et al., 2015). Making an early diagnosis is often critical as many patients with DEE experience daily seizures, which cause significant morbidity and quick deterioration of quality of life. These rare neurodevelopmental conditions often cause seizures that are difficult to control and are highly resistant to multiple conventional antiseizure medications (ASMs) (Scheffer et al., 2017; Steward et al., 2019), thus representing a significant unmet medical need. Currently, some DEE do not have access to US Food and Drug Administration-approved therapies, whereas DS and LGS have only limited options.

The investigational drug soticlestat (TAK-935/OV935) is a first-in-class, selective inhibitor of cholesterol 24-hydroxylase (CH24H) being evaluated for adjunctive treatment of seizures in association with DEE. This novel mechanism of action is thought to have the potential to reduce seizure frequency and severity, with therapeutic benefit in epilepsy and disorders associated with overactivated glutamatergic regulation (Nishi et al., 2020), presumably through the inhibition of CH24H and associated reduction of the cholesterol metabolite 24*S*-hydroxycholesterol (24HC).

Although the role of CH24H in the pathology of disorders of the central nervous system has not been fully elucidated (Famer et al., 2007; Fourgeux et al., 2009; Jeitner et al., 2011), it has been shown that CH24H is predominantly expressed in neurons (Lund et al., 2003; Russell et al., 2009; Xie et al., 2003), and preclinical and human *postmortem* studies have shown that neurodegeneration and brain insults may lead to induction of CH24H expression in reactive astrocytes and microglia (Bogdanovic et al., 2001; Cartagena et al., 2008). This 'ectopic' expression in glia lowers cholesterol levels in the cellular environment (Cartagena et al., 2008), leading to disruption of plasma-membrane lipid rafts and astrocytic glutamate homeostasis, with markedly increased levels of extracellular glutamate, which is normally sequestered by glutamate transporters on neighboring astrocytes (Perez-Nievas and Serrano-Pozo, 2018; Tian et al., 2010). This may contribute to enhanced glutamatergic activity observed in epilepsy disorders (Chapman, 2000).

When CH24H converts cholesterol to 24HC, the circulating levels of this metabolite will increase, which may further contribute to underlying pathophysiological processes. Excessive levels of extracellular glutamate and 24HC are thought to play major roles in excitotoxicity, either through sustained activation of the *N*-methyl-D-aspartate receptor channel or as a positive allosteric modulator of the receptor (Paul et al., 2013). In addition, neuronal 24HC may have a role in the regulation of glial function, including potassium homeostasis and inflammation, as well as neurotoxic processes such as oxidative stress and necroptosis (Noguchi et al., 2014; Nury et al., 2015; Vo et al., 2015). Soticlestat is thought to reduce excessive glutamatergic action by reducing levels of 24HC through its inhibition of CH24H.

Preclinical evidence from CH24H-knockout mice compared with wild-type mice has shown that soticlestat selectively binds to CH24H (Nishi et al., 2020). In a transgenic mouse model carrying mutated human amyloid precursor protein and presenilin 1 (APP/PS1-Tg), characterized by an excitatory/inhibitory imbalance, soticlestat dose-dependently reduced 24HC. Furthermore, in APP/PS1-Tg mice, soticlestat was shown to suppress potassium-evoked extracellular glutamate elevations suggesting that soticlestat-mediated inhibition of CH24H may have therapeutic potential for disorders associated with neural hyperexcitation, such as DEEs (Nishi et al., 2020).

This phase 1b/2a clinical study examined the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of soticlestat as adjunctive therapy in adults with a diagnosis of DEE who demonstrated bilateral motor seizures.

2. Material and methods

2.1. Study design

The study (ClinicalTrials.gov ID: NCT03166215) consisted of two periods: a randomized, double-blind, placebo-controlled Part A, in which the participants were randomized to receive soticlestat or matching placebo concomitantly with standard ASM treatment regimens; and an open-label Part B, which followed immediately upon the conclusion of Part A (Fig. 1). In Part B, all participants received soticlestat to investigate its safety, tolerability, PK, and PD in an open-label manner.

The study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Conference on Harmonisation guidelines (International Council for Harmonisation, 2016), and all applicable country-specific regulations. The study protocol (available at https://clinicaltrials.gov/ct2/show/NCT03166215) was approved by an independent ethics committee or institutional review board at each site according to local regulations. Written informed consent was obtained from the participants, or their legally authorized representative, at the time of the screening (Visit 1), prior to any study procedures.

2.1.1. Inclusion/exclusion criteria

Adults (age, 18–65 years inclusive) with DEE and an average of at least two bilateral motor seizures per month during the 3 months prior to enrollment entered a 4-week prospective baseline period. Those with an average of at least one bilateral motor seizure during the baseline period (i.e. drop seizures, tonic-clonic, tonic, bilateral clonic, atonic, myoclonic-atonic, myoclonic-tonic-clonic, or focal seizures with bilateral hyperkinetic motor features) were eligible for the study.

Individuals with DEE were enrolled using the following inclusion criteria: established diagnosis of DEE, such as LGS, DS, or tuberous sclerosis complex; history of special education classes; full scale intelligence quotient < 70; or generalized background slowing (posterior dominant rhythm persistently < 8 Hz) on interictal electroencephalogram. Other inclusion criteria included a stable regimen of 1–4 ASMs for ≥ 4 weeks before screening (Visit 1). Exclusion criteria included: degenerative eye disease; an abnormal and clinically significant electrocardiogram (ECG) at screening (Visit 1); and admission to a medical facility for treatment of status epilepticus requiring mechanical respiration in the 3 months prior to screening (Visit 1).

Concomitant stiripentol use was exclusionary, however, rescue benzodiazepine use more than 3 times a week counted as an allowed ASM. Participants were advised not to consume alcohol or drugs such as cannabis (medical marijuana was allowed) during the study. No medications were allowed, including over-the-counter products, without first consulting with the investigator.

2.1.2. Objectives and endpoints

The primary objective of this study was to characterize the multiple-dose safety and tolerability profile of soticlestat in adults with a diagnosis of DEE. The secondary objective was to characterize the multiple-dose PK profile of soticlestat in adults with DEE receiving concomitant ASMs.

The primary endpoint was the percentage of participants with at least one treatment-emergent adverse event (TEAE), as reported by the participant or participants' caregivers or observed by the investigator. Additional safety assessments included clinical laboratory evaluations, vital signs, ECG parameters, Columbia-Suicide Severity Rating Scale (C-

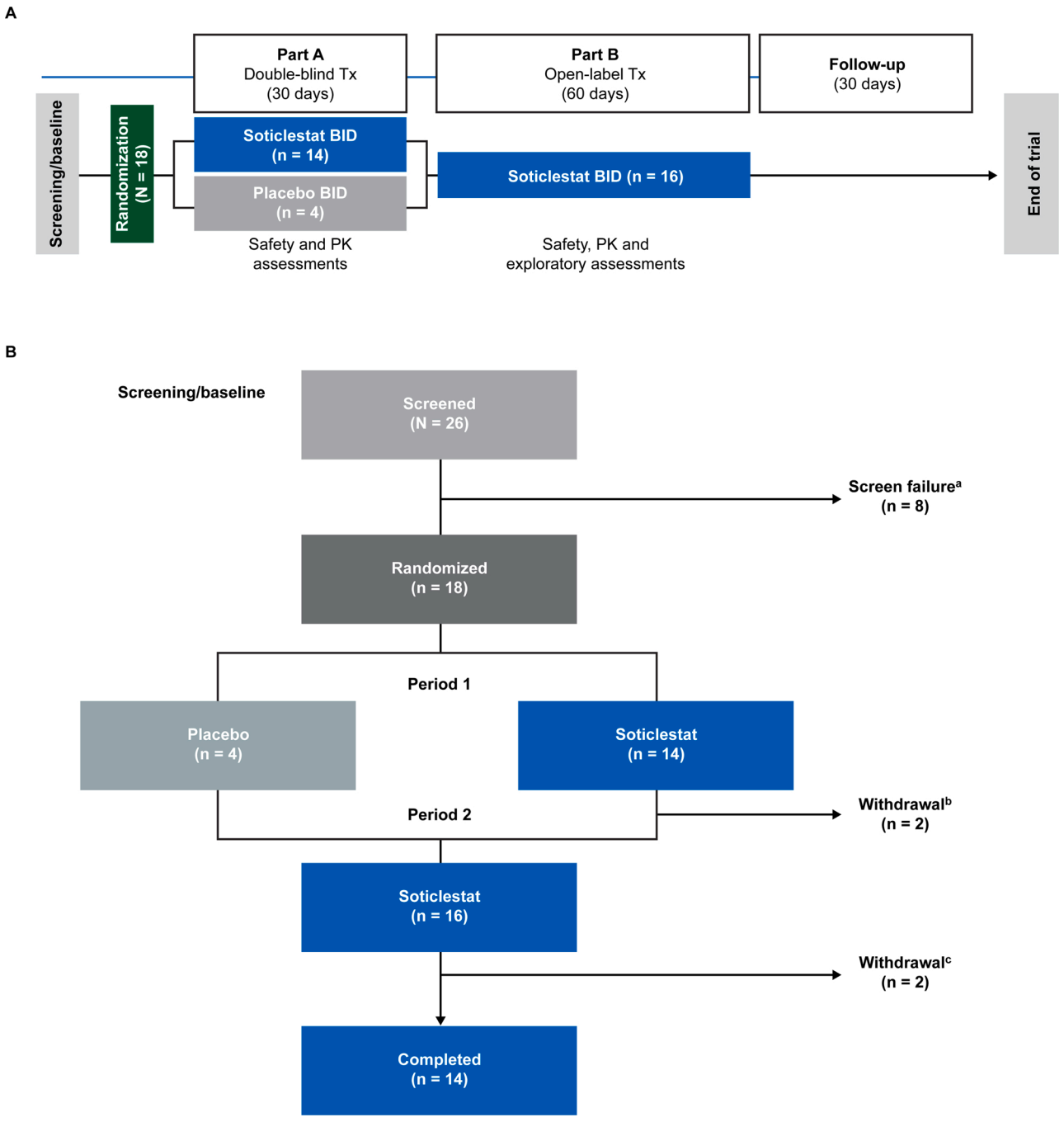

Fig. 1. Study flow charts showing (A) study schematics and (B) participants disposition.
[a]Did not meet entrance criteria (n = 5) and withdrawal by patient (n = 3).
[b]Weakness (n = 1); difficulty with walking/worsening lethargy (n = 1).
[c]Seizure cluster (n = 2).
BID, twice daily; PK, pharmacokinetics; Tx, treatment.

SSRS), and the Aberrant Behavior Checklist-Community Edition (ABC-C). PK endpoints included population mean estimates of drug clearance, volume of distribution of the central compartment, absorption rate constant, volume of distribution of the peripheral compartment, intercompartmental clearance, maximum observed plasma concentration, area under the plasma concentration–time curve during a dosing interval ($AUC_{0-\tau}$), average plasma concentration at steady state, and observed plasma concentration at the end of a dosing interval (C_{trough}) for soticlestat. Efficacy of soticlestat on seizure reduction was evaluated as an exploratory endpoint.

2.2. Study parts, doses, and titrations

2.2.1. Screening/baseline

Demographic information included age, sex, Hispanic ethnicity, and race. At screening (Visit 1), all caregivers were provided with a paper seizure diary (booklet) and instructed to keep a daily written record of all seizure events throughout the study up until the follow-up visit. Participants and/or participants' caregivers were required to capture seizure type and frequency, monitor for any worsening of seizure frequency, and denote any seizure free days on a daily basis.

The 4-week prospective baseline period began after informed

consent was signed. Seizure diary data was used for eligibility confirmation and endpoint analysis. Participants had to exhibit at least one bilateral motor seizure during the 4-week baseline period.

2.2.2. Part A

Part A was a randomized, placebo-controlled, double-blind period consisting of a titration phase (Days 1–20) and a maintenance phase (Days 21–30). On Day 1 (Visit 2), participants were randomized (4:1) to soticlestat or matching placebo (orally or via gastrostomy tube/percutaneous endoscopic gastrostomy tube) for 30 days.

Participants were initially administered soticlestat 100 mg twice daily (BID; Days 1–10), then titrated up to 200 mg BID (Days 11–20), and then 300 mg BID (Days 21–30). Those who could not tolerate the 100 mg BID dosage were withdrawn from the study. During Days 11–30, the dosage could be reduced by 100 mg BID in participants who could not tolerate the 200 mg BID or 300 mg BID dosages, or in those who demonstrated safety concerns, based on the investigator's judgment and in consultation with the participant's caregiver. Participants who had received a reduced dose remained on that dose level until the end of Part A. Three days after each titration step, participants were evaluated for study-drug adherence, concomitant medication use, and TEAEs.

2.2.3. Part B

Part B was an open-label extension period designed to explore longer-term safety, tolerability, PK, and 24HC plasma levels of soticlestat, and consisted of a titration, a maintenance, and a down-titration phase. Efficacy of soticlestat on seizure frequency was investigated in an exploratory manner. All participants who completed Part A were given the option to continue to Part B and to return to the clinic on Day 31 (Visit 5).

In Part B, participants were initially administered 200 mg BID (Days 31–40), followed by 300 mg BID (Days 41–85, the maintenance phase). The dosage could be reduced by 100 mg BID for those who could not tolerate higher doses, or who demonstrated safety concerns, based on the investigator's judgment and in consultation with the participant's caregiver. Those who could not tolerate the 100 mg BID dosage were withdrawn from the study. Participants who had received a reduced dose remained on that dose level until the end of the maintenance phase on Day 85 (Visit 7), at which time the dose level was tapered over 3–6 days. All participants were followed up for 30 days after the last dose for safety.

2.3. Statistical and analytical methods

Descriptive statistics were used to summarize data for continuous and categorical variables. A formal sample size calculation was not performed for this pilot study. All data analyses and figures were generated using SAS System Version 9.4.

2.3.1. Analysis sets

The randomized set included all participants who had been randomly assigned to treatment. The PK analysis set included those who had received at least one dose of study drug and had at least one post-dose measurable soticlestat plasma concentration. The PD analysis set included those who had received at least one dose of study drug and had at least one measurable plasma 24HC concentration.

The full analysis set (FAS) for Parts A and B included all participants who had received at least one dose of study drug and had at least one post-baseline value for assessment of the efficacy endpoints in Part A or Part B. The FAS efficacy summaries were presented according to treatment assignment in Part A. The safety analysis set included those who had received at least one dose of study drug, and the safety summaries were presented according to the actual treatment they received. Seizure frequency data from participants who completed Part B (completers) were analyzed *post hoc* for Days 58–85 and 65–92, relative to the first dose (soticlestat or placebo) date in Part A (Day 1).

2.3.2. Safety/tolerability assessments

TEAEs, clinical laboratory tests, vital sign measurements (temperature, blood pressure, heart rate, and respiratory rate), ECG parameters, physical, neurological and ophthalmic examination findings, and C-SSRS were used to assess safety and tolerability. Furthermore, the ABC-C was used to measure the severity of a range of behaviors commonly observed in individuals with intellectual and developmental disabilities.

TEAEs were summarized using descriptive statistics for Parts A and B separately. No statistical testing was performed.

2.3.3. PK/PD assessments

Blood samples for the measurement of plasma concentrations of soticlestat were collected before and after the morning dose on Days 1, 11, and 21 and before the morning dose on Days 31, 41, and 85, when feasible. Plasma concentrations of soticlestat were measured by validated high-performance liquid chromatography with tandem mass spectrometry assays. PK parameters were determined from the concentration–time profiles for all evaluable participants using a population PK approach.

Blood samples for PD measurement of baseline plasma 24HC levels were collected at the screening visit, before and after the morning dose on Days 1, 11, and 21, before the morning dose on Days 31, 41, and 85, and on Day 121, when feasible. Plasma concentrations of 24HC were measured by high-performance liquid chromatography with tandem mass spectrometry.

2.3.4. Efficacy assessments

The effect of soticlestat on seizure frequency was evaluated using percent changes from baseline in seizure frequency during Part A and Part B. Participants with an average of at least one bilateral motor seizure, excluding myoclonic jerks and spasms, during the 4-week baseline period were included in the evaluation of this exploratory efficacy endpoint.

The derivation of the monthly seizure frequency is described in the Statistical Analysis Plan (available at https://clinicaltrials.gov/ct2/show/NCT03166215). All bilateral motor seizures, except myoclonic seizures, were included in the derivation. The baseline time period includes all seizure diary data prior to study drug initiation on Day 1. Because of the small number of participants, no missing data imputation was performed.

The summaries of monthly seizure frequency and percent changes from baseline for Parts A and B were provided. A *post hoc* sensitivity analysis was performed for participants who were not taking perampanel. No inferential statistical analysis was performed.

Responders were evaluated in Part A and Part B *post hoc*. Two responder categories were examined: participants who had 50 % to < 100 % reduction in primary seizure frequency and those who had 100 % reduction (seizure free).

3. Results

3.1. Demographics

Eighteen adults with DEE (median age [min, max], 28.5 [19, 45] years) (Table 1), who had experienced at least one motor seizure during the baseline period, were enrolled from 10 sites in North America. A total of 14 participants (78 %) completed the study (Fig. 1A and B). Seven participants were able to take the study medication without dose adjustment and the other participants required various dose adjustments (Table 2).

Participants had heterogeneous DEE diagnoses and presented with multiple seizure types, including tonic, tonic-clonic, atonic, myoclonic, clonic, and hyperkinetic seizures. Participants randomized to placebo had fewer baseline seizures per 28 days than those randomized to soticlestat (median, 10.10 and 33.75, respectively).

ASMs that were being taken by at least five participants at baseline

Table 1
Participant demographics and diagnoses.

	Placebo (n = 4)	Soticlestat (n = 14)	Total (N = 18)
Demographics			
Age, years			
Median (min, max)	26.4 (19, 39)	28.7 (20, 45)	28.5 (19, 45)
Sex, n (%)			
Male	4 (100)	10 (71)	14 (78)
Female	–	4 (29)	4 (22)
Race, n (%)			
Caucasian	3 (75)	13 (93)	16 (89)
Black or African American	1 (25)	–	1 (6)
Not reported	–	1 (7)	1 (6)
Seizures at baseline, n per 28 days			
Median (min, max)	10.10 (3.7, 49.5)	33.75 (3.4, 277.1)	–
Diagnoses, n (%)			
Lennox–Gastaut syndrome	1 (25)	4 (29)	5 (27.8)
Epileptic encephalopathy[a]	1 (25)	3 (21.4)	4 (22.2)
Partial seizures with	–	1 (7)	1 (6)
Frontal lobe epilepsy	–	1 (7)	1 (6)
Tuberous sclerosis complex	–	1 (7)	1 (6)
Cerebral dysgenesis	–	1 (7)	1 (6)
Hypothalamic hamartoma	–	1 (7)	1 (6)
Dravet syndrome	–	1 (7)	1 (6)

[a] Epileptic encephalopathies not otherwise specified.

Table 2
Dose adjustment pattern.

	Dosage (mg BID)				
Number of patients, n (%) (N = 18)	Days 1–10	Days 11–20	Days 21–30	Days 31–40	Days 41–84
4 (22.2)	0	0	0	200	300
1 (5.6)	100				
1 (5.6)	100	100	100	200	300
1 (5.6)	100	200			
1 (5.6)	100	200	200	200	100
1 (5.6)	100	200	200	200	300
1 (5.6)	100	200	300	200	100
1 (5.6)	100	200	300	200	200
7 (38.9)	100	200	300	200	300

Dosage (mg BID) in each interval reflects the final dose the patient is on during that interval. 0 mg in Days 1–10, 11–20, and 21–30 intervals are patients who were assigned to the placebo group in Part A of the study. BID, twice daily.

were lamotrigine (n = 6 [33.3 %]), clobazam (n = 5 [27.8 %]), clonazepam (n = 5 [27.8 %]), and zonisamide (n = 5 [27.8 %]).

3.2. Study endpoints

3.2.1. Safety/tolerability

In the placebo-controlled Part A, the overall frequency of TEAEs was lower in participants treated with soticlestat versus placebo (71.4 % and 100 %, respectively). In Part B, 68.8 % of participants experienced at least one TEAE. In Part A, the only TEAEs that occurred in more than one patient in the soticlestat group were dysarthria (three patients [21.4 %]), and lethargy, upper respiratory tract infection, fatigue, and headache (two patients each [14.3 %]). Of these, fatigue and headache were reported in one placebo-treated patient each (25.0 %).

Four participants discontinued treatment while on soticlestat due to TEAEs or serious adverse events (SAEs) – two each in Part A and Part B, respectively. The first participant reported gait disturbance and lethargy, which were both considered to be mild in intensity and related to the study drug. The second participant reported asthenia, which was considered to be moderate in intensity and related to the study drug. In Part A, a third participant reported an SAE of seizure cluster, which was considered to be severe in intensity and not related to the study drug. The same participant experienced two additional SAEs of seizure cluster in Part B, which were both considered to be severe; one of the two latter seizure clusters was considered to be related to the study drug, and the patient withdrew from the study. The fourth participant reported an SAE of seizure cluster, which was considered to be severe in intensity and related to the study drug; therefore, the patient withdrew from the study.

In addition to these four participants who discontinued, a fifth participant experienced an SAE of seizure, which was considered to be of moderate intensity and not related to the study drug. This patient did not discontinue from the study. Therefore, in total, five seizure-related SAEs were reported by three participants (Table 3).

Overall, no changes from baseline in clinical laboratory evaluations, vital signs, ECG parameters, C-SSRS, and ABC-C were considered to be clinically significant. One participant reported intellectual impairment as an abnormal finding on the physical examination at Day 22 (Part A, placebo group) and Day 87 (Part B, soticlestat), but not at screening.

3.2.2. PK/PD

Individual PK model parameter estimates at dosages of 100, 200, and 300 mg BID showed: mean clearance at 259.4, 195.8, and 190 L/h, respectively; systemic exposures of soticlestat with mean steady state area under the curve at 562.5, 1437, and 2188 ng/h/mL, respectively; mean maximum observed concentration during a dosing interval at steady state at 269.6, 639.8, and 975.3 ng/mL, respectively; and mean C_{trough} at 10.5, 26, and 30.2 ng/mL, respectively. These exposures were similar to those seen in previous phase 1 studies in healthy volunteers.

In Part A, decreased plasma 24HC concentrations were found in the soticlestat versus placebo group. Pre-dose mean percent changes from baseline were −69.76 % at Day 11 and −76.88 % at Day 21 for soticlestat versus −4.30 % and −0.71 % for placebo, respectively. At the end of Part B (Day 85), the overall mean percent change from baseline in plasma 24HC was −80.97 %. Following soticlestat washout, plasma 24HC concentrations recovered to pretreatment levels (Fig. 2). The 24HC-lowering effect of soticlestat showed a trend towards plateauing when soticlestat $AUC_{0-\tau}$ was greater than 800 ng/h/mL.

Table 3
Adverse events and serious adverse events.

	Part A		Part B
	Placebo (n = 4)	Soticlestat (n = 14)	All (N = 16)
Frequency and severity			
Number of participants with at least one TEAE, n (%)			
AEs	4 (100)	10 (71.4)	11 (68.8)
Mild AE	4 (100)	7 (50)	4 (25)
Moderate	–	2 (14.3)	5 (31.3)
Severe	–	1 (7.1)	2 (12.5)
AE-related withdrawal[a]	–	2 (14.3)	2 (12.5)
SAEs[b,c]	–	1 (7.1)	3 (18.8)
Number of participants with most common (≥ three participants overall [10 %]) non-serious AEs, n (%)[d]			
Dysarthria	–	3 (21)	–
Fatigue	1 (25)	2 (14)	–
Headache	1 (25)	2 (14)	–
Insomnia	–	–	3 (19)
Lethargy	–	2 (14)	2 (12.5)
Seizure	–	–	3 (19)
Upper respiratory tract infection	–	2 (14)	1 (6)

AE, adverse event; SAE, serious AE; TEAE, treatment-emergent AE.
[a] Four participants discontinued in the soticlestat treatment arm.
[b] SAEs were seizure clusters (n = 2) and seizure (n = 1).
[c] There were no deaths across the soticlestat and placebo treatment arms.
[d] All participants who received at least one dose of study drug.

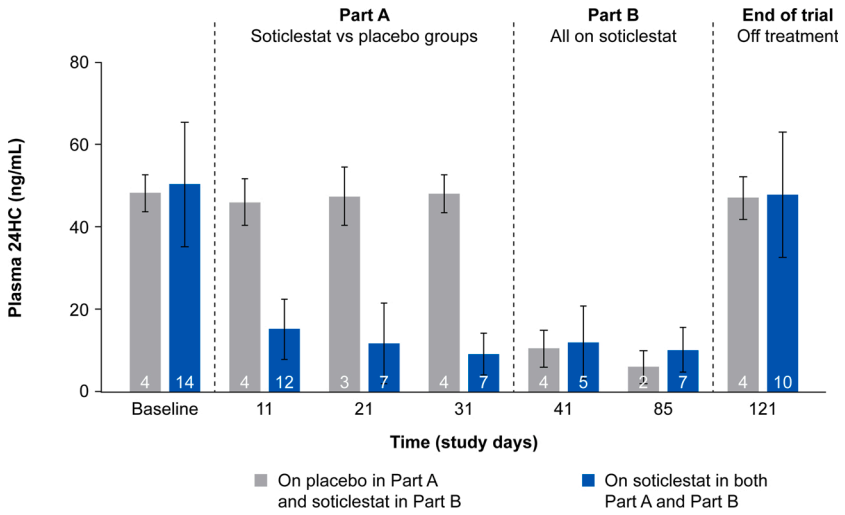

Fig. 2. Mean (SD) 24HC plasma levels[a].
[a]Plasma 24HC levels assessed at baseline and pre-dose at Days 11–85 and Day 121 (~30 days following the end of the treatment). 24HC, 24*S*-hydroxycholesterol; SD, standard deviation.

3.2.3. *Seizure frequency*

The baseline median seizure frequency per 28 days for participants randomized to soticlestat (n = 14) and placebo (n = 4) were 33.75 (range, 3–277) and 10.10 (range, 4–50), respectively. In Part A (Days 2–31), the median percent change in seizure frequency from baseline was +16.71 % (n = 14; range, −63 % to +465 %) for soticlestat and +22.16 % (n = 4; range, −73 % to +142 %) for placebo. All three participants treated with concomitant perampanel demonstrated seizure increase compared with their baseline during Part A (percent change from baseline seizure frequency, +107 %, +465 %, and +4 %). There were no participants treated with perampanel in the placebo group. The sensitivity analysis for participants who were not taking perampanel showed that the baseline median seizure frequency was 30.9 per 28 days, with a median percent change from baseline of +7.54 % in Part A.

For all patients treated with soticlestat in Part B (maintenance phase; Days 42–85), the median percent change in seizure frequency was −36.38 % (n = 16; range of % change, −100 % to +398 %) from baseline. For the three patients taking concomitant perampanel in Part B, specifically during the maintenance phase, percent changes from baseline seizure frequency were +297 %, +398 %, and +175 %. All three participants completed the study. Excluding the participants taking perampanel, the median percent change in seizure frequency was −44.66 % (n = 13) from baseline (Fig. 3). At Days 65–92, the last 28 days of treatment including tapering based on the scheduled visit, there was a median percent change in seizures per 28 days of −60.74 % in the *post hoc* analysis of patients not taking perampanel who completed Part B. The median seizure frequency for all completers, excluding those taking perampanel, was 25.60 seizures per 28 days at baseline. Two participants (12.5 %) had a 100 % reduction in seizure frequency (seizure free) in last 4 weeks of treatment.

4. Discussion

The current study provides further evidence for the safety and tolerability of soticlestat, which has previously been found to be generally well tolerated at dosages of 1350 mg once daily in healthy adults (Bialer et al., 2018; Chen et al., 2018; Wang et al., 2018). In addition, the findings reported here show that the PK profile of soticlestat is generally comparable between healthy adults and adult patients with DEE. Furthermore, consistent with the pharmacology as well as with previous observations in healthy individuals, a clear effect of soticlestat exposure in reducing plasma 24HC levels was observed. Based on these data, plasma 24HC levels may serve as a biomarker for pharmacodynamic activity and central target engagement.

Due to the small number of participants and imbalanced randomization, the effect of soticlestat on seizures was evaluated only with

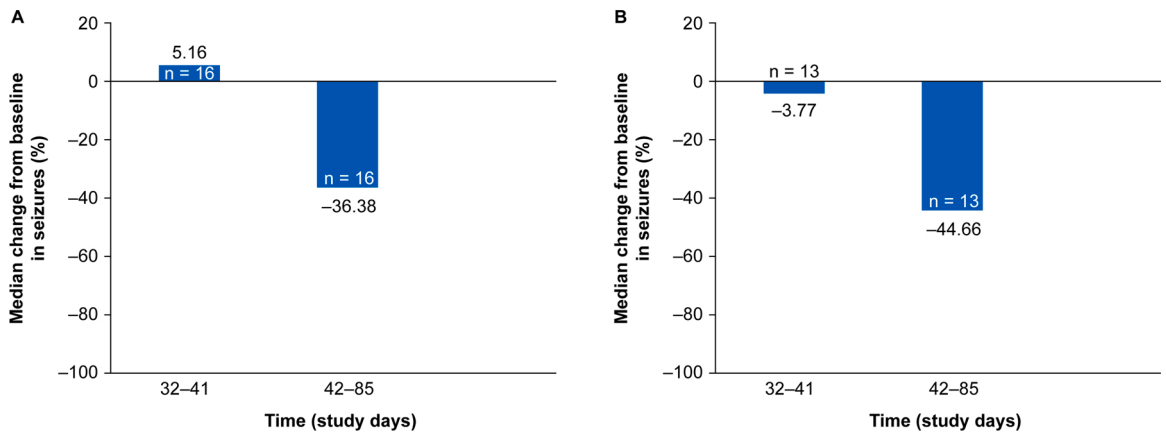

Fig. 3. Seizure frequency in Part B in (A) the FAS including patients on perampanel and (B) the FAS excluding three patients on perampanel. Median change from baseline in seizures as per the SAP. Based on an interval averaged over 28 days, excluding myoclonic seizures. The first dose day is study Day 1. FAS, full analysis set; SAP, Statistical Analysis Plan.

descriptive statistics. In both the soticlestat and the placebo treatment groups, an increase in seizure frequency from baseline during the double-blind treatment phase (Days 2–30) was observed. During open-label treatment with soticlestat (Days 31–85 in Part B), there was a modest reduction in seizure frequency relative to baseline. In addition, three participants who received concomitant treatment with perampanel experienced an increased seizure frequency versus baseline. In two of these individuals, seizures were exacerbated, although clear conclusions cannot be made because of the small sample size. All three participants who were taking perampanel completed the study. Given that there is no known reason for a pharmacokinetic interaction between soticlestat and perampanel, the increased seizure frequency observed in the patients taking concomitant perampanel might be due to a pharmacodynamic interaction, or because of the variability in seizures associated with the DEE itself. Future studies with larger sample sizes would be needed to investigate the possible effects of soticlestat adjunctive to perampanel. In addition, further evaluation is needed regarding how specific etiologies influence treatment response, which was not possible in the current study.

4.1. Conclusions

In conclusion, soticlestat was generally well tolerated in this study at dosages up to 300 mg BID for up to 90 days, as measured by the incidence of primarily mild TEAEs in adults with DEE. Exploratory efficacy evaluation showed a reduction in seizure frequency over time in the open-label period (Part B) of the study. The study supports further investigation of adjunctive soticlestat treatment for seizures associated with DEE, with plasma 24HC as a potential peripheral biomarker for pharmacodynamic activity.

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Data statement

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants data supporting the results reported in this article, will be available three months after the submission of a request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

Declaration of Competing Interest

M. Asgharnejad and D. Arkilo are employees of Takeda and own stock or stock options. R. Xu is a former employee of Takeda. M. During and C. Zinger are employees of Ovid Therapeutics and own stock or stock options. The following authors have received compensation for serving as consultants or speakers, or they or the institutions they work for have received research support or royalties from the companies or organizations indicated: J. A. French (Adamas Pharmaceuticals, Aeonian/Aeovian Pharmaceuticals, Anavex Life Sciences, Arvelle Therapeutics, Axovant Gene Therapies, Biogen, BioMotiv/Koutif Therapeutics, BioXcel Therapeutics, Blackfynn, Bloom Science, Bridge Valley Ventures, Carnot Pharma, Cavion, Cerebral Therapeutics, Cerevel Therapeutics, Crossject, CuroNZ, Eisai, Encoded Therapeutics, Engage Therapeutics, Epilepsy Foundation, The Epilepsy Study Consortium, Epiminder, Epitel, Fortress Biotech, GW Pharmaceuticals, Idorsia Pharmaceuticals, Ionis Pharmaceuticals, Janssen Pharmaceutical, Johnson & Johnson, Knopp Biosciences, Lundbeck, Marinus Pharmaceuticals, Merck & Co., NeuCyte, Inc., Neurelis, Neurocrine Biosciences, National Institute of Neurological Disorders and Stroke [NINDS], Novartis, Otsuka Pharmaceutical, Ovid Therapeutics, Passage Bio, Pfizer, Praxis Pharmaceutical, Redpin Therapeutics, Sage Therapeutics, Shire (now part of Takeda), SK Life Sciences, SpringWorks Therapeutics, Stoke Therapeutics, Sunovion Pharmaceuticals, Supernus Pharmaceuticals, Takeda, UCB, West Therapeutic Development, Xenon Pharmaceuticals, Xeris Pharmaceuticals, Zogenix, and Zynerba Pharmaceuticals); J. J. Halford (Greenwich Biosciences, NCGS, SK Life Sciences, and Takeda); and M. R. Sperling (Cerevel Therapeutics, Eisai, Engage Therapeutics, Medtronic, Neurelis, SK Life Sciences, Takeda, UCB, and Xenon Pharmaceuticals).

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