Epilepsy & Behavior 142 (2023) 109173

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Efficacy, safety, and tolerability of soticlestat as adjunctive therapy for the treatment of seizures in patients with Dup15q syndrome or CDKL5 deficiency disorder in an open-label signal-finding phase II study (ARCADE)

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ARTICLE INFO

Article history:
Received 16 November 2022
Revised 6 March 2023
Accepted 8 March 2023

Keywords:
Soticlestat
CDKL5 deficiency disorder
Dup15q syndrome
Developmental and epileptic encephalopathies
Cholesterol 24-hydroxylase
24S-hydroxycholesterol

ABSTRACT

Objective: Chromosome 15q duplication (Dup15q) syndrome and cyclin dependent kinase-like 5 deficiency disorder (CDD) are rare neurodevelopmental disorders associated with epileptic encephalopathies, with a lack of specifically approved treatment options. ARCADE assessed the efficacy and safety of adjunctive soticlestat (TAK-935) for the treatment of seizures in patients with Dup15q syndrome or CDD (NCT03694275).

Methods: ARCADE was a phase II, open-label, pilot study of soticlestat (≤300 mg/day twice daily, weight-adjusted) in pediatric and adult patients 2–55 years of age with Dup15q syndrome or CDD who experienced ≥3 motor seizures per month in the 3 months before screening and at baseline. The 20-week treatment period consisted of a dose-optimization period and a 12-week maintenance period. Efficacy endpoints included the change from baseline in motor seizure frequency during the maintenance period and the proportion of treatment responders. Safety endpoints included the incidence of treatment-emergent adverse effects (TEAEs).

Results: The modified-intent-to-treat population included 20 participants who received ≥1 dose of soticlestat and had ≥1 efficacy assessment (Dup15q syndrome, $n = 8$; CDD, $n = 12$). Soticlestat administration during the maintenance period was associated with a median change from baseline in motor seizure frequency of +11.7% in the Dup15q syndrome group and −23.6% in the CDD group. Reductions in all seizure frequency of −23.4% and −30.5% were also observed during the maintenance period in the Dup15q syndrome group and the CDD group, respectively. Most TEAEs were of mild or moderate severity. Serious TEAEs were reported by three patients (15.0%); none were considered drug related. The most common TEAEs were constipation, rash, and seizure. No deaths were reported.

Conclusions: Adjunctive soticlestat treatment was associated with a decrease in motor seizure frequency from baseline in patients with CDD and a decrease in all seizure frequency in both patient groups. Soticlestat treatment was associated with an increase in motor seizure frequency in patients with Dup15q syndrome.

Abbreviations: 24HC, 24S-hydroxycholesterol; ASM, antiseizure medication; Care GI-C, Caregiver Global Impression of Change; CDD, cyclin-dependent kinase-like 5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5; CGI-C, Clinical Global Impression of Change; CH24H, cholesterol 24-hydroxylase; DEE, developmental and epileptic encephalopathy; Dup15q, chromosome 15q duplication syndrome; mITT, modified-intent-to-treat; TEAE, treatment-emergent adverse event.

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https://doi.org/10.1016/j.yebeh.2023.109173
1525-5050/

1. Introduction

Chromosome 15q duplication (Dup15q) syndrome and cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) are rare developmental and epileptic encephalopathies (DEEs), a group of conditions characterized by developmental delay and treatment-resistant epilepsy starting in early childhood, whereby frequent epileptic activity is associated with further development delays [1–4].

Dup15q syndrome has an estimated incidence of 1:30 000 live births and is caused primarily by two forms of chromosomal duplication: isodicentric chromosome 15q and interstitial maternal duplication [5]. The disorder is associated with multiple medical and neurodevelopmental conditions that contribute to poor quality of life for patients and caregivers, including early central hypotonia, global developmental delay, intellectual disability, and autism [5–7]. With regard to epilepsy, patients with Dup15q syndrome experience a high rate of seizures, including infantile spasms, followed by multiple generalized seizure types with increasing age, including tonic-clonic, atonic, myoclonic, tonic, and absence, as well as focal-onset seizures [6].

CDD is an X-linked disorder with an estimated incidence of 1:40 000–1:60 000 live births [8] and is caused by mutations in the gene encoding CDKL5 [8,9]. Symptoms include hypotonia, global developmental delay, intellectual disability, and cortical visual impairment [8,10]. Patients with CDD often experience early onset seizures, including infantile spasms, and then evolve into having multiple seizure types, which can include atonic, atypical absence, epileptic spasms, focal impaired with motor components, myoclonic, tonic, typical absence, and tonic-clonic seizures [10,11].

Most broad-spectrum antiseizure medications (ASMs) are used in the treatment of Dup15q syndrome and CDD [6,10]. Development of treatment resistance, or in the case of CDD, exacerbation of seizures, is commonly observed with current medications [8,10]. The poor control of symptoms and treatment resistance highlight the unmet need that exists for effective treatments for both Dup15q syndrome and CDD [7,8].

Soticlestat is a first-in-class, selective inhibitor of cholesterol 24-hydroxylase (CH24H), the enzyme responsible for catabolizing cholesterol to 24*S*-hydroxycholesterol (24HC) in the brain [12]. The mechanism of action of soticlestat is thought to involve the reduction of glutamatergic signaling and attenuation of the neural hyperexcitation associated with epilepsy disorders [12]. Because broad-spectrum ASMs and medications targeting GABAergic signaling show low efficacy in patients with Dup15q syndrome or CDD, the unique mechanism of action of soticlestat may provide a beneficial alternative treatment strategy in these disorders [6,13]. Soticlestat has been evaluated in phase I clinical studies in healthy volunteers [14,15] and in a phase Ib/IIa study in adults with Dravet syndrome or Lennox–Gastaut syndrome. In the latter, treatment was associated with a reduction in median seizure frequency over the study duration [16] (ClinicalTrials.gov identifiers: NCT02201056, NCT02539134, NCT03166215).

Here, we present results from ARCADE, a phase II, open-label, pilot study to investigate the efficacy, safety, and tolerability of soticlestat as adjunctive therapy in individuals with Dup15q syndrome or CDD (ClinicalTrials.gov identifier: NCT03694275).

2. Materials and methods

2.1. Patients

Patients with a documented diagnosis of Dup15q syndrome or CDD, 2–55 years of age, and weighing ≥10 kg at the screening visit were eligible for this study. Patients were required to be taking from one to six ASMs at a stable dose for 4 weeks before the screening visit, to have a history of failure of at least two ASMs, and to have experienced at least three motor seizures per month in the 3 months before screening and during the 4–6-week prospective baseline period. Concomitant use of perampanel was excluded owing to a potential pharmacodynamic drug–drug interaction. Patients on a ketogenic diet must have started the diet at least 3 months before the screening visit and have been stable for 4 weeks. Any patients using a vagal nerve stimulator (VNS) must have had the VNS fitted at least 3 months before the screening visit, with stable settings for more than 1 month. Ketogenic diet and VNS were not counted as ASMs. ASMs, VNS settings, and ketogenic diet were not permitted to be altered during the study.

Patients who had been admitted to a medical facility and intubated for treatment of status epilepticus at least twice in the 3 months before screening were excluded from the study. Other exclusion criteria included abnormal laboratory test results or clinically significant electrocardiogram abnormality at screening.

2.2. Ethics

The study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for good clinical practice (E6) as well as current ethics guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences international ethical guidelines. All other applicable laws and local regulations were followed. Written informed consent was obtained from each patient or his/her legally authorized representative before the patient entered the study. In addition, documented assent was obtained from the patient when applicable. This study was conducted in compliance with the institutional review boards or independent ethics committees of each study location.

2.3. Study design

ARCADE was a phase II, multicenter, open-label, two-cohort pilot study, conducted across eight study sites in the USA. Following a 4–6-week prospective baseline period, patients entered a 20-week treatment period, which included an 8-week dose-optimization period followed by a 12-week maintenance period (Fig. 1). Soticlestat was administered orally or via gastrostomy, percutaneous endoscopic gastrostomy, or jejunostomy tube at up to 300 mg twice daily, with or without food, with weight-based dosing used for patients weighing <60 kg. During the dose-optimization period, patients received gradually increasing doses of soticlestat up to the appropriate maximum dose, while being monitored for safety and tolerability. The dose could be changed within the dose-optimization period; however, it was kept constant during the maintenance period that followed unless a dose decrease was required for reasons of safety and/or tolerability. Following study completion, patients were given the option to enroll in the open-label extension study ENDYMION 1 (ClinicalTrials.gov identifier: NCT03635073) or enter a 4 week taper period.

2.4. Efficacy endpoints

The primary efficacy endpoint was the percentage change from baseline in motor seizure frequency per 28 days during the maintenance period in both patient groups. Secondary efficacy endpoints included the percentage change from baseline in motor seizure frequency in both patient groups during the full 20-week treatment period and the percentage change from baseline in all seizure frequency during the maintenance and full treatment periods. Other secondary endpoints included the proportion of patients with Dup15q syndrome or CDD who were considered treatment

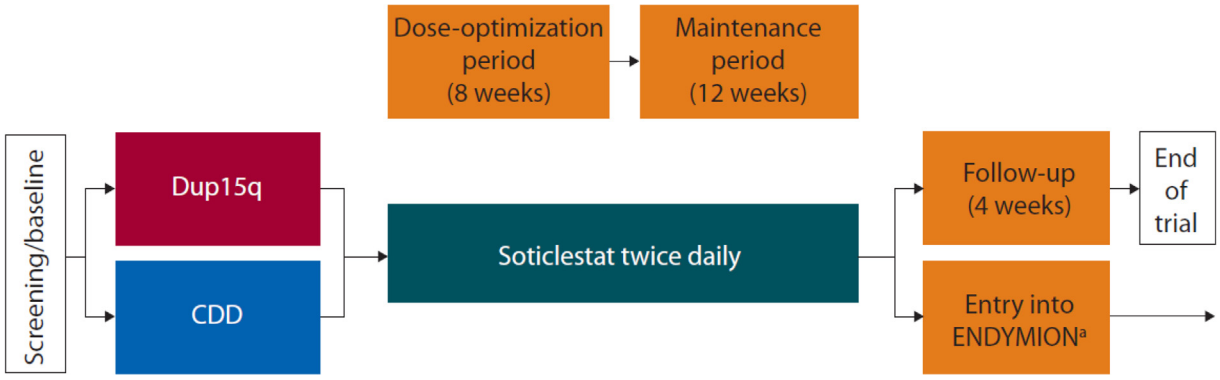

Fig. 1. Flowchart showing ARCADE study design. [a]Open-label extension study (ClinicalTrials.gov identifier: NCT03635073). CDD, CDKL5 deficiency disorder.

responders, defined as those experiencing a reduction in motor seizure frequency from baseline of ≥25%, ≥50%, ≥75%, or 100% during the maintenance period and full treatment period. Global functioning was assessed using the investigator-reported Clinical Global Impression of Change (CGI-C) and the Caregiver Global Impression of Change (Care GI-C) scales. The change from baseline in plasma 24HC levels was also measured in patients treated with soticlestat.

Patients and/or their caregivers were issued a paper seizure diary and instructed to record seizure data daily, starting at the first screening visit and continuing throughout the rest of the study. Seizure types were defined as motor seizures or non-motor seizures. Motor seizures included hemiclonic, focal with motor signs, focal to bilateral tonic-clonic convulsion, generalized tonic-clonic convulsion, tonic, atonic, bilateral clonic, infantile spasms, epileptic spasms, and convulsive status (>30 minutes). Isolated myoclonic seizures were not recorded. The motor seizure data were used to determine the baseline seizure frequency for the primary endpoint analyses. Non-motor seizures included absence or atypical absence seizures, focal seizures without motor signs, myoclonic, non-convulsive status (>30 min), and 'other'.

2.5. Safety endpoints

Safety endpoints included the incidence of treatment-emergent adverse events (TEAEs), which were defined as any adverse event that started or increased in severity during or after the first dose of the study drug and the change in the percentage of absence seizure–free days over the maintenance period and the 20-week treatment period in patients who reported absence seizures during baseline. New seizure types were also reported as TEAEs. TEAEs were classified as mild if they required minimal or no treatment and did not interfere with daily activities, moderate if they resulted in a low level of inconvenience or concerns with the therapeutic measures, and severe if they interrupted the patient's daily activities and may have required systemic drug therapy or treatment.

2.6. Data analysis

Descriptive statistics were used to summarize continuous variables, and frequency and percentage were used for categorical and ordinal variables. For analysis of seizure endpoints, 'baseline' refers to the 4—6-week baseline period. To assess the change in seizure frequency, motor seizure frequency per 28 days was determined for the baseline period, maintenance period, and full treatment period. CGI-C and Care GI-C scores were summarized over time with descriptive statistics.

The analysis sets for this study included modified-intent-to-treat (mITT) and safety analysis sets. The mITT analysis set included all patients who received at least one dose of the study drug and were assessed for at least one day during the treatment period.

The safety analysis set comprised all patients who received at least one dose of the study drug. All analyses of primary and secondary efficacy endpoints were based on the mITT set.

TEAEs were divided by patient group and summarized using descriptive statistics. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc.).

3. Results

3.1. Patient disposition

Of a total of 28 patients screened, 20 were enrolled in the study and included in the mITT and safety populations, and 18 completed the study. The mITT population included eight patients with Dup15q syndrome and 12 patients with CDD. Two patients with CDD in the mITT population withdrew from the study. One patient was withdrawn by the investigator based on abnormal, prolonged QT interval corrected for heart rate (QTc) values at screening that continued after initiation of the study drug. However, after a manual review of electrocardiograms by an external expert, it was concluded that the patient had a normal QTc using Fridericia's formula (QTcF), or Bazett's formula (QTcBat) at enrollment, with subsequent normal variability of QTc while receiving therapy. One patient discontinued the study and was enrolled in the open-label extension study because of a concern with the need for modification of current ASM treatments.

3.2. Baseline demographics and clinical characteristics

Overall, 60.0% of patients were female (Table 1). The median age of patients with Dup15q syndrome was 13.5 years (range, 9–27 years), and the median age of patients with CDD was 5.5 years (range, 2–17 years). Baseline median motor seizure frequencies for patients with Dup15q syndrome and CDD were 128.4 and 77.8 per 28 days, respectively (Table 1). There was a wide variation in reported motor seizure frequency at baseline, with ranges of 35–224 and 10–374 per 28 days in the Dup15q syndrome and CDD groups, respectively (Table 1). In addition to motor seizures, a wide variety of seizure types were reported in both Dup15q syndrome and patients with CDD at baseline (**Table S1**).

Most patients were taking more than one ASM at baseline, with 13 (65.0%) taking at least three ASMs (Table 1). The most common ASMs used by patients with Dup15q syndrome were rufinamide (50.0%), lamotrigine (50.0%), clobazam (37.5%), and levetiracetam (37.5%). Common ASMs used by patients with CDD included clobazam (41.7%), cannabidiol (33.3%), and topiramate (25.0%).

Table 1
Baseline demographics and clinical characteristics in the modified ITT analysis set.

	All patients (*n* = 20)	Dup15q syndrome (*n* = 8)	CDKL5 deficiency disorder (*n* = 12)
Age, years			
Mean (SD)	10.7 (6.7)	15.4 (6.0)	7.6 (5.3)
Minimum, maximum	2, 27	9, 27	2, 17
Sex, *n* (%)			
Male	8 (40.0)	5 (62.5)	3 (25.0)
Female	12 (60.0)	3 (37.5)	9 (75.0)
Race, *n* (%)			
White	19 (95.0)	8 (100)	11 (91.7)
Other	1 (5.0)	0	1 (8.3)
Ethnicity, *n* (%)			
Not Hispanic or Latino	20 (100)	8 (100)	12 (100)
Number of antiseizure medications at baseline, *n* (%)[a]			
1	4 (20.0)	1 (12.5)	3 (25.0)
2	3 (15.0)	1 (12.5)	2 (16.7)
3	8 (40.0)	2 (25.0)	6 (50.0)
4	3 (15.0)	3 (37.5)	0
5	2 (10.0)	1 (12.5)	1 (8.3)
Baseline motor seizure frequency[b]			
Mean (SD)	130.4 (109.9)	132.3 (72.0)	129.1 (132.4)
Median	82.8	128.4	77.8
Minimum, maximum	10, 374	35, 224	10, 374

[a] Data from safety analysis set.
[b] Seizure frequency was calculated per 28 days (28 × [number of seizures in the interval]/[days with no missing seizure count in the interval]). Baseline frequency was calculated over the 4–6-week screening period before the first dose.

3.3. Efficacy

3.3.1. Changes in seizure frequency

In patients with Dup15q syndrome, the median changes from baseline in motor seizure frequency were +11.7% and +13.4% during the maintenance period and full 20-week treatment period, respectively (Fig. 2**A**). However, patients in this group showed median changes from baseline in all seizure frequency (motor and non-motor) of −23.4% and −18.2% during the maintenance period and full treatment period, respectively (Fig. 2**B**).

In patients with CDD, the median changes from baseline in motor seizure frequency were −23.6% and −13.6% during the maintenance period and full treatment period, respectively (Fig. 2**C**). Patients in this group showed median changes from baseline in all seizure frequency of −30.5% and −26.0% during the maintenance period and full treatment period, respectively (Fig. 2**D**).

3.3.2. Treatment response

In the Dup15q syndrome group, during the maintenance period, one patient (12.5%) experienced a reduction in motor seizure frequency from baseline of ≥75%, one patient (12.5%) experienced a reduction of ≥50%, and two patients (25.0%) experienced reductions of ≥25% (Fig. 3**A**).

In the CDD group, during the maintenance period, one patient (9.1%) experienced a reduction of ≥75%, three patients (27.3%) experienced reductions of ≥50%, and five patients (45.5%) experienced reductions of ≥25% (Fig. 3**B**).

Similar results were observed in both groups during the full treatment period.

3.3.3. Global functioning

Treatment with soticlestat was associated with a general improvement in global functioning in both patient populations. At the last visit, of the eight patients with Dup15q syndrome, relative to baseline, 50% reported improvement in CGI-C score and 50% reported improvement in Care GI-C score (Fig. 4**A**). At the last visit, of the 12 patients with CDD, improvements in CGI-C and Care GI-C scores relative to baseline were observed in 66.7% and 91.7% of patients, respectively (Fig. 4**B**).

3.3.4. Plasma 24HC levels

After 2 weeks of treatment, median decreases from baseline in plasma 24HC levels of 73.3% and 82.0% were observed in the Dup15q syndrome and CDD groups, respectively. These values remained relatively stable throughout the remainder of the study.

3.4. Safety and tolerability

In total, 19 patients (95.0%) reported TEAEs, with most reporting mild (*n* = 15; 75.0%) or moderate (*n* = 9; 45.0%) as the worst severity (Table 2). Seven patients (87.5%) with Dup15q syndrome reported TEAEs, with the most common being fatigue (25.0%), seizure (25.0%), and lethargy (25.0%). TEAEs were reported by 12 patients with CDD (100%), the most common being constipation (33.3%), ear infection (16.7%), decrease in blood bicarbonate (16.7%), partial seizures (16.7%), tonic convulsions (16.7%), and rash (16.7%) (Table 2). None of the mild or moderate TEAEs in either the Dup15q syndrome group or the CDD group led to study discontinuation.

Three patients (25.0%) with CDD reported severe TEAEs of constipation, asthenia, respiratory syncytial virus bronchiolitis, and seizure. Of the severe TEAEs reported by patients with CDD, constipation, asthenia, and seizure were considered treatment related. No severe TEAEs were reported in patients with Dup15q syndrome. TEAEs classed as seizures in patients with CDD and considered to be related to treatment (in addition to the severe TEAE of seizure listed above) included partial seizures (*n* = 2), tonic convulsions (*n* = 2), and atonic seizures (*n* = 1). A TEAE of seizure considered to be related to treatment was reported in one patient (12.5%) with Dup15q syndrome.

Five patients with CDD reported one or more new seizure types not identified at baseline, which included focal with motor signs as well as tonic, atonic, and absence or atypical absence seizures. New seizures not recorded at baseline were reported by two patients with Dup15q syndrome, who reported one myoclonic seizure and two absence or atypical absence seizures.

Serious TEAEs were reported by three patients (15.0%) in total: one patient (12.5%) in the Dup15q syndrome group and two patients (16.7%) in the CDD group; none of these serious TEAEs were considered related to treatment.

TEAEs led to dose modification in six patients (30.0%) and occurred during the dose-optimization period in four patients, and during the maintenance period in two patients. In all cases, the dose was reduced. Thirteen patients (65.0%) reported TEAEs that were considered drug related by the investigator, none of which were considered serious or led to study discontinuation. No deaths were reported in this study.

The percentage of absence seizure-free days remained unchanged from baseline, with a median of 100% for both treatment groups and in both study periods.

4. Discussion

Results from the open-label, signal-detection ARCADE study were inconclusive with regard to efficacy in both the Dup15q syndrome and CDD cohorts. Over the full 20-week period of adjunctive soticlestat treatment, a moderate median reduction from baseline in motor seizure frequency was observed in patients with CDD

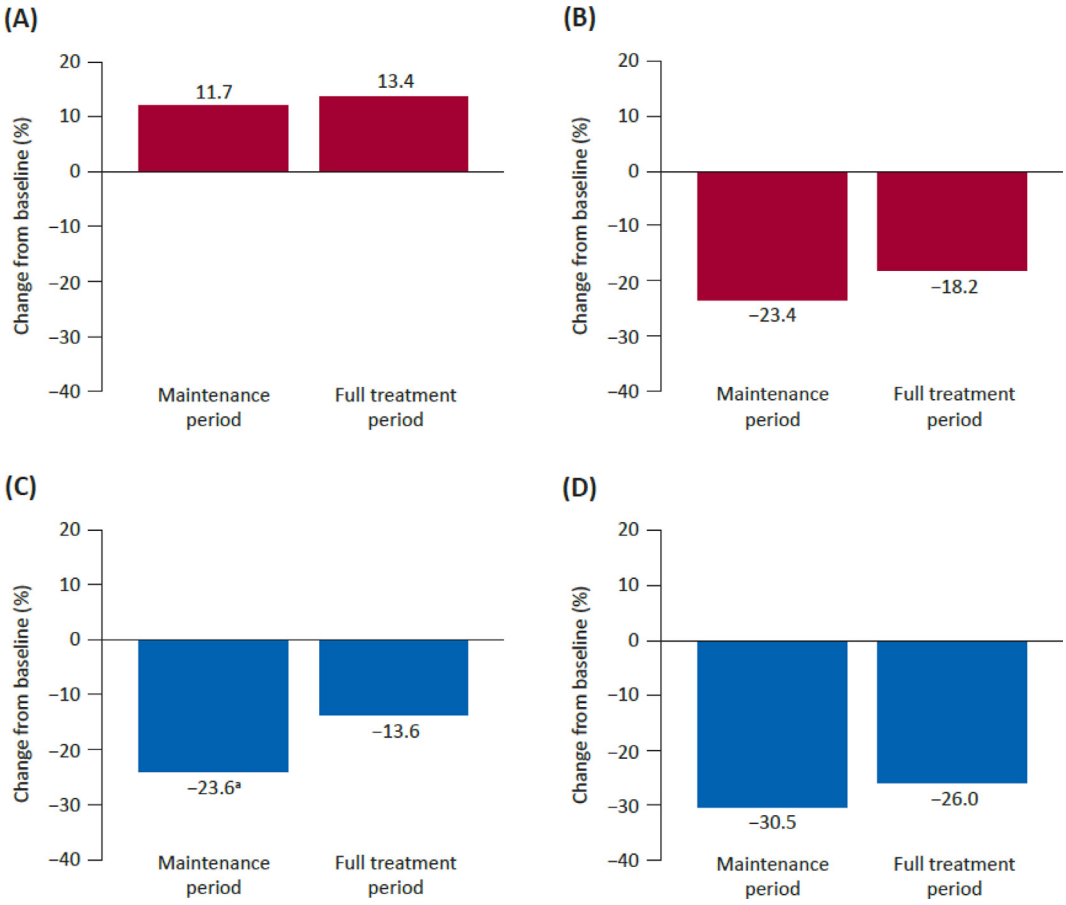

Fig. 2. Change in seizure frequency in patients with Dup15q syndrome or CDKL5 deficiency disorder during the maintenance and full treatment periods. Median percentage change from baseline in (A) motor seizure frequency and (B) all seizure frequency in patients with Dup15q syndrome (n = 8), and median percentage change from baseline in (C) motor seizure frequency and (D) all seizure frequency in patients with CDKL5 deficiency disorder (n = 12). Data are shown for the 12-week maintenance period and the full 20-week treatment period. [a] n = 11.

and a moderate median increase from baseline in motor seizure frequency was observed in patients with Dup15q syndrome. However, in both groups of patients, a decrease in all seizure frequency (motor and non-motor combined) was observed during the study. Corresponding decreases in plasma 24HC levels were also observed in this study, providing evidence for the pharmacodynamic activity of soticlestat and suggesting high treatment adherence.

The improvement in seizure frequency seen in the CDD group during the maintenance period in the present study (–23.6% from baseline) was similar to that observed in a recent trial of ganaxolone, which is the first ASM to be approved specifically for the treatment of CDD. In patients with CDD (n = 100), ganaxolone treatment was associated with a median percent change in 28-day major motor seizure frequency of – 30.7%, with a – 6.9% change observed in the placebo group [17]. Although no direct comparison can be made, this finding suggests that the magnitude of reductions in motor seizure frequency observed in patients with CDD in ARCADE may have been treatment effects, although a larger placebo-controlled study would be needed to confirm any potential efficacy signal.

ARCADE was not designed to analyze the effects of soticlestat in combination with any particular ASMs. Drug–drug interaction studies in healthy volunteers (ClinicalTrials.gov identifiers: NCT05064449 and NCT05098041) have shown that while soticlestat can be administered with CYP3A4 or UGT1A9 inhibitors without clinically meaningful DDIs, strong CYP3A inducers significantly reduce the concentration of soticlestat in plasma and have been excluded from ongoing studies. An exception to this is for ASMs that are also CYP3A inducers (e.g. carbamazepine, phenobarbital, phenytoin, oxcarbazepine, and clobazam) [18]. Population PK analyses will be performed to evaluate the impact of these ASMs on soticlestat exposure upon phase III study completion.

Despite the median increase in motor seizure frequency seen in patients with Dup15q syndrome, two patients in this group were classed as treatment responders showing a reduction from baseline in motor seizure frequency. Patients with CDD had a potential treatment response, showing a moderate median reduction from baseline in motor seizure frequency, with five patients classed as treatment responders. This potential signal of efficacy would need to be confirmed in a larger, adequately powered, controlled clinical trial.

Both groups had a substantial percentage of patients showing improvements in CGI-C and Care GI-C scores, suggesting a benefit of treatment on global functioning. However, an evaluation of non-seizure symptoms was not included in the present study. Existing clinical outcome assessment measures are generally not appropriate for conditions with heterogenous symptoms and intellectual disability because included items lack optimal content validity or sensitivity to change [19]. As such, a novel CGI measure for clinical outcome assessment of non-seizure symptoms has been developed and will be included in phase III studies of soticlestat in patients with DEEs (ClinicalTrials.gov identifiers: NCT04940624 and NCT04938427) [19].

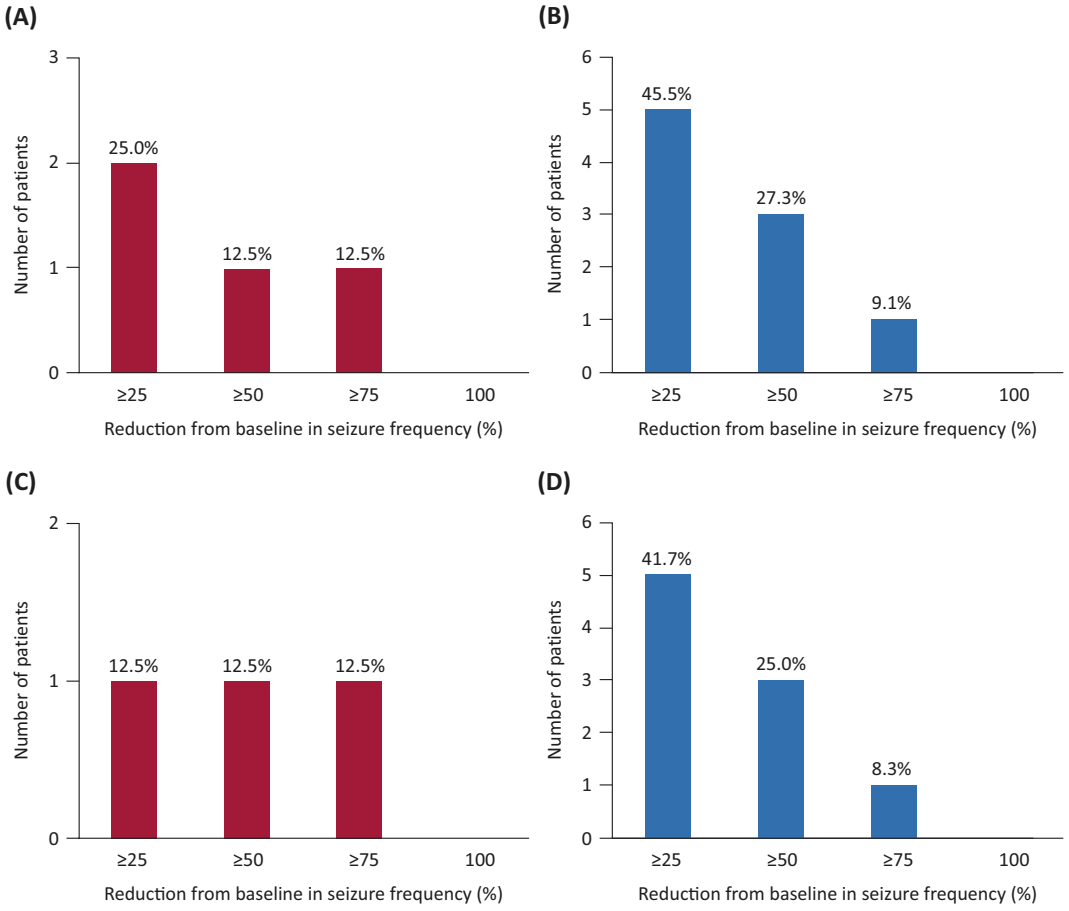

Fig. 3. Number of treatment responders during the maintenance period and full treatment period. Number of patients with (A) Dup15q syndrome (n = 8) or (B) CDKL5 deficiency disorder (n = 12) who were classed as treatment responders during the 12-week maintenance period, and the number of patients with (C) Dup15q syndrome (n = 8) or (D) CDKL5 deficiency disorder (n = 11) who were classed as treatment responders during the 20-week treatment period.

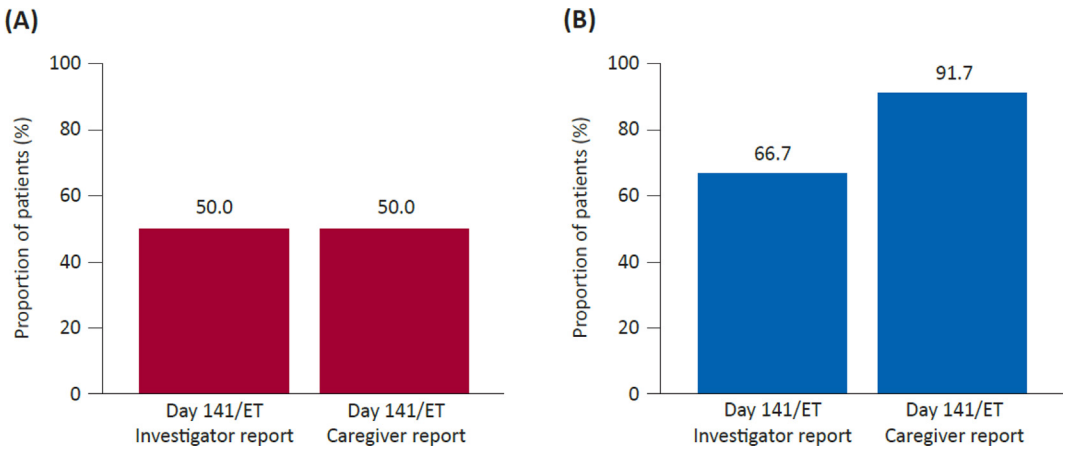

Fig. 4. Proportion of patients with (A) Dup15q syndrome or (B) CDKL5 deficiency disorder showing any improvement in global functioning at the last visit as determined from the investigator report (Clinical Global Impression of Change) and the caregiver report (Caregiver Global Impression of Change).

In support of previously reported results, treatment with soticlestat resulted in a reduction of plasma 24HC levels, which was maintained throughout the full treatment period. The findings reported here build on those from clinical studies in healthy volunteers and adults with DEEs to support the use of 24HC as a peripheral biomarker for soticlestat activity in the brain; they also indicate engagement of soticlestat with CH24H, resulting in systemic reductions of 24HC [14–16].

Although reductions were observed in 24HC in the Dup15q cohort, patients experienced a median increase in seizure frequency, which might be explained by several possible reasons. Given the relatively low number of patients with Dup15q syndrome included in the study (n = 8), it is possible that the median increase in motor seizure frequency seen in this group may have been due to normal statistical variation. It is also possible that baseline seizure frequency may have been underestimated earlier

Table 2
Incidence of treatment-emergent adverse events.

	All patients (n = 20)	Dup15q syndrome (n = 8)	CDKL5 deficiency disorder (n = 12)
Any TEAEs,[a] n (%)	19 (95.0)	7 (87.5)	12 (100.0)
Mild	15 (75.0)	7 (87.5)	8 (66.7)
Moderate	9 (45.0)	3 (37.5)	6 (50.0)
Severe	3 (15.0)	0	3 (25.0)
TEAEs related to study drug,[b] n (%)	13 (65.0)	4 (50.0)	9 (75.0)
TEAEs leading to dose modification, n (%)	6 (30.0)	2 (25.0)	4 (33.3)
Serious TEAEs,[c] n (%)	3 (15.0)	1 (12.5)	2 (16.7)
Deaths, n (%)	0	0	0
TEAEs leading to drug withdrawals, n (%)	1 (5.0)	0	1 (8.3)
TEAEs occurring in ≥10% of patients, n (%)			
Constipation	4 (20.0)	0	4 (33.3)
Rash	3 (15.0)	1 (12.5)	2 (16.7)
Seizure	3 (15.0)	2 (25.0)	1 (8.3)
Agitation	2 (10.0)	1 (12.5)	1 (8.3)
Blood bicarbonate decreased	2 (10.0)	0	2 (16.7)
Ear infection	2 (10.0)	0	2 (16.7)
Fatigue	2 (10.0)	2 (25.0)	0
Lethargy	2 (10.0)	2 (25.0)	0
Nasopharyngitis	2 (10.0)	1 (12.5)	1 (8.3)
Partial seizures	2 (10.0)	0	2 (16.7)
Tonic convulsions	2 (10.0)	0	2 (16.7)

[a] Patients with adverse events of the same Medical Dictionary for Regulatory Activities Preferred Terms were counted once for the highest severity. Patients with adverse events of different Preferred Terms of the same highest severity levels were counted once. Patients with adverse events of different Preferred Terms and different highest severity levels were counted separately for each of the highest severity level.
[b] Defined as events that were 'possibly related' or 'related' to the study drug.
[c] None of the serious TEAEs were considered to be related to treatment by the investigators.

in the study, with values increasing as caregivers became more experienced at reporting seizures as the study progressed. However, this could equally be true for the CDD cohort. Patients with Dup15q syndrome had a mean age of 15.4 years. Respondents to a survey of families with Dup15q syndrome (n = 95) reported seizures to be more prevalent in older than in younger individuals, with the highest rates found in those of 15–17 years of age [6]. Older children with long-standing epilepsy are also more likely to be treatment resistant.

The exact etiology of seizures in Dup15q syndrome is unknown. A role for GABAergic synapses in the etiology of seizure semiology has also been reported in those with inherited 15q11-q13 duplications [20]. Further evidence for the role of GABAergic signaling in Dup15q syndrome was shown in a study in which administration of the benzodiazepine, midazolam, in healthy adults recapitulated the beta electroencephalography phenotype that is often observed in patients with this disease [21]. Soticlestat targets CH24H rather than GABAergic signaling; therefore, these findings may explain the lack of efficacy seen in patients with Dup15q syndrome in the present study.

Most patients in ARCADE experienced TEAEs that were mild or moderate in severity. A third of patients with CDD reported constipation (including one severe TEAE), which is a relatively common comorbidity in this patient population [8]. The remaining two severe TEAEs were asthenia and seizure, both of which are frequently observed in patients with epilepsy who are treated with ASMs [22,23]. Some assessments, including measurement of weight, could only be assessed in those patients who attended study centers. As such, certain data are not available for all patients at all scheduled visits. For example, final visit weight measurements are available for five patients with Dup15q syndrome and eight patients with CDD. Disruption caused by the COVID-19 pandemic was a key reason for patients missing visits.

Inherent challenges of clinical trials in rare disorders include recruitment, enrollment, and retention of patients. For example, it is possible that only the most severely affected patients choose to enroll in a study, which could lead to selection bias of treatment-resistant patients. Another limitation when conducting clinical trials in Dup15q syndrome or CDD is the high number of patients who experience multiple seizure types [1,6], which can make accurate reporting challenging. Additionally, in patients with Dup15q syndrome, the number of different seizure types experienced is known to increase with age [6]. Many patients with this disorder progress from infantile spasms to multiple generalized seizure types, which may develop as late as 9 years of age in the case of tonic seizures [6].

Despite the improvements in motor seizure frequency and global functioning seen in patients with CDD in the present study, a high incidence of new seizure types not present at baseline was observed in this group and included focal seizures with motor signs, tonic, atonic, and absence or atypical absence seizures. The onset of new seizure types has also been reported in another study that assessed the efficacy of ASMs in reducing convulsive seizure frequency in patients with CDD, suggesting that this may be a general finding rather than a treatment-specific response [24].

The strengths of this study included the wide range of efficacy assessments, involving the measurement of motor seizures, non-motor seizures, responder analysis, and global functioning using the CGI-C and Care GI-C scales.

5. Conclusions

Results from ARCADE showed a median motor seizure reduction from baseline in patients with CDD and a median reduction from baseline in all seizure frequency (motor and non-motor) in both treatment groups. An increase from baseline in motor seizure frequency was observed in patients with Dup15q syndrome, most likely due to the older age of this cohort.

Improvements in CGI-C and Care GI-C scores were observed in both groups of patients, and all patients in this open-label study elected to enroll in the open-label extension study, indicating a perceived benefit of treatment.

Safety findings in ARCADE were consistent with findings from previous studies, with no new safety signals identified.

Funding

This study was funded by the sponsor, Takeda Pharmaceutical Company Limited, Cambridge, MA, USA.

Author contributions

All authors interpreted the results and contributed to the writing of and approved the final version of the manuscript for submission.

Ethical publication statement

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

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 from initial 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.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Scott Demarest has served as a paid consultant for BioMarin, Neurogene, Upsher-Smith Laboratories, Taysha Gene Therapies, and Zogenix on unrelated subject matters and for Marinus Pharmaceuticals and Ovid Therapeutics on related subject matters. Furthermore, he has received funding from the US National Institutes of Health, the International Foundation for CDKL5 Research, Mila's Miracle Foundation, and Project 8p. He also serves on the advisory board for the nonprofit foundations FamilieSCN2A, Project 8p, Ring14 USA, and SLC6A1 Connect. Shafali Jeste has served as a consultant for Roche Pharmaceuticals. Nitin Agarwal currently serves on a speaker panel for Livanova. Dimitrios Arkilo is a former employee of Takeda Pharmaceutical Company Limited. Mahnaz Asgharnejad and Samuel Hsiao are employees of Takeda Pharmaceutical Company Limited and own stock or stock options. Ronald Thibert has served as a paid consultant for Ovid Therapeutics, Takeda, and Roche on related subject matters.

Acknowledgments

This study was funded by the sponsor, Takeda Pharmaceutical Company Limited. We thank the participants and investigators involved in the studies. We also thank Peter B. Forgacs and Yin Yang (Ovid Therapeutics Inc.) for their contribution to this study. Under the direction of the authors and funded by Takeda Pharmaceutical Company Limited, William Luderman, Ph.D., and Aimee Jones, Ph.D., of Oxford PharmaGenesis, Oxford, UK, provided medical writing support for this publication. Editorial assistance in formatting, proofreading, copyediting, and fact-checking was also provided by Oxford PharmaGenesis, Oxford, UK.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2023.109173.

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