Efficacy, safety and tolerability of soticlestat (TAK-935/OV935) as adjunctive therapy in pediatric patients with Dravet syndrome or Lennox–Gastaut syndrome (ELEKTRA)

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Cecil D. Hahn,[1] Yuwu Jiang,[2] Vicente Villanueva,[3] Marta Zolnowska,[4] Dimitrios Arkilo,[5] Julia Tsai,[6] Mahnaz Asgharnejad,[5] Ying Yan,[6] Dennis Dlugos[7]

[1]Division of Neurology, Department of Paediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada; [2]Department of Pediatrics, Peking University First Hospital, Beijing, China; [3]Refractory Epilepsy Unit, Hospital Universitario y Politécnico La Fe, Valencia, Spain; [4]Plejady Medical Center, Krakow, Poland; [5]Takeda Pharmaceutical Company Ltd, Cambridge, MA, USA; [6]Ovid Therapeutics Inc., New York, NY, USA; [7]Division of Neurology, The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA

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Background

- Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) are rare childhood-onset epilepsies often resistant to therapy using current antiseizure medications (ASMs).
- Soticlestat (TAK-935/OV935) is a novel, potent, selective inhibitor of cholesterol 24-hydroxylase, which metabolizes cholesterol to 24S-hydroxycholesterol (24HC) in the brain.[1] 24HC is implicated in various biological systems relevant to neurological disorders, including epilepsy.[1] In preclinical studies, soticlestat has shown antiseizure activity, including in models relevant to DS.[2]
- In phase 1 clinical studies, soticlestat has been shown to decrease plasma 24HC in a dose-dependent manner.[3]
- Here, we report the effects of soticlestat on seizure frequency, safety and tolerability in children with DS or LGS (ClinicalTrials.gov identifier: NCT03650452).

Objectives

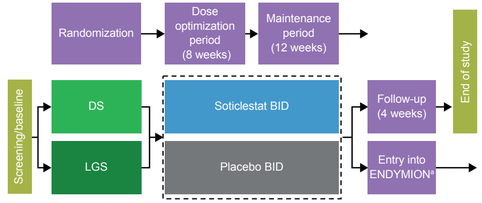
- The primary objective was to assess the frequency of convulsive seizures (for DS) and drop seizures (for LGS) in the combined patient population treated with soticlestat as an adjunctive therapy compared with placebo in the maintenance period.
- Secondary objectives included assessment of the seizure frequency over the full treatment period, change in investigator- and caregiver-reported Clinical Global Impression of Change (CGI-C) scores, and treatment response (≥ 50% reduction in seizures vs baseline).
- Safety objectives included the incidence of treatment-emergent adverse events (TEAEs).

Methods

Study design

- ELEKTRA was a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group study in pediatric patients (aged 2–17 years) with DS or LGS.
- The study consisted of a 4–6-week screening/baseline period, and up to 20-week treatment period that included 8 weeks of dose optimization and 12 weeks of dose maintenance (**Figure 1**).
- Patients and/or their caregivers were provided with a seizure diary to record daily seizure frequency, starting at the screening visit and continuing through to the end of the study.
- Patients who met the eligibility criteria were randomized in a 1:1 ratio to receive either soticlestat or placebo (≤ 600 mg/day, weight adjusted for children weighing < 60 kg) twice daily for the 20-week treatment period.

Figure 1. Study design.



[a]Open-label extension study.
BID, twice daily; DS, Dravet syndrome; LGS, Lennox–Gastaut syndrome.

- Soticlestat or placebo was administered either orally with or without food or via gastrostomy tube/percutaneous endoscopic gastrostomy tube.

Key eligibility criteria

- Eligible children had a clinical diagnosis of either DS, with a history of three or more convulsive seizures per month, or LGS, with a history of four or more drop seizures per month at baseline, and were currently taking 1–4 ASMs at a stable dose.

Results

Baseline demographic and clinical characteristics

- Patient demographics were generally similar between placebo and active treatment arms (**Table 1**).
- Of 141 enrolled patients, 139 (modified intent-to-treat population; mean age, 9.5 years; 36% female) received at least one dose of study drug and 126 completed the study.

Efficacy

- Patients in the combined population receiving soticlestat demonstrated a 29.8% median reduction in seizure frequency compared with a 0.0% median change in those receiving placebo during the full treatment period (median placebo-adjusted reduction in seizure frequency of 25.1%; $p = 0.0024$; n = 139). During the maintenance period, the patients in the soticlestat arm demonstrated a 27.8% median reduction in seizure frequency, compared with a median increase of 3.1% in the placebo arm (median placebo-adjusted reduction in seizure frequency of 30.5%; $p = 0.0007$; n = 120).

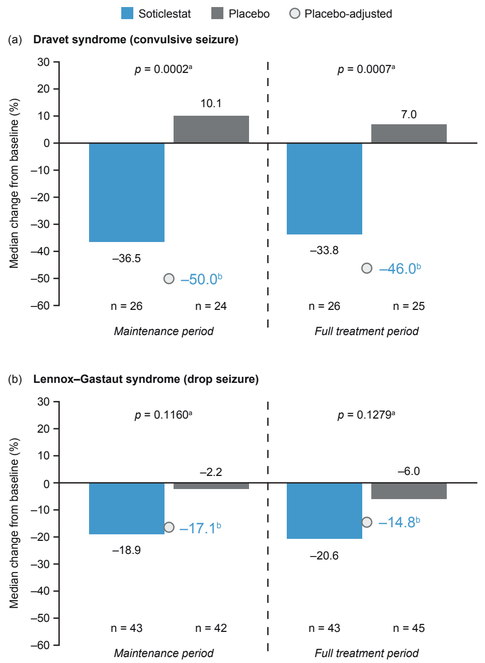
Table 1. Baseline demographic and clinical characteristics (modified intent-to-treat population).

	DS		LGS	
	Placebo n = 25	Soticlestat n = 26	Placebo n = 45	Soticlestat n = 43
Age (years)				
Mean (SD)	8.8 (4.5)	8.7 (3.9)	9.8 (3.6)	10.0 (4.2)
Min, max	2, 16	4, 17	3, 17	2, 17
Sex, n (%)				
Male	14 (56)	17 (65)	28 (62)	30 (70)
Female	11 (44)	9 (35)	17 (38)	13 (30)
Race, n (%)				
American Indian or Alaska Native	1 (4)	0	0	0
Asian	5 (20)	11 (42)	16 (36)	11 (26)
African American	0	0	1 (2)	0
White	19 (76)	15 (58)	28 (62)	32 (74)
Ethnicity, n (%)				
Hispanic or Latino	6 (24)	2 (8)	4 (9)	8 (19)
Nonhispanic and Latino	19 (76)	24 (92)	41 (91)	35 (81)
Weight (kg)				
Mean (SD)	30 (15)	29 (11)	34 (16)	36 (17)
Min, max	14, 68	15, 61	12, 82	10, 73
Number of ASMs,[a] n (%)				
Any	25 (100)	26 (100)	45 (100)	43 (100)
1	1 (4.0)	0	1 (2.2)	2 (4.65)
2	6 (24.0)	11 (42.3)	11 (24.4)	12 (27.9)
3	11 (44.0)	10 (38.5)	19 (42.2)	18 (41.9)
4	7 (28.0)	5 (19.2)	13 (28.9)	10 (23.3)
5	0	0	1 (2.22)	1 (2.3)
Seizure frequency[b]				
Mean (SD)	13.2 (23.9)	13.8 (11.0)	150.0 (203.8)	441.0 (1133.5)
Median	6.0	9.1	89.8	67.3
Min, max	2.5, 125.0	2.6, 40.3	4.0, 1040.1	8.1, 5187.7

[a]Ongoing ASMs are included if start date is prior to first dose date or is missing.
[b]Seizure frequency is based on convulsive seizures for DS and drop seizures for LGS.
ASM, antiseizure medication; DS, Dravet syndrome; LGS, Lennox–Gastaut syndrome; max, maximum; min, minimum; SD, standard deviation.

- Patients with DS receiving soticlestat demonstrated a statistically significant median reduction of 33.8% in convulsive seizure frequency during the full treatment period compared with a median increase of 7.0% in the placebo arm (median placebo-adjusted reduction in seizure frequency of 46.0%; $p = 0.007$) (**Figure 2a**).
- Patients with LGS receiving soticlestat demonstrated a 20.6% median reduction in drop seizure frequency compared with a 6.0% median decrease in patients receiving placebo during the full treatment period (median placebo-adjusted reduction in seizure frequency of 14.8%; $p = 0.1279$) (**Figure 2b**).
- At last visit, more patients receiving soticlestat demonstrated an improvement in investigator- and caregiver-reported CGI-C scores than those receiving placebo (**Figure 3**).
- Proportions of patients who met responder criteria were 30.8% for those with DS who received soticlestat (placebo, 0.0%) and 16.3% for those with LGS who received soticlestat (placebo, 13.3%).

Figure 2. Seizure frequency during the 12-week maintenance period and full 20-week treatment period.

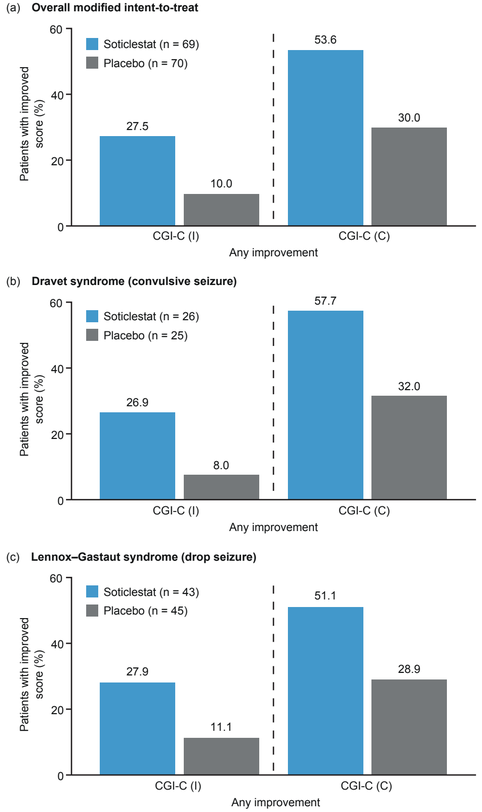


[a]Rank-transformed ANCOVA adjusting for baseline seizure frequency and protocol amendment cohort.
[b]Hodges–Lehmann estimation of the median treatment difference (percentage change from baseline in soticlestat vs percentage change from baseline in placebo).
ANCOVA, analysis of covariance.

Safety and tolerability

- Seven patients (5.0%; based on the safety population) withdrew from the study due to adverse events (**Table 2**).
- Overall, 18 patients experienced a TEAE that led to dose modification and two patients interrupted their dose due to TEAEs (**Table 2**).
- Soticlestat was generally safe and well tolerated at all doses tested.
  - No deaths were reported (**Table 2**).
  - The most common TEAEs occurring with a difference of 5% or more over placebo were lethargy and constipation (**Table 2**).

Figure 3. Proportion of patients with any improvement in CGI-C score at the last visit.



CGI-C, Clinical Global Impression of Change; CGI-C (C), Clinical Global Impression of Change (caregiver); CGI-C (I), Clinical Global Impression of Change (investigator)

Table 2. TEAEs by system organ class.

	Placebo (n = 70) n (%)	Soticlestat (n = 71) n (%)	Total (N = 141) N (%)
Patients with any TEAEs	52 (74.3)	57 (80.3)	109 (77.3)
Mild	47 (67.1)	47 (66.2)	94 (66.7)
Moderate	19 (27.1)	25 (35.2)	44 (31.2)
Severe	11 (15.7)	10 (14.1)	21 (14.9)
Withdrawal due to TEAEs	3 (4.3)	4 (5.6)	7 (5.0)
DS	1	1	2
LGS	2	3	5
Result of TEAE			
Dose modification	8 (11.4)	10 (14.1)	18 (12.8)
Dose interruption	0	2 (2.8)	2 (1.4)
Serious adverse events	13 (18.6)	11 (15.5)	24 (17.0)
Deaths	0	0	0
Common TEAEs			
Upper respiratory tract infection	12 (17.1)	13 (18.3)	25 (17.7)
Pyrexia	8 (11.4)	11 (15.5)	19 (13.5)
Seizure (worsening or new)	9 (12.9)	6 (8.5)	15 (10.6)
Nasopharyngitis	6 (8.6)	6 (8.5)	12 (8.5)
Decreased appetite	5 (7.1)	6 (8.5)	11 (7.8)
Vomiting	4 (5.7)	6 (8.5)	10 (7.1)
Somnolence	3 (4.3)	6 (8.5)	9 (6.4)
Diarrhea	4 (5.7)	5 (7.0)	9 (6.4)
Lethargy	0	5 (7.0)[a]	5 (3.5)
Fatigue	3 (4.3)	4 (5.6)	7 (5.0)
Pneumonia	2 (2.9)	4 (5.6)	6 (4.3)
Irritability	2 (2.9)	4 (5.6)	6 (4.3)
Constipation	0	4 (5.6)[b]	4 (2.8)

The text in *italics* indicates TEAEs occurring with a difference of 5% or more over placebo.
[a]Lethargy: 4 mild; 1 severe.
[b]Constipation: 3 mild; 1 moderate.
DS, Dravet syndrome; LGS, Lennox–Gastaut syndrome; TEAE, treatment-emergent adverse event.

Conclusions

- In this phase 2 study, soticlestat treatment resulted in a statistically significant reduction in median convulsive seizure frequency compared with baseline in children with DS.
- Treatment with soticlestat resulted in a directional reduction in median drop seizure frequency in patients with LGS.
- Soticlestat was generally safe and well tolerated, which is consistent with findings from previous studies.

Disclosures

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