A phase 1b/2a study of soticlestat (TAK-935 /OV935) as adjunctive therapy in patients with developmental and epileptic encephalopathies

Jonathan J Halford,[1] Michael R Sperling,[2] Dimitrios Arkilo,[3] Mahnaz Asgharnejad,[3] Asif M Paker,[4] Rengyi Xu,[3a] Matthew During,[4] Jacqueline A French[5]

[1]Medical University of South Carolina, Charleston, SC; [2]Thomas Jefferson University, Philadelphia, PA; [3]Takeda Pharmaceuticals, Cambridge, MA; [4]Ovid Therapeutics, New York, NY; [5]NYU Langone Health, New York, NY

All studies were funded by the sponsor, Takeda Pharmaceutical Company, Ltd. Takeda Pharmaceutical Company, Ltd provided funding to Oxford PharmaGenesis for editorial assistance in formatting, proofreading, copy editing, and fact checking. 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 French (Adamas, Aeonian/Aeovian, Anavex, Arvelle Therapeutics, Inc., Axovant, Biogen, Biomotiv/Koutif, BioXcel Therapeutics, Blackfynn, Bloom Science, Bridge Valley Ventures, Carnot Pharma, Cavion, Cerebral Therapeutics, Cerevel, Crossject, CuroNZ, Eisai, Encoded Therapeutics, Engage Therapeutics, Epilepsy Foundation, Epilepsy Study Consortium, Epiminder, Epitel, Fortress Biotech, GW Pharma, Idorsia, Ionis, Janssen Pharmaceutica, J&J Pharmaceuticals, Knopp Biosciences, Lundbeck, Marinus, Merck, NeuCyte, Inc., Neurelis, Neurocrine, NINDS, Novartis, Otsuka Pharmaceutical Development, Ovid Therapeutics Inc., Passage Bio, Pfizer, Praxis, Redpin, Sage, Shire, SK Life Sciences, Springworks, Stoke, Sunovion, Supernus, Takeda, UCB Inc., West Therapeutic Development, Xenon, Xeris, Zogenix, Zynerba); J Halford (Greenwich Biosciences, SK Life Sciences and Takeda); M Sperling (Cerevel, Eisai, Engage Therapeutics, Medtronic, Neurelis, SK Life Sciences, Takeda, UCB Inc, Xenon)

[a]R Xu was an employee of Takeda at the time the study was conducted

START

Introduction

- Developmental and epileptic encephalopathies (DEEs) comprise a range of rare epilepsy syndromes that include Dravet syndrome, Lennox-Gastaut syndrome, chromosome 15q duplication syndrome and cyclin-dependent kinase-like 5 deficiency disorder (CDD)
  - DEEs typically present with unremitting seizure activity that begins in infancy or early childhood; treatment is a significant unmet medical need[1]
- Soticlestat (TAK-935/OV935) is a potent and selective inhibitor of cholesterol 24-hydroxylase (CH24H), an enzyme that converts brain cholesterol to 24S-hydroxycholesterol (24HC), a positive allosteric modulator of the *N*-methyl-D-aspartate (NMDA) receptor[2–5]
  - Preclinical studies have suggested that CH24H is the primary metabolic pathway for neuronal cholesterol[4]
  - 24HC can drive glutamatergic overactivation by modulation via NMDA channel activity; excessive excitation is considered one of the key mechanisms underlying epileptic seizures[6]
  - Preclinical studies have shown that the benefits of soticlestat in epilepsy models are correlated with reduction of brain 24HC, which supports the therapeutic relevance of CH24H inhibition
  - Phase 1 studies have shown the pharmacokinetics (PK) and pharmacodynamics (PD) of soticlestat in healthy volunteers[7]
- Soticlestat is a first-in-class therapeutic candidate with a novel mechanism of action
- Soticlestat has the potential to control seizures in treatment-resistant patients

1. Scheffer IE *et al*. *Epilepsia* 2017;58:512–21; 2. Xie C *et al*. *J Lipid Res* 2003;44:1780–9; 3. Lund EG *et al*. *J Biol Chem* 2003;278:22980–8; 4. Russell DW *et al*. *Ann Rev Biochem* 2009;78:1017–40; 5. Paul SM *et al*. *J Neurosci* 2013;33:17290–300; 6. Amakhin DV *et al. Front Cell Neurosci* 2018;12:486; 7. During M *et al.* Presentation: EILAT 2018

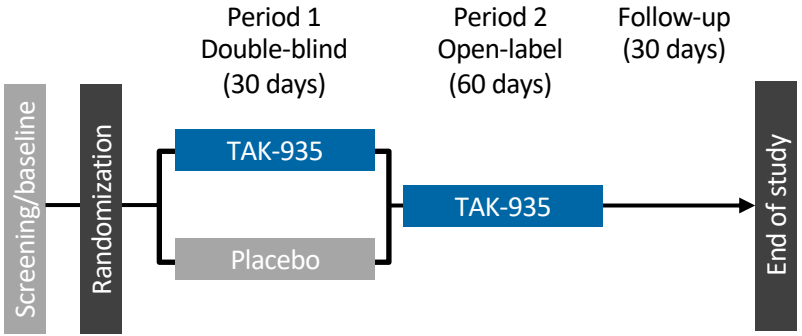
Methods

- This was a phase 1b/2a, randomized, double-blind, placebo-controlled, parallel-group, dose-titration study with an open-label extension, to examine soticlestat as an adjunctive therapy in adult patients with developmental and/or epileptic encephalopathies (**Table 1**, **Figure 1**)
  - **Period 1:** double blind; soticlestat or matching placebo (randomization 4:1) was administered twice daily (b.i.d.) orally, with titration to 100, 200 or 300 mg/day; safety and PK assessments
  - **Period 2:** open label; soticlestat was administered b.i.d., with titration starting at 200 and going up to 300 mg/day; safety, PK and exploratory efficacy assessments

Table 1. Inclusion criteria

Main enrollment criteria
18–65 years of age
Documented clinical diagnosis of DEE with bilateral motor seizures[a]
1–4 AEDs at a stable dose for ≥ 4 weeks before screening
Average of ≥ 1 bilateral motor seizure per month during the 4-week baseline period

Figure 1. Study schematic



[a]Tonic-clonic, tonic, bilateral clonic, atonic, myoclonic-atonic, myoclonic-tonic-clonic, or focal seizures with bilateral hyperkinetic motor features

AED, antiepileptic drug

BACK NEXT

Results

Patient demographics and baseline characteristics

- Patients in the placebo arm had lower median baseline seizure frequency than those in the soticlestat arm

Table 2. Baseline patient demographics and diagnoses

	Placebo (n = 4)	Concomitant perampanel[a] (n = 3)	TAK-935 (n = 14)	Total (N = 18)
Mean age, years (min, max)	27.8 (19, 39)	29 (22, 34)	29.4 (20, 45)	29.1 (19, 45)
Sex, n (%)				
Male	4 (100)	2 (66.7)	10 (71)	14 (78)
Female	–	1 (33.3)	4 (29)	4 (22)
Race, n (%)				
Caucasian	3 (75)	3 (100)	13 (93)	16 (89)
Black/African American	1 (25)		–	1 (6)
Not reported			1 (7)	1 (6)
Median 28-day seizure frequency (min, max)	10.10 (3.7, 49.5)		33.75 (3.4, 277.1)	
Diagnosis, n (%)				
Lennox-Gastaut syndrome	1 (25)		5 (36)	6 (33)
Epileptic encephalopathy[b]	3 (75)		3 (22)	6 (33)
Partial seizures with secondary generalization	–		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]Patients were receiving concomitant perampanel and are included in the TAK-935 cohort
[b]Not otherwise specified

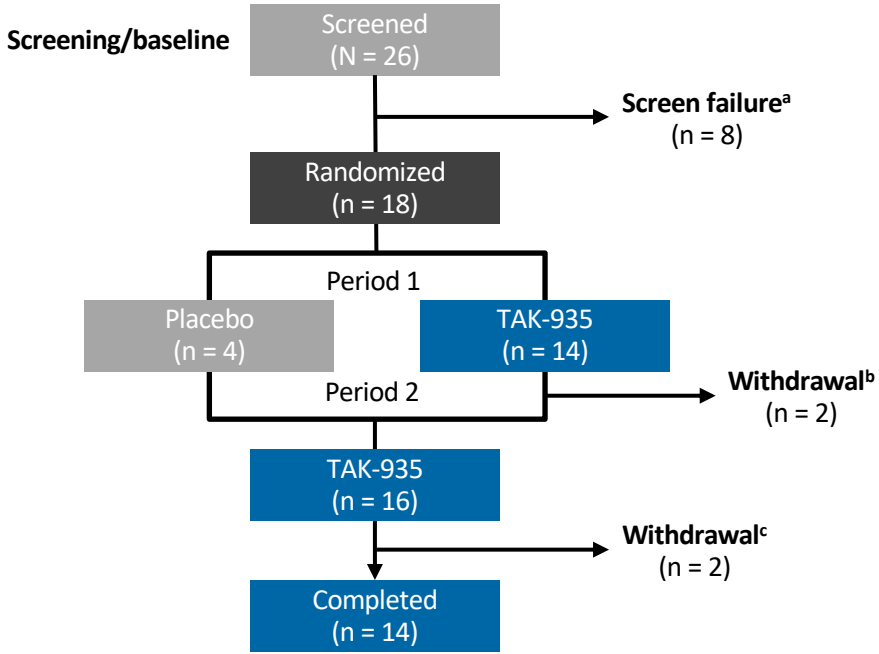
BACK NEXT

Results

Patient disposition

- Four discontinuations (22%) occurred owing to treatment-emergent adverse events (TEAEs), all in the soticlestat treatment group (**Figure 2**)
  - Weakness (n = 1)
  - Difficulty with walking/worsening lethargy (n = 1)
  - Increased seizure frequency (n = 2)

Figure 2. Patient disposition



[a]Did not meet entrance criteria (n = 5) and withdrawal by patient (n = 3)
[b]Weakness (n = 1) and difficulty with walking/worsening lethargy (n = 1)
[c]Seizure cluster (n = 2).

BACK NEXT

Results

Safety/tolerability (primary outcome measure)

- TEAEs are presented in **Table 3**
- Most TEAEs (95%) were mild to moderate in severity

Table 3. TEAEs

	Period 1		Period 2
	Placebo (n = 4)	TAK-935 (n = 14)	All (N = 16)
Severity of TEAEs, number of events (%)			
AEs	10 (100)	36 (100)	40 (100)
Mild	10 (100)	32 (89)	31 (78)
Moderate	–	3 (8)	6 (15)
Severe	–	1 (3)	3 (8)
AE-related withdrawal[a]	–	3 (8)	2 (5)
Serious AEs[b,c]	–	1 (3)	4 (10)
Most common non-serious TEAEs, number of patients (%)			
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)

[a]Four patients discontinued in the soticlestat treatment arm
[b]All serious TEAEs were seizure clusters, reported by three patients
[c]There were no deaths across the soticlestat and placebo treatment groups
AE, adverse event

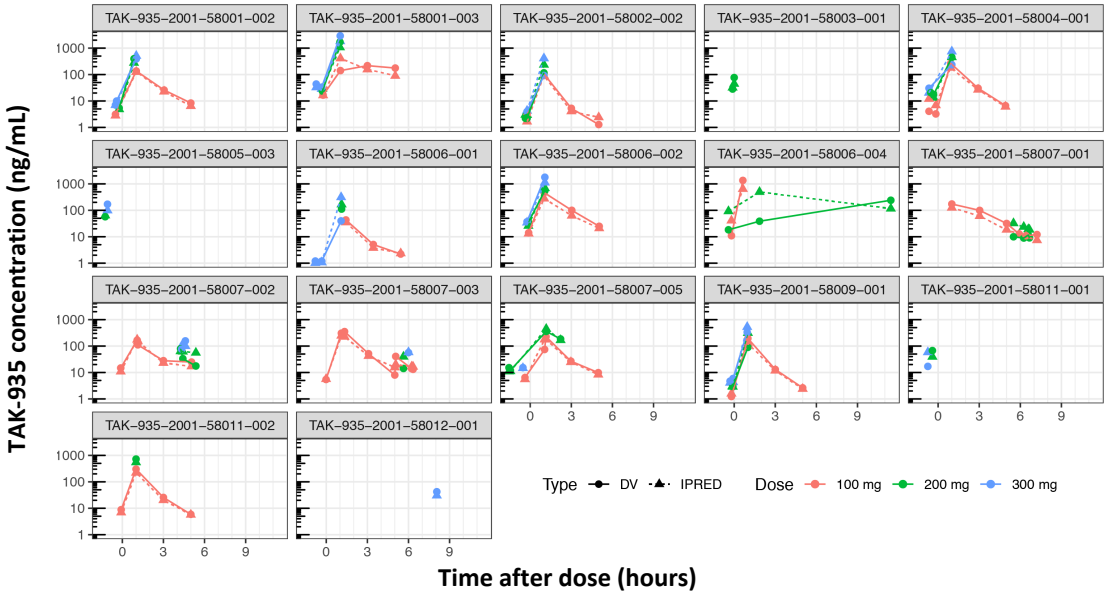
BACK NEXT

Results

PK profile (secondary outcome measure)

- A model-based approach was used to derive individual PK model parameter estimates and systemic exposures of soticlestat. A trend towards lower clearances (20%) of soticlestat than predicted was observed in this patient population but the data was limited (**Figure 3**)

Figure 3. Individual soticlestat fit plots[a]



[a]Observed (●) vs predicted (▲) PK values
DV, dependent variable (observations); IPRED, individual predictions

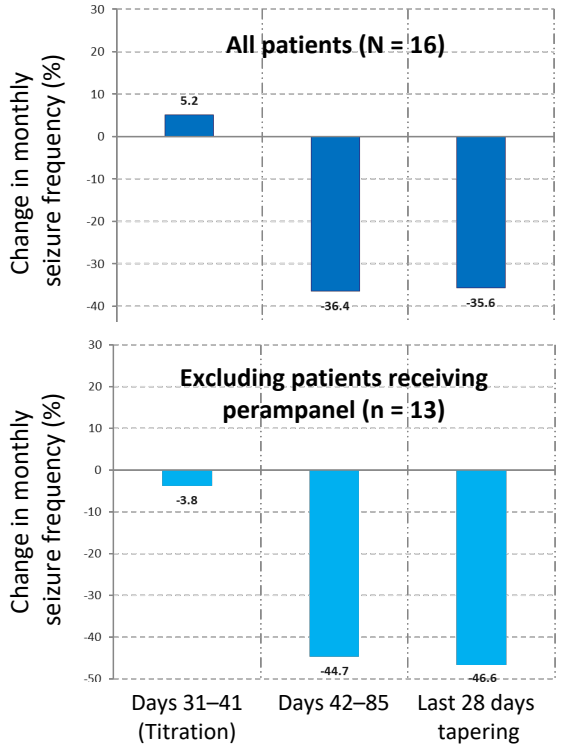
BACK
NEXT

Results

Seizure frequency (exploratory outcome measure)

- Analysis in the open-label phase of all 16 patients receiving at least one dose of soticlestat showed a 36.4% median reduction in seizure frequency from baseline to day 85 or early termination (end of maintenance) (**Figure 4**)
  - Three patients receiving perampanel had increases in seizure frequency, potentially related to a pharmacodynamic interaction
  - A sensitivity analysis excluding patients receiving perampanel during days 42–85 indicated a median seizure frequency reduction of 46.6% (n = 13). A *post hoc* analysis in completers excluding patients receiving perampanel and using the last scheduled visits day, indicated a median seizure frequency reduction of 60.74% per 28 days (n = 11)
  - Two patients (12.5%) became seizure free in the last 28 days of treatment

Figure 4. Median monthly seizure frequency, change over time[a]



[a]Based on an interval arranged over 28 days, excluding myoclonic seizures. The first dose day is study day 1

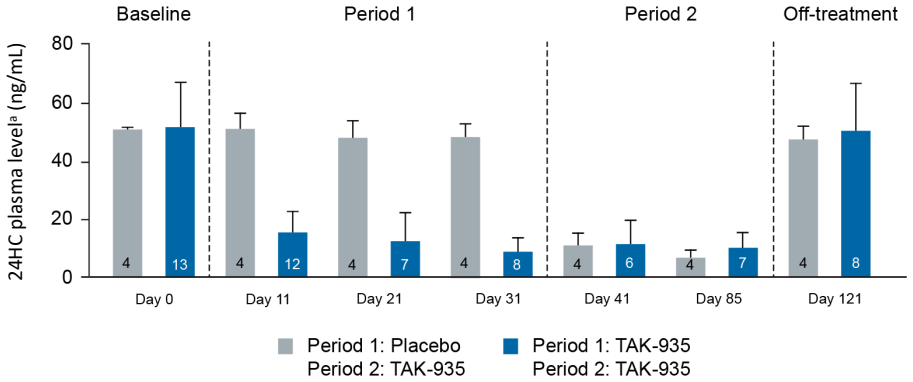
BACK NEXT

Results

Plasma levels (exploratory outcome measure)

- A dose- and time-dependent reduction trend in 24HC plasma levels was observed with soticlestat vs placebo, as predicted (**Figure 5**)
  - Mean 24HC levels decreased 81% from baseline to day 85 (end of maintenance) during treatment with soticlestat
  - Following washout, 24HC plasma levels recovered to pretreatment levels, thus representing a biomarker of target engagement

Figure 5. Dose- and time-dependent reduction in plasma 24HC[a]



[BACK](#)

[a]Assessed before treatment at day 0, pre-dose at days 11–85 and off-treatment at day 121 (~30 days after the last dose)

[NEXT](#)

Conclusions

- Study results were consistent with a favorable safety and tolerability profile
- The trend towards lower clearance of soticlestat vs the prediction based on the healthy volunteer data was small and mainly due to the limited number of subjects with sparse PK sampling in this study. Overall, the systemic exposure to soticlestat was consistent across the dose range of 100 to 300 mg b.i.d. with those observed in healthy volunteers
- The seizure frequency data provides encouraging results for this exploratory outcome measure in a limited number of patients with highly heterogenous DEE
- Decreased 24HC plasma levels indicate utility as a biomarker for central target engagement
  - Three patients taking concomitant perampanel had increased seizure frequency with soticlestat, indicating a potential pharmacodynamic interaction
- In summary, the results from this phase 1b/2a trial support the continued development of soticlestat in pediatric patients with various DEEs, including Dravet syndrome, Lennox-Gastaut syndrome, CDKL5 and chromosome 15q duplication syndrome

BACK NEXT