

# Initial data from the ongoing ENDYMION open-label extension trial of soticlestat (TAK-935/OV935) in participants with developmental and/or epileptic encephalopathies (DEE)

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# Introduction

- Developmental and epileptic encephalopathies (DEEs) comprise a range of rare epilepsy syndromes that include Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), chromosome 15q duplication syndrome (Dup15q) 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<sup>1</sup>
- Soticlestat (TAK-935/OV935) is a potent and selective cholesterol 24-hydroxylase (CH24H) inhibitor that dose-dependently reduces plasma 24S-hydroxycholesterol (24HC) levels<sup>2</sup>
- In support of the therapeutic relevance of CH24H inhibition, preclinical studies have shown that the benefits of soticlestat correlate with reduced brain 24HC in epilepsy models<sup>3-7</sup>
- In a recent phase 1b/2a study in adult patients with DEE (NCT03166215), soticlestat was well tolerated with initial evidence of possible efficacy and demonstration of a promising biomarker<sup>8</sup>

## Aim

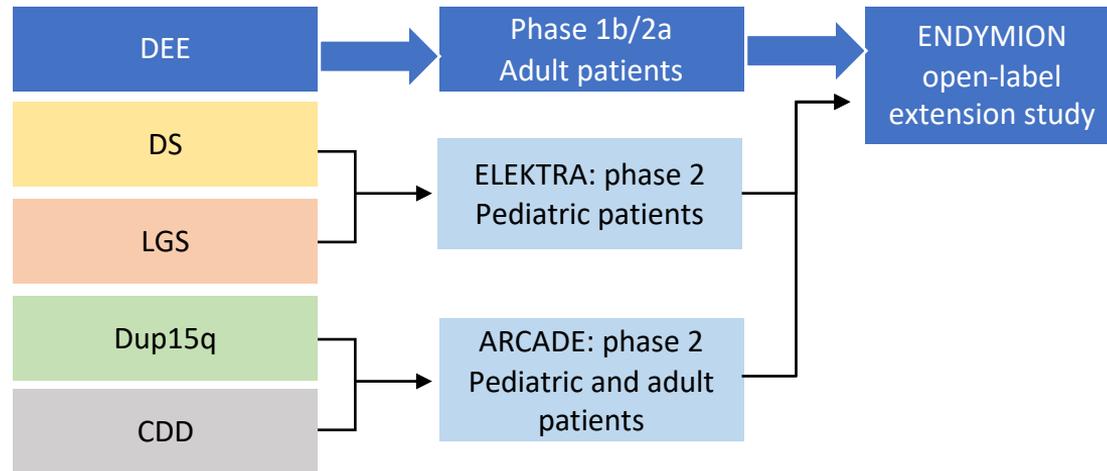
- The current presentation reports interim data from patients who completed the 12-week phase 1b/2a adult DEE clinical trial and subsequently enrolled in the ENDYMION open-label extension study (NCT03635073)

1. Scheffer IE *et al. Epilepsia* 2017;58:512–21; 2. Salamone A *et al.* Presented at the 13th European Congress on Epileptology (ECE), August 26–30, 2018, Vienna, Austria; 3. Xie C *et al. J Lipid Res* 2003;44:1780–9; 4. Lund EG *et al. J Biol Chem* 2003;278:22980–8; 5. Russell DW *et al. Ann Rev Biochem* 2009;78:1017–40; 6. Paul SM *et al. J Neurosci* 2013;33:17290–300; 7. Amakhin DV *et al. Front Cell Neurosci* 2018;12:486; 8. Halford JJ *et al.* Presented at the 12th International Epilepsy Colloquium, May 26–28, 2019, Lyon, France

# Methods

- ENDYMION is a multi-site, open-label extension study of soticlestat as adjunctive therapy in patients with rare epilepsy
  - **Primary study objective:** to assess the long-term safety and tolerability of soticlestat
  - **Secondary study objective:** to evaluate the effect of soticlestat on seizure frequency
- Participants were enrolled from three previous soticlestat clinical studies (Figure 1)

Figure 1. Study schematic



The DEE trial was a randomized, double-blind, placebo-controlled, parallel-group, dose-escalation study with an open-label part in patients aged 18–65 years (NCT03166215)

ELEKTRA is a randomized, double-blind, placebo-controlled study in patients aged 2–17 years (NCT03650452)

ARCADE is an open-label pilot study in patients aged 2–55 years (NCT03694275)

# Methods

## Study design

- All patients experienced an interruption in treatment with soticlestat from the end of the DEE trial to the start of ENDYMION, ranging from 6 to 52 weeks
- Patients rolling over to the open-label ENDYMION trial from the adult DEE study underwent a 4-week screening/baseline period, a 2-week dose-optimization period and a 103-week dose maintenance period, followed by a 4-week safety follow-up period of soticlestat dose tapering ( $\leq 2$  weeks) and safety follow-up (week 108)
  - Adults initiated treatment with 200 mg/day and were titrated up to a maximum dose of 600 mg/day
- At the screening visit and subsequent visits, patients and/or patients' caregivers were given a seizure diary and instructed to record seizure data daily

## Key inclusion/exclusion criteria

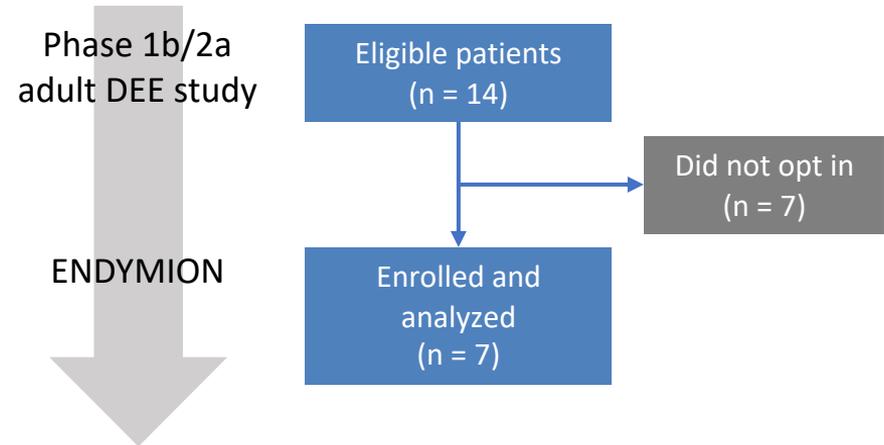
- Patients must have participated in a previous soticlestat study and either successfully completed the study or received soticlestat treatment for at least 10 weeks without a serious or severe drug-related adverse event
- With the exception of an antecedent study involving soticlestat, participants were not eligible if they had enrolled in any other clinical trial involving an investigational drug, device or treatment in the past 90 days

# Results

## Patient disposition

- Patient disposition is presented in Figure 2
- The patient population was not enriched for any specific epilepsy syndrome
- Patients were each diagnosed with one of multiple DEEs
- Most patients were receiving multiple anti-epileptic drugs (AEDs)
- The most common AEDs (taken by at least two patients) were lamotrigine, oxcarbazepine, rufinamide, topiramate and valproate

Figure 2. Patient disposition



# Results

## Patient demographics

- Patients enrolled in ENDYMION from adult DEE study (n = 7)

**Table 1. Patient demographics**

<b>Age, years</b>	
Mean (SD)	27.9 (7.03)
Median	27
Minimum, maximum	19, 40
<b>Sex, n (%)</b>	
Male	6 (85.7)
Female	1 (14.3)
<b>Ethnicity, n (%)</b>	
Not Hispanic or Latino	7 (100.0)
<b>Race, n (%)</b>	
White	6 (85.7)
African American	1 (14.3)

# Results

## Safety and tolerability

- Treatment-emergent adverse events (TEAEs) were consistent with those reported in the adult DEE study, and the majority were mild (Table 2)
- Reported TEAEs (all n = 1) were: upper abdominal pain, nausea, pyrexia, bronchial wall thickening, rales, unsteadiness, lacerations and contusions (secondary to seizures)
- Nausea was the only drug-related adverse event
- There were no discontinuations due to adverse events

**Table 2. Treatment-emergent adverse events  
(patients enrolled in ENDYMION from adult DEE study, n = 7)**

<b>Summary of TEAEs</b>	<b>Patients, n (%)</b>
Overall TEAEs	4 (57.1)
Mild	2 (28.6)
Moderate	2 (28.6)
Severe	0 (0)
TEAE-related withdrawal	0 (0)
Serious	0 (0)

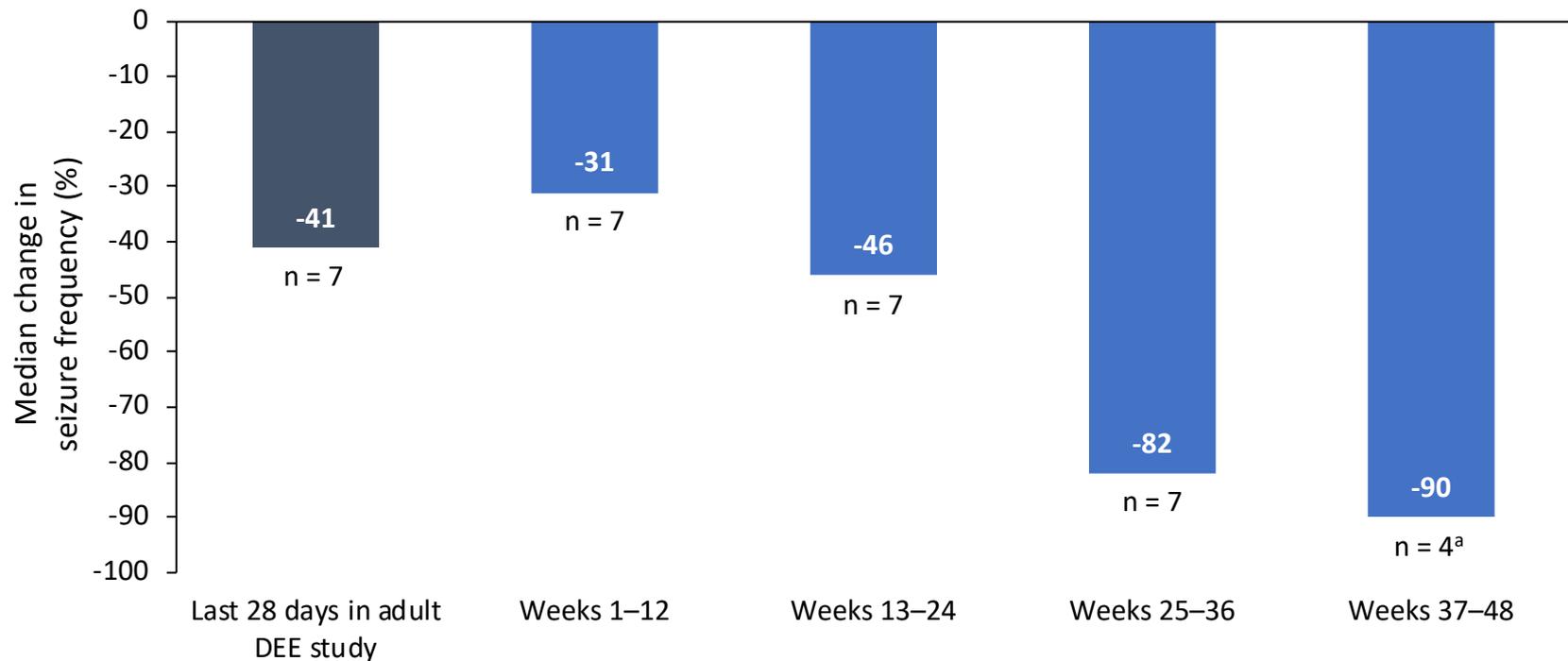
# Results

## Seizure frequency

- Median baseline seizure frequency was 11.5 seizures per 28 days
- Patients rolled over to ENDYMION with an interruption in treatment ranging from 6 to 52 weeks
- Reduction in median seizure frequency increased over time with prolonged soticlestat treatment, with median seizure frequency reductions of 82% following 25–36 weeks of treatment (n = 7), and 90% following 37–48 weeks of treatment (n = 4)
  - Only four patients had completed 37–48 weeks of treatment at the time of the analysis, two had achieved 25–36 weeks of treatment and 1 patient withdrew from the trial at week 40 (Figure 3)
- The longest seizure-free interval so far is 264 days out of a total treatment duration of 350 days

# Results

Figure 3. Reduction in median seizure frequency over time (patients enrolled in ENDYMION from adult DEE study, n = 7)



# Conclusions

## Safety

- Interim safety data from ENDYMION indicate that long-term soticlestat treatment has a favorable safety and tolerability profile, consistent with observations from the antecedent adult DEE study
- No new safety signals were identified and the majority of TEAEs were mild, with no serious events reported

## Efficacy

- Interim efficacy data from ENDYMION are encouraging, despite the small number of patients studied so far
- Consistent with observations from the antecedent adult DEE study, the findings reported here indicate a progressive reduction in seizure frequency
- These data support the continued development of soticlestat for the treatment of epileptic encephalopathies