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Newcastle University

Health Technology Briefing
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Soticlestat as an adjunctive therapy in patients with Dravet syndrome

Company/Developer	Takeda UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 33921	NICE ID: Not Available	UKPS ID: 664002

Licensing and Market Availability Plans

Currently in phase lll clinical development.

Summary

Soticlestat is in clinical development as an adjunctive therapy in patients with Dravet syndrome, a rare neurological condition characterized by treatment-resistant epilepsy, intellectual disability, and a spectrum of associated conditions such as behaviour, speech, feeding and mobility difficulties. Typically, Dravet syndrome involves multiple, frequent, and often prolonged seizures that do not respond well to treatment. Additionally, after the first year of life, a child's development may slow down or regress. Children with the condition have an 85% likelihood of surviving into adulthood. However, children with the condition face a significant risk of seizure-related premature mortality, known as sudden unexpected death in epilepsy.

Soticlestat is a medication that has been designed to be taken along with existing medication to reduce the frequency of seizures by blocking related receptors in the brain that has been linked with seizure activity. It is typically administered orally in the form of tablets or capsules. If licensed, it will offer improved outcomes in reducing seizures without introducing additional safety concerns over an extended period for patients with Dravet syndrome.

Proposed Indication

Treatment of seizures associated with Dravet syndrome (DS) in patients 2 years and older.[1]

Technology

Description

Soticlestat (TAK-935; OV935) is a first-in-class enzyme cholesterol 24-hydroxylase (CH24H) inhibitor. This enzyme converts cholesterol into 24-hydroxycholesterol (24HC), which can activate certain receptors in the brain.[2] 24HC is a positive allosteric modulator of the N-methyl-D-aspartate receptor that can contribute to neuronal hyperexcitability. Activation of CH24H decreases excitatory amino acid transporter 2 function, which in turn reduces glutamate reuptake from the peri-synaptic space and potentially contributes to exaggerated neuronal hyperexcitability. In addition, increased levels of tumour necrosis factor-alpha are reported to enhance vesicular release of glutamate into the synaptic cleft and decrease glutamate reuptake, further increasing peri-synaptic glutamate levels. This works to reduce seizure susceptibility and improve seizure control.[2]

Soticlestat is currently in clinical development as an adjunctive therapy in patients with DS. In the phase II clinical trial (NCT03650452), paediatric patients with developmental and/or epileptic encephalopathies were administered soticlestat mini-tablets or tablets, orally or via gastrostomy tube (G-tube)/percutaneous endoscopic gastrostomy (PEG). Participants weighing <60 kg received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day.[3]

Key Innovation

Soticlestat is a potent, highly selective, oral, first-in-class inhibitor of cholesterol 24-hydroxylase, which has been shown to decrease glutamatergic signalling and, in turn, help reduce seizures.[4] Another benefit of this technology is that it serves as an adjunctive therapy, improving the effectiveness of existing treatments. Adjunctive therapy for epilepsy involves using more than one anti-epileptic drug (AED) to prevent seizures. Often, the only way to achieve adequate seizure control is through adjunctive therapy.[5]

Soticlestat leads to sustained reduction in frequency of convulsive seizures among DS patients. Sustained reductions were also seen in the frequency of all-seizures from baseline for up to 2 years across cohorts.[6]

If licensed, soticlestat will offer significant benefits for patients with DS who have no other similar treatment options available, as a generally safe and well-tolerated adjunctive therapy.

Regulatory & Development Status

Soticlestat does not currently have marketing authorisation in the EU/UK for any indication.

Soticlestat is also in the phase III/II clinical development for the following indications:[7]

- Rare Epilepsies
- 15Q Duplication Syndrome (Dup 15q) or Cyclin-Dependent Kinase-Like 5 (CDKL5) Deficiency Disorder
- Complex Regional Pain Syndrome

Soticlestat received an orphan drug designation from the FDA in 2017 for the treatment of both Dravet syndrome and Lennox–Gastaut syndrome. [8]

Patient Group

Disease Area and Clinical Need

DS is a rare genetic syndrome characterized by recurrent seizures and refractory epileptogenic encephalopathies (i.e., abnormal brain activity that is not responsive to anti-seizure medications), resulting in long-term neurocognitive sequelae.[9] A mutation in the SCN1A gene has been identified in over 70% of individuals with DS which encodes the Nav1.1 sodium channel. These mutations lead to reduced levels of functional Nav1.1 channels, affecting neuronal excitability and contributing to seizures.[10] DS is characterised by prolonged and recurrent seizures, often triggered by fever (febrile seizures). Children with DS typically experience their first seizure in their infantile years of life and experience neurodevelopmental decline, leading to premature mortality. Children with DS experience developmental delays, including speech and motor skills. Behavioural problems, such as hyperactivity, impulsivity, and aggression, are also common. Individuals may experience many forms of epilepsy and seizure types throughout their lifetime, including absence seizures, tonic-clonic seizures, and status epilepticus.[11]

DS is a rare condition, occurring in an estimated 1 in 15,700 to 40,000 live births, affects all genders equally, and commonly presents in childhood.[11] In the UK, DS-related mortality rate is estimated to be around 20%, with most deaths occurring before 10 years of age. Sudden Unexpected Death in Epilepsy and status epilepticus cause around half and a third of deaths in this condition respectively.[12]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the following regimen for the treatment of DS:[13]

- Sodium valproate as the first-line treatment
- Triple therapy with sodium valproate, stiripentol and clobazam if monotherapy unsuccessful
- Cannabidiol in combination with clobazam as a second-line add-on treatment option
- Fenfluramine as a second-line add-on treatment option
- Add-on options if the above medications are unsuccessful include:
  - Ketogenic diet
  - Levetiracetam
  - Topiramate
- Potassium bromide: If all other treatment options for DS are unsuccessful

Clinical Trial Information

Trial	NCT04940624, 2021-002480-22; A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Soticlestat as Adjunctive Therapy in Paediatric and Young Adult Subjects With Dravet Syndrome (DS) **Phase III -** Completed **Location(s):** 11 EU countries, USA, Canada, and other countries **Completion date:** April 2024
Trial Design	Randomized, parallel assignment, quadruple blind, placebo-controlled
Population	N=144; Participants with DS who are currently taking 0 to 4 ASMs at stable doses.
Intervention(s)	Soticlestat, oral or feeding tube administration, 40mg to 200mg, BID

Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: • Percent Change from baseline in convulsive seizure frequency per 28 days during the full treatment period [Time Frame: Baseline up to Week 16] • Convulsive seizure frequency per 28 days is defined as total number of convulsive seizures reported during the period divided by number of days during the period seizures were assessed multiplied by 28. Percent change from Baseline will be defined as (frequency of seizures per 28 days during Treatment Period - frequency of seizures per 28 days at Baseline) divided by the frequency of seizures per 28 days at Baseline multiplied by 100. • Percent Change from Baseline in Convulsive Seizure Frequency per 28 days During the Maintenance Period (EMA Region Specific) [Time Frame: Baseline up to Week 16] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**ENDYMION 1; NCT03635073, 2018-002485-39;** A Phase 2, Prospective, Interventional, Open-Label, Multi-Site, Extension Study to Assess the Long-Term Safety and Tolerability of Soticlestat (TAK-935) as Adjunctive Therapy in Subjects With Developmental Epileptic Encephalopathies Including Dravet Syndrome, Lennox Gastaut Syndrome, CDKL5 Deficiency Disorder, and Chromosome 15 Duplication Syndrome **Phase II -** Active, not recruiting **Location(s):** Three EU countries, USA, Canada, and other countries **Primary completion date:** May 2026
Trial Design	Interventional, single group assignment, open label
Population	N=156; participants must have participated in a previous soticlestat study aged 2 years and older.
Intervention(s)	Soticlestat, tablets or mini tablets, orally twice daily at optimized dose, titrated in up to 2 weeks of Dose Optimization Period, followed by Maintenance Period
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Incidence of Adverse Events [Time Frame: up to Week 108] • Incidence of potentially clinically significant clinical safety laboratory test [Time Frame: up to Week 108] • Incidence of potentially clinically significant vital sign evaluation [Time Frame: up to Week 108]

	• Incidence of potentially clinically significant weight evaluation [Time Frame: up to Week 108] • Incidence of potentially clinically significant height/length evaluation [Time Frame: up to Week 108] • Incidence of potentially clinically significant Electrocardiography (ECG) evaluation [Time Frame: up to Week 108] • The percentage of participants with changes from baseline in clinically significant standard safety laboratory values including haematology and serum chemistry [Time Frame: up to Week 108] • The percentage of participants with changes from baseline in clinically significant vital sign measurements including blood pressure, pulse, body temperature, and respiratory rate [Time Frame: up to Week 108] • Change from Baseline in clinically significant body weight [Time Frame: up to Week 108] • The percentage of participants with changes in clinically significant 12-lead ECG findings [Time Frame: up to Week 108] • Change from Baseline in behavioural and adaptive functional measures using the Vineland Adaptive Behaviour Scale (VABS) [Time Frame: up to Week 108] • Change from Baseline in behaviour measures using total scores and subscale scores of the Aberrant Behaviour Checklist-Community Edition, Aberrant Behaviour Checklist-Community Edition (ABC-C) for patients ≥6 years of age [Time Frame: up to Week 108] • Change from Baseline in the Columbia-Suicide Severity Rating Scale Columbia-Suicide Severity Rating Scale (C-SSRS) categorization based on Columbia Classification Algorithm of Suicide Assessment categories 1,2,3,4, and 7 for patients ≥6 years of age [Time Frame: up to Week 108] See trial record for full list of other outcomes.
Results (efficacy)	–
Results (safety)	–

Trial	NCT03650452, 2018-002484-25; A Phase 2, Multicentre, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-935 (OV935) as an Adjunctive Therapy in Paediatric Patients With Developmental and/or Epileptic Encephalopathies **Phase II** - Completed **Location(s):** Three EU countries, USA, Canada, and other countries **Completion date:** July 2020
Trial Design	Interventional, randomised, parallel assignment, double-blinded, placebo-controlled
Population	N=141; Participants meet the following conditions:

	• Male and female participants aged greater than or equal to (>=) 2 and less than or equal to (<=) 17 years • Clinical diagnosis of DS or LGS • Currently taking 1 to 4 anti-epileptic drugs (AEDs) at a stable dose Failed to become and remain seizure free with trials of at least 2 AEDs
Intervention(s)	Soticlestat, tablets or mini-tablets, orally or via G-tube/PEG tube, BID
Comparator(s)	Matching placebo
Outcome(s)	Primary outcome measure: • Percent Change from baseline in seizure frequency per 28 days during the maintenance period [Time Frame: Baseline; Maintenance Period: Weeks 9 to 20] ○ Seizure frequency per 28 days is defined as total number of seizures (convulsive seizures for DS, drop seizures for LGS) reported during the period divided by number of days during the period seizures were assessed multiplied by 28. Percent change from Baseline is defined as (frequency of seizures per 28 days during maintenance period - frequency of seizures per 28 days at baseline) divided by frequency of seizures per 28 days at baseline multiplied by 100. Negative percent change from Baseline indicates improvement. See trial record for full list of other outcomes.
Results (efficacy)	–
Results (safety)	–

Estimated Cost

The cost of soticlestat is not yet known.

Relevant Guidance

NICE Guidance

- NICE Technology appraisal guidance. Fenfluramine for treating seizures associated with Dravet syndrome (TA808). July 2022.
- NICE guideline. Epilepsies in children, young people, and adults (NG217). April 2022.
- NICE single technology appraisal guidance. Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome (TA614). April 2019.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical commissioning policy: Everolimus for refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 years and above). 170093P. December 2018.
- NHS England. Clinical commissioning policy: Clinical Commissioning Policy: Deep Brain Stimulation for Refractory Epilepsy (all ages). 170036P. March 2018.

Other Guidance

- Chin RF, Mingorance A, Ruban-Fell B, Newell I, Evans J, et.al. Treatment Guidelines for Rare, Early-Onset, Treatment-Resistant Epileptic Conditions: A Literature Review on Dravet Syndrome, Lennox-Gastaut Syndrome and CDKL5 Deficiency Disorder. 2021.[14]
- Cardenal-Muñoz E, Auvin S, Villanueva V, Cross JH, Zuberi SM, Lagae L, Aibar JÁ. Guidance on Dravet syndrome from infant to adult care: Road map for treatment planning in Europe. 2021.[15]

Additional Information

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