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Health Technology Briefing
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Soticlestat as an adjunctive therapy for treatment of Lennox-Gastaut syndrome

Company/Developer	Takeda UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 18317	NICE ID: 10632	UKPS ID: 663971

Licensing and Market Availability Plans

Currently in phase lll clinical development.

Summary

Soticlestat is in clinical development as a secondary treatment used together with a primary treatment to enhance its effectiveness for patients with Lennox-Gastaut syndrome (LGS). LGS is a rare and severe form of childhood epilepsy characterized by tonic seizures (sudden stiffening of the body, often causing falls and injuries), atypical absence seizures (brief episodes of appearing vacant or blank), atonic seizures (sudden loss of muscle tone, leading to falls), focal seizures (affecting one side of the brain, causing movement changes, or altered responsiveness), and generalized tonic-clonic seizures (unconsciousness and jerking movements). Seizures occur frequently, even multiple times a day. LGS affects around 1 or 2 in every 100 children with epilepsy. It typically starts between ages 3 and 5 but can begin as early as 18 months or as late as age 10. Various factors contribute to LGS, including genetic conditions, brain structural abnormalities during pregnancy, birth-related issues (e.g., lack of oxygen during birth), infections, brain damage from severe head injuries, metabolic disorders, etc. In some cases, no specific cause is identified.

Soticlestat is generally safe and well tolerated by patients with LGS. It is typically administered orally in the form of tablets or capsules. Soticlestat has demonstrated a sustained reduction in the frequency of drop seizures by blocking related receptors in the brain in LGS patients for up to two years. If licensed, it will offer improved outcomes in reducing seizures without introducing additional safety concerns.

Proposed Indication

Soticlestat will be used as an adjunctive therapy along with other anti-seizure treatments for patients aged 2 years and older diagnosed with Lennox-Gastaut syndrome (LGS).[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 is 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 LGS. 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, designed to block the CH24H enzyme and reduce 24S-HC levels, 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 drop seizures in LGS patients. Sustained reductions were also seen in the frequency of all-seizures from baseline for up to 2 years.[6]

If licensed, soticlestat will offer significant benefits for patients with LGS who have limited treatment options available, as a generally safe and well-tolerated adjunctive therapy.[7]

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:[8]

- 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. [9]

Patient Group

Disease Area and Clinical Need

LGS is a severe form of epilepsy that typically begins in early childhood, usually before age 4. Individuals with LGS experience multiple types of seizures, including tonic, atonic, atypical absences, myoclonic, and generalized tonic-clonic seizures. Impaired intellectual functioning, developmental delays, and behavioural disturbances are common. There may be periods of frequent seizures mixed with relatively seizure-free periods. Although not always present at the onset of seizures, most people living with LGS experience some degree of impaired intellectual functioning or information processing, along with developmental delays and behavioural disturbances. LGS can be caused by a variety of conditions, including brain malformations, tuberous sclerosis, perinatal asphyxia, severe head injury, central nervous system infection, or inherited genetic and inherited degenerative or metabolic conditions. No cause can be found in 30-35% of individuals. The prognosis for individuals with Lennox-Gastaut syndrome varies. There is no cure for the disorder. Complete recovery, including freedom from seizures, is very rare.[10]

UK data (2107) suggests the prevalence of LGS was 0.578/10,000 (n = 180), with 74 and 106 patients identified with confirmed (0.289/10,000) and probable LGS (0.420/10,000).[11] The prognosis for LGS is challenging. Childhood mortality is around 5%. Persistent seizures continue into adulthood, with at least 90% of adults still experiencing seizures. Patients with LGS are 24 times more likely to die prematurely due to seizures, sudden unexpected death in epilepsy, accidents, or underlying brain disorders.[12]

Recommended Treatment Options

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

- Sodium valproate: considered as first-line treatment
- Lamotrigine: second-line treatment
- Third-line add-on treatment options: If second-line treatment is unsuccessful, the following are considered as third-line add-on treatment options for people with LGS:
  - Cannabidiol in combination with clobazam if the child is over 2 years old
  - Clobazam
  - Rufinamide
  - Topiramate
- Ketogenic diet: If seizures continue with third-line treatments for LGS, a ketogenic diet as an add-on treatment under the supervision of a ketogenic diet team should be considered.
- Felbamate: If all other treatment options for LGS are unsuccessful, felbamate as an add-on treatment should be considered under the supervision of a neurologist with expertise in epilepsy.

Clinical Trial Information

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
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 electrocardiogram (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 [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 for patients ≥6 years of age [Time Frame: up to Week 108] • Change from Baseline in the Columbia-Suicide Severity Rating Scale 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	NCT04938427, 2021-002481-40; A Study of Soticlestat as an Add-on Therapy in Children, Teenagers, and Adults With Lennox-Gastaut Syndrome **Phase III** - Completed **Location(s):** Eleven EU countries, USA, Canada, Russia, Japan and China, and other countries **Completion date:** Jan 2024
Trial Design	Parallel Assignment, Randomised, double blinded
Population	N=270; participants must have documented clinical diagnosis of LGS; has had ≥8 MMD seizures each month in the 3 months prior to Screening based on the historical information and has had ≥8 MMD seizures per 28 days during the 4 to 6 week prospective Baseline Period, weighs ≥10 kg at the Screening Visit (Visit 1), failure to control seizures despite appropriate trials of at least 1 ASM based on historical information, and is currently on an antiseizure therapy or other treatment options considered as standard of care (SOC); aged 2 years to 55 years.
Intervention(s)	Soticlestat, tablets or mini tablets, orally twice daily at optimized dose
Comparator(s)	Placebo
Outcome(s)	Primary outcome measure: • Percent Change from Baseline in Major Motor Drop (MMD) Seizure Frequency Per 28 Days During the Full Treatment Period [Time Frame: Baseline up to Week 16] • MMD seizure frequency per 28 days is defined as total number of MMD 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 full 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 Major Motor Drop (MMD) Seizure Frequency Per 28 Days During the Maintenance Period (EMA Region Specific) [Time Frame: Baseline up to Week 16] • MMD seizure frequency per 28 days is defined as total number of MMD 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 the Maintenance Period - frequency of seizures per 28 days at Baseline) divided by the frequency of seizures per 28 days at Baseline multiplied by 100. This outcome measure is European Medicines Agency (EMA) region specific. 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 aged 2-17 years with a clinical diagnosis of DS or LGS who are currently taking 1 to 4 anti-epileptic drugs (AEDs) at a stable dose.
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] See trial record for full list of other outcomes.
Results (efficacy)	_
Results (safety)	_

Trial	NCT03166215; A Phase 1b/2a multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Escalation Study with an Open-Label Part to Examine the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-935 as an Adjunctive Therapy in Subjects with developmental and/or epileptic encephalopathies **Phase I/II** - Completed **Location(s):** USA **Completion date:** September 2018
Trial Design	Randomised, parallel assignment, double blinded, placebo-controlled
Population	N=18; adult participants with developmental and/or epileptic encephalopathies with countable bilateral motor seizures, who have been taking 1 to 4 AEDs at a stable dose for >=4 weeks before screening.
Intervention(s)	Soticlestat, oral administration BID
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: • Percentage of Participants With at Least One TEAE, as Reported by the Participants or Participant's Caregivers or Observed by the Investigator,

	After soticlestat Treatment [Time Frame: From first dose up to 30 days post last dose (approximately up to 120 days)] See trial record for full list of other outcomes.
Results (efficacy)	Soticlestat was well tolerated at doses of up to 300 mg BID and was associated with a reduction in median seizure frequency over the study duration. Pharmacokinetic analysis showed dose-dependent increases in systemic exposure and peak plasma soticlestat concentrations. At the end of Part B, the overall mean percent change from baseline in plasma 24HC was -80.97 %. Changes from baseline in median seizure frequency were +16.71 % and +22.16 % in the soticlestat and placebo groups, respectively, in Part A, and -36.38 % in all participants in Part B.[14]
Results (safety)	In Part A, TEAEs occurred in 71.4 % of soticlestat-treated patients and 100 % of placebo-treated patients. In Part B, the overall incidence of TEAEs was 68.8 %. In Part A, TEAEs that occurred in more than one patient in the soticlestat group were dysarthria (n = 3, 21.4 %), lethargy (n = 2, 14.3 %), upper respiratory tract infection (n = 2, 14.3 %), fatigue (n = 2, 14.3 %), and headache (n = 2, 14.3 %). Four patients discontinued treatment because of TEAEs, of whom two reported drug-related seizure clusters as serious TEAEs. There were no deaths.[14]

Estimated Cost

The cost of soticlestat is not yet known.

Relevant Guidance

NICE Guidance

- NICE guideline. Epilepsies in children, young people, and adults [NG217]. April 2022.
- NICE technology appraisal guidance. Cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome (TA615). December 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.[15]

Additional Information

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