A Phase 3, Prospective, Open-Label, Multisite, Extension of Phase 3 Studies to Assess the Long-Term Safety and Tolerability of Soticlestat as Adjunctive Therapy in Subjects With Dravet Syndrome or Lennox-Gastaut Syndrome (ENDYMION 2)

Published: 27-12-2021
Last updated: 14-09-2024

This study has been transitioned to CTIS with ID 2022-502802-34-00 check the CTIS register for the current data. Primary Objective:To assess the long-term safety and tolerability of soticlestat when administered as adjunctive therapy to standard of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Seizures (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON53987

Source
ToetsingOnline

Brief title
TAK-935-3003 (ENDYMION 2)

Condition

- Seizures (incl subtypes)

Synonym
Dravet Syndrome (DS) and Lennox-Gastaut Syndrome (LGS)

Research involving
Human

Sponsors and support

Primary sponsor: Takeda
Source(s) of monetary or material Support: Takeda Development Center Americas Inc.

Intervention

Keyword: Dravet Syndrome (DS), Drug Therapy, Lennox-Gastaut Syndrome (LGS), Soticlestat

Outcome measures

Primary outcome

The primary endpoints are for safety and include the following:

- Incidence of treatment-emergent AEs.

- Incidence of abnormal values for clinical laboratory tests and ECG

evaluations.

- Change from baseline in clinical laboratory test values, vital signs, C-SSRS,

and ECG parameters.

- Change from baseline in height and weight for all age groups.

- Absolute value for Tanner stage for children 6 to 17 years of age during the

study.

- Absolute values for IGF-1 for children 2 to 17 years of age during the study.

Secondary outcome

The secondary endpoints include the following:

- Percent change from baseline in total seizure frequency per 28 days (DS and

LGS) cohort.

- Percent change from baseline in convulsive seizure frequency (DS) per 28 days.

- Percent change from baseline in MMD seizure frequency (LGS) per 28 days.

- Effect on the CGI-I and Care GI-I.

- Effect on CGI-I Seizure Intensity and Duration.

- Effect on the CGI-I Nonseizure Symptoms completed by clinician with input

from the caregivers.

- Effect on QI-Disability.

Study description

Background summary

Dravet syndrome (DS) or severe myoclonic epilepsy in infancy is one of the most well-described disorders of epileptic encephalopathies. Clinically, DS is characterized at onset by frequent convulsive febrile seizures, followed by frequent status epilepticus and nonfebrile seizures that are mainly clonic, unilateral, and of long duration.
Lennox-Gastaut syndrome (LGS) is one of the most severe forms of childhood epilepsy. The syndrome usually has its onset between the ages of 1 and 8 years, but occasionally it occurs in children who are older than 8 years, or even into adulthood. LGS includes the presence of multiple seizure types: the hallmark tonic-atonic drop seizures. Other seizure types include atypical absence seizures, but tonic-clonic, myoclonic, and partial seizures are also frequently present.

Soticlestat is a first-in-class small molecule inhibitor of cholesterol-24 hydroxylase (CH24H) in the brain. Based on the efficacy, safety, and tolerability data collected in the phase 2 ELEKTRA study, combined with the safety and tolerability data from phase 1 and other completed or ongoing studies (please see the IB), soticlestat is being proposed as adjunctive therapy in pediatric and adult subjects with DS or LGS, highly impacted populations with great unmet need.

This is a multisite, phase 3, open-label extension (OLE) study designed to obtain additional safety and tolerability data related to soticlestat administered long-term in subjects who participated in an antecedent soticlestat phase 3 clinical study. Additional aims are to assess efficacy in terms of seizure frequency, non-seizure-related symptoms, impact on quality of life, and the pharmacokinetics (PK) and pharmacodynamics (concentration of 24Shydroxycholesterol [24HC]) of soticlestat administration in pediatric and

adult subjects with DS or LGS, as well as assessing palatability and acceptability of soticlestat in the pediatric population.

Study objective

This study has been transitioned to CTIS with ID 2022-502802-34-00 check the CTIS register for the current data.

Primary Objective:
To assess the long-term safety and tolerability of soticlestat when administered as adjunctive therapy to standard of care (SOC) (eg, antiseizure medications [ASMs], vagus nerve stimulation, ketogenic diet, or modified Atkins diet) in subjects with DS or LGS.

Secondary Objectives:
- To assess the effect of soticlestat on seizure frequency (convulsive seizures for the DS cohort, MMD seizures for the LGS cohort, and total seizure count for each cohort).
- To assess the effect of soticlestat on the Clinical Global Impression of Improvement (CGI-I) (clinician) and Caregiver Global Impression of Improvement (Care GI-I).
- To assess the effect of soticlestat on CGI-I Seizure Intensity and Duration.
- To assess the effect of soticlestat on the CGI-I Nonseizure Symptoms completed by clinician with input from the caregiver.
- To assess the effect on Quality of Life Inventory-Disability (QI-Disability).

Study design

This is a multisite, phase 3, open-label extension (OLE) study designed to obtain additional safety and tolerability data related to soticlestat administered long-term in subjects who participated in an antecedent soticlestat phase 3 clinical study. Additional aims are to assess efficacy in terms of seizure frequency, non-seizure-related symptoms, impact on quality of life, and the pharmacokinetics (PK) and pharmacodynamics (concentration of 24Shydroxycholesterol [24HC]) of soticlestat administration in pediatric and adult subjects with DS or LGS, as well as assessing palatability and acceptability of soticlestat in the pediatric population. After an initial 2-week titration period, the planned treatment duration is approximately 4 years, or until the study is stopped at the discretion of the sponsor, or the product is approved for marketing. The total daily dose of soticlestat will be calculated based on body weight at Visit 1 and given twice daily (BID). Subjects will receive the initial dose of the study drug (200 mg BID adult reference dose, weight-based dosing for weight <45 kg) for the first 7 days of the dose titration period; the study drug dose will then be increased to the target dose (300 mg BID adult reference dose, weight-based dosing for weight <45 kg). If the subjects do not experience any tolerability issues, they will remain on the target dose for the remaining 7 days of the titration period, followed by a safety follow-up phone call. The minimum dose allowed during the study is 100 mg BID (weight-based dosing <45 kg). Subjects who cannot tolerate the minimum dose will be discontinued from the study. The

dose may be adjusted every 6 months, depending on the subject's weight. Dose changes (increased or decreased) during the maintenance period are allowed as assessed by the investigator; however, if possible, dose changes due to safety or tolerability may need to be discussed with the medical monitor and/or the sponsor. In the absence of weight change or safety or tolerability considerations, the final dose tolerated by the end of the 2-week titration period should be maintained until the end of the maintenance period. At the end of the maintenance period, whether after the full duration or for early termination, the dose will be tapered for approximately 1 week (unless already at the lowest dose), followed approximately 2 weeks later by a safety follow-up visit or phone call.

Intervention

Soticlestat will be available as yellow-red colored, film-coated tablets and mini-tablets. Soticlestat (tablets/mini-tablets) can be swallowed whole or can be crushed and mixed well in applesauce or a thick liquid. Soticlestat should be taken by you 2 times a day (morning and evening). Soticlestat can be taken orally, with or without food, or via a gastrostomy tube (G tube) or via a percutaneous endoscopic gastrostomy tube (PEG tube).

Study burden and risks

The following side effects are common:
- Feeling tired and sluggish
- Difficulty sleeping
- Headache
- Nausea or feeling like you need to vomit
- Difficulty paying attention or confusion
- Feeling constantly tense, on guard, or abnormally aware of one*s environment
- Difficulty speaking
- Sleepiness or drowsiness (somnolence)
- Decreased appetite
- Abnormal bowel movements (constipation and diarrhea)

Potential discomforts from the measurements are:
- Blood draw: Obtaining blood may sometimes cause pain/discomfort, bruising, or bleeding at the site where the blood is drawn, occasional light-headedness, and, rarely, infection or fainting.
- ECG: The ECG sticky patches or suction cups placed on the skin may cause slight discomfort during their placement and removal. The patient may also feel a little embarrassed as some upper clothing may need to be removed.
- Ophthalmological assessments: The patient may feel temporary discomfort during the eye examinations due to the bright lights and with the drops which will be put in your eyes before performing any examinations to make the pupils larger.
- Questionnaires about well-being, behavior, quality of life and risk for

suicide: Some questions may cause distress or make the patient feel uncomfortable.

Contacts

Public
Takeda

Hayden Avenue 95
Lexington, MA 02421
US
Scientific
Takeda

Hayden Avenue 95
Lexington, MA 02421
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

- Pediatric and adult subjects with DS or LGS from antecedent soticlestat phase 3 clinical studies;
- received at least 12 weeks of treatment (combined titration and Maintenance Period) with soticlestat or placebo in the antecedent study;
- did not have a serious or severe adverse event (AE) that, in the investigator*s or sponsor*s opinion, was related to the study drug and would

make it unsafe for the subject to continue receiving the study drug; and
- in the opinion of the investigator, have the potential to benefit from the administration of soticlestat.

Exclusion criteria

- Unstable, clinically significant neurologic (other than DS or LGS), psychiatric, cardiovascular, ophthalmologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, hematopoietic, endocrine disease, malignancy including progressive tumors, or other abnormality that may impact the ability to participate in the study or that may potentially confound the study results. - Abnormal and clinically significant electrocardiogram (ECG) abnormality at Visit 1, including QT interval with Fridericia correction method (QTcF) >450 ms. - Currently pregnant or breastfeeding or is planning to become pregnant within 30 days of the last dose of study drug. - Considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or has positive answers on item numbers 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) at Visit 1.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-06-2022
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Soticlestat

Generic name:	Soticlestat

Ethics review

Approved WMO Date:	27-12-2021
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	17-03-2022
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	02-06-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	30-06-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	03-08-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	20-09-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	21-10-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	17-11-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	31-08-2023
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	07-09-2023
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2022-502802-34-00
EudraCT	EUCTR2021-002482-17-NL
CCMO	NL79796.075.21