A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Soticlestat as Adjunctive Therapy in Pediatric and Adult Subjects With Lennox-Gastaut Syndrome (LGS)

Published: 09-08-2021
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Primary Objectives:• To assess the efficacy of soticlestat in reducing major motor drop (MMD) seizure frequency as add-on therapy to SOC as compared with placebo during the full treatment period (titration + maintenance).For European Medicines...

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

Summary

ID

NL-OMON54350

Source
ToetsingOnline

Brief title
Tak-935-3002 (Skyway)

Condition

- Seizures (incl subtypes)

Synonym
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: Lennox-Gastaut Syndrome (LGS), Soticlestat

Outcome measures

Primary outcome

Primary Endpoint:

• Percent change from baseline in MMD seizure frequency per 28 days in subjects receiving soticlestat as compared with placebo during the full treatment period.

For EMA registration:

• Percent change from baseline in MMD seizure frequency per 28 days in subjects receiving soticlestat as compared with placebo during the maintenance period.

Secondary outcome

Secondary Endpoints: To assess the following in subjects receiving soticlestat as compared with placebo during the full treatment period, unless otherwise noted: • Proportion of responders defined as those with >=50% reduction from baseline in MMD seizures during the maintenance period and the full treatment period. • Percent change from baseline in frequency of all seizures per 28 days during the maintenance period and the full treatment period. • Percent change from baseline in MMD seizure frequency per 28 days during the maintenance period. • Responder analysis of the proportion of subjects with <=0%, >0% to

<=25%, >25% to <=50%, >50% to <=75%, and >75% to <=100% reduction from baseline in MMD seizures in a cumulative response curve. • Change from baseline in proportion of MMD seizure-free days. • Longest MMD seizure-free interval. • Number of days when rescue ASM is used. • CGI-I (clinician). • Care GI-I (caregiver). • CGI-I Seizure Intensity and Duration. • CGI-I Nonseizure Symptoms. • Change in QI-Disability score.

Study description

Background summary

Lennox-Gastaut syndrome (LGS) is rare and 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. It is hypothesized that soticlestat treatment will decrease the levels of 24S-hydroxycholesterol (24HC) and improve MMD seizure control in LGS subjects. Nonclinical studies have demonstrated that soticlestat modulates the glutamatergic signaling and significantly reduces spontaneous seizure in murine models of LGS. Clinical Study TAK-935-2002 (ELEKTRA) showed efficacy of soticlestat in subjects with DS or LGS.

Study objective

Primary Objectives:

• To assess the efficacy of soticlestat in reducing major motor drop (MMD) seizure frequency as add-on therapy to SOC as compared with placebo during the full treatment period (titration + maintenance).
For European Medicines Agency (EMA) registration:
• To assess the efficacy of soticlestat in reducing MMD seizure frequency as add-on therapy to SOC compared with placebo during the maintenance period only.

Study design

This is a phase 3, global, multicenter,1:1 randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of soticlestat as an adjunctive therapy in pediatric and adult subjects with Lennox-Gastaut Syndrome (LGS). The treatment period is 16 weeks. The total duration of the study is approximately 25 weeks for subjects who complete the study and choose not to roll over to the open-label extension (OLE) study. For those who roll over to the OLE study, the study duration is 3 weeks shorter.

The study will consist of the following periods:
• 4- to 6-week screening/baseline period.
• 16-week treatment period.
- 4-week titration period.
- 12-week maintenance period.
• 1-week taper period for those discontinuing study drug, followed by a 2-week safety follow-up visit or a phone call.
This is a 2-arm study. All subjects will be randomized at a 1:1 ratio to receive standard of care (SOC) plus one of the following adjunctive therapies: soticlestat or placebo.

Intervention

Soticlestat or placebo will be available as yellow-red colored, film-coated tablets and mini-tablets. The study drug (tablets/minitablets) can be swallowed whole or can be crushed and mixed well in applesauce or a thick liquid.
The study drug should be taken by the subject 2 times a day (morning and evening). Study drug 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 commun:
- Feeling tired and sluggish
- Common cold
- Difficulty sleeping
- Headache
- Nausea or feeling like he/she needs to vomit
- Difficulty paying attention or confusion
- Anxiety or feeling nervous
- Euphoric mood (exaggerated feeling of happiness) or feeling abnormally happy
- Feeling constantly tense, on guard, or abnormally aware of one*s environment
- Difficulty speaking
- Hallucinations include seeing, feeling, smelling, tasting, or hearing things that are not real and which can be disturbing

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

Contacts

Public
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Scientific
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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

• Male or female and aged 2 to 35 years, inclusive, at the time of informed consent. • Documented clinical diagnosis of LGS supported by: - Onset of seizures usually between ages of 1 and 8 years. - Presence of multiple seizure types: including drop seizures (eg, tonic-atonic seizures) and other seizure types including atypical absence seizures, tonic-clonic, myoclonic, and partial seizures. - History of abnormal electroencephalogram (EEG) (eg, slow spike and wave [<2.5 Hz], slow or disorganized EEG background, generalized paroxysmal fast activity). - Developmental delay or intellectual disability consistent with LGS. • The participant has >=8 MMD seizures each month in the 3 months prior to screening based on the historical information and has >=8 MMD seizures per 28 days during the 4- to 6-week prospective baseline period. MMD seizures include: - Hemi-clonic or focal clonic. - Focal to bilateral tonic-clonic. - Generalized tonic-clonic. - Bilateral clonic. - Focal seizures with major motor signs (eg hypermotor seizures or involving major body areas such as lower extremities or trunk) leading to fall or likely fall. - Tonic seizures involving major body areas such as lower extremities or trunk leading to fall or likely fall. - Atonic seizures involving major body areas such as lower extremities or trunk leading to fall or likely fall. - Convulsive status. • Weighs >=10 kg at the screening visit (Visit 1). • Failure to control seizures despite appropriate trials of at least 1 ASMs based on historical information, and is currently on an anti-seizure therapy (eg, ASMs, vagus nerve stimulation, ketogenic/modified Atkins diet) or other treatment options considered as SOC. • Artisanal cannabidiols are allowed at a stable dose for at least 4 weeks before the screening visit (Visit 1); the dosing regimen and manufacturer should remain constant throughout the study. • Currently taking 0 to 3 ASMs at stable doses for at least 4 weeks before the screening visit (Visit 1); benzodiazepines used chronically (daily) to treat seizures are considered ASMs. Fenfluramine and cannabidiol (Epidiolex) are allowed where available and counted as an ASM. ASM dosing regimen must remain constant throughout the study. • If on a diet, the subject's diet should be stable for 4 weeks before the screening visit; the subject should continue this diet throughout the duration of the study • Stable liver function • Female subjects of childbearing potential (defined as first menarche) must have a negative pregnancy test and agree to use an effective or highly effective method of birth control during

the study and for 30 days following the last dose of study drug.

Exclusion criteria

• Currently enrolled in a clinical study involving an investigational product (meaning not approved in that country other then soticlestat), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. Note: compatibility will be determined based on consultation with the medical monitor or the sponsor. • Participated in a clinical study involving another study drug in the last 30 days (or 5 half-lives of the study drug, whichever is longer) before screening (Visit 1). • Received soticlestat in a previous clinical study. • Known hypersensitivity to any component of the soticlestat formulation. • Admitted to a medical facility and intubated for treatment of status epilepticus 2 or more times in the 3 months immediately before screening (Visit 1). For this study status epilepticus is defined as continuous seizure activity lasting longer than 5 minutes or repeated seizures without return to baseline in between seizures. • Unstable, clinically significant neurologic (other than the disease being studied), 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. It is the responsibility of the investigator to assess the clinical significance; however, consultation with the medical monitor may be warranted. • Any history of alcohol, opioid, or other drug use disorder, as per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, within the 2 years immediately before the screening(Visit 1). • Abnormal and clinically significant ECG abnormality at screening (Visit 1) or before randomization (Visit 2, including QT interval with Fridericia correction method (QTcF) >450 ms, confirmed with a repeat ECG using manual measurement of QTcF. Clinically significant ECG abnormalities should be discussed with medical monitor. • Abnormal clinical laboratory test results at screening (Visit 1) that suggest a clinically significant underlying disease that would compromise the well-being of the subject. If the subject has a serum alanine aminotransferase and/or aspartate aminotransferase level >2.5 times the upper limit of normal (ULN), the medical monitor should be consulted. • Currently pregnant or breastfeeding or is planning to become pregnant within 30 days of the last dose of study drug.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	27-01-2022
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Soticlestat
Generic name:	Soticlestat

Ethics review

Approved WMO Date:	09-08-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-11-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-03-2022
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-06-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-06-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-04-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
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Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-07-2023
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2021-002481-40-NL
CCMO	NL78269.075.21