Protocol Summary

of Clinical Trial

The protocol of a clinical study is a document that explains why and how a study will be carried out.

A Phase Ib/II first-in-human, multicentre, open-label, multiple ascending dose study of S230815 in paediatric participants with KCNT1-related Developmental and Epileptic Encephalopathy

Full scientific title: *A Phase Ib/II first-in-human, multicentre, open-label, multiple ascending dose study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamic effect of intrathecal S230815 in paediatric participants with KCNT1-related Developmental and Epileptic Encephalopathy (EU trial number : 2024-513332-17-00)*

1 Why is this study needed?

This study aims to test a new drug called S230815 in children with a condition called *KCNT1*-related Developmental and Epileptic Encephalopathy (DEE). *KCNT1*-related DEE is a group of severe epilepsies that cause frequent seizures and slow down a child's development. It is caused by changes in the *KCNT1* gene, which helps control brain activity. The changes in the *KCNT1* gene cause too much electrical activity in the brain, resulting in seizures. Studies in animals found that S230815, the new study drug, acts by blocking *KCNT1* activity. Researchers believe that S230815 may help reduce seizures in children with *KCNT1*-related DEE by targeting *KCNT1*. This study is important because it could lead to a treatment option for children with this condition.

2 What are we mainly looking for?

What is the main goal of the study?

The main goal of this study is to evaluate if the new study drug, S230815, is safe and well-tolerated by children with *KCNT1*-related DEE.

What is the main study endpoint?

A study endpoint is the measurement used to decide whether a study goal is reached or not. In this study, the main endpoint is to observe how many participants experience unwanted medical events and how severe they are.

3 What about the other goals of the study ?

What are the other goals of this study?

- To understand what your body does to S230815, a process known as pharmacokinetics.
- To observe how S230815 affects the number of seizures.

What are the other study endpoints?

- Pharmacokinetics measurements, including the levels of S230815 in the blood and spinal fluid at different times. Spinal fluid is the liquid surrounding the brain and spinal cord.
- The frequency of seizures after S230815 is given.
- The frequency of rescue medication use to calm or stop a seizure in emergency.

4 Who is participating in the study ?

About 20 participants will take part in the study.

They will have to:

- Be a child aged 2 to 12 years old.
- Have confirmed *KCNT1*-related DEE.
- Have frequent seizures.
- Be on a stable dose of their current anti-seizure medication and/or any other treatment before starting the study.
- Be able to undergo several lumbar puncture procedures, which involve inserting a needle into the lower back to access the spinal fluid.

Participants will not be able to join the study if:

- They have another type of epilepsy related to the *KCNT1* gene.
- They have changes in other genes that cause epilepsy.
- They have an implantable device in their brain or spinal cord that may affect the ability to perform study procedures, such as lumbar puncture or brain scans. Implantable devices are a treatment option for people with epilepsy.

5 How is the study carried out ?

The study is called an "open-label" study. This means that the doctors, the participants and their caregivers know the treatment given. Participation in the study is completely voluntary. The participant and/or their caregivers can change their mind and withdraw from the study at any stage, for any reason.

The study consists of a screening period followed by two parts:

Screening period:

During this time, the doctors will check if the participants meet all of the requirements to take part in the study.

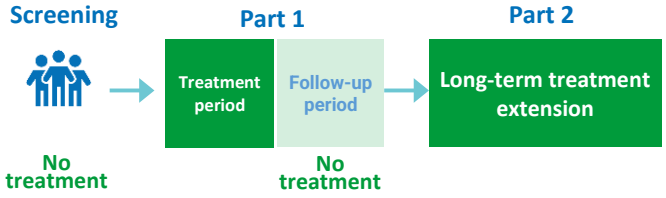
Part 1: Dose Finding Phase (split into 2 periods):

- The treatment period, during which a given dose of S230815 will be tested in a small group of participants. Independent experts will closely check the participants' health to make sure the dose is safe. The researchers will then decide whether to increase the dose in the next group of participants.
- The follow-up period, during which the doctors will regularly check the participants' health and if they have any unwanted medical events. Doctors will also check the effect that S230815 treatment has on the disease.

Part 2: Long-term Treatment Phase:

- Participants who complete Part 1 will continue to receive S230815 until the end of the study. They will continue to have regular check-ups for any unwanted medical events.

The study design is presented in the image below:



6 What are the treatment(s) and tests used in the study?

Participants will receive S230815 as an injection into the spinal fluid in the lower back. This will be done through lumbar puncture at the hospital and may require sedation. This allows doctors to deliver S230815 directly to the brain.

The participants will continue taking their usual DEE treatment, as well as rescue medication when necessary.

The participants will visit the doctors regularly at the hospital or clinic. During the visits, the doctors will collect information about the participants' DEE and overall health condition. Participants will give blood, urine and spinal fluid samples, and undergo exams to see how the brain and body are working (neurological and physical exams). They will have tests to record brain and heart electrical activity, and imaging tests of the brain and spinal cord. The participants' caregivers will complete an electronic diary to record the number of daily seizures. Participants will also have to wear a bracelet to record their seizures. These tests will help researchers understand the effects of S230815 on the body and ensure the participants' safety.

7 What are the possible benefits and risks?

This is the first study where S230815 is given to humans. The disease may or may not improve with S230815 treatment. In any case, participants will receive close medical follow-up. This study could help develop a treatment for *KCNT1*-related DEE.

KCNT1-related DEE affects children, many of whom do not live to be teenagers or adults. Therefore, the participants of this study are aged 2 to 12 years. Current available treatments do not work well enough and do not target the root cause of the disease. Therefore, there is a strong need for better treatments.

The study is designed to be safe, with strict safety rules and regular check-ups. Some discomfort may be felt during the lumbar puncture and the planned tests (blood sampling, imaging, recording of brain and heart electrical activity). Like all medicines, S230815 may cause unwanted medical events which will be treated if they occur.