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 study to evaluate S227928 as a Single Agent and in Combination with Venetoclax in Patients with R/R AML, MDS/AML, or CMML

Full scientific title: *Phase 1/2 Clinical Trial of S227928, an Anti-CD74 Antibody-Drug Conjugate Targeting MCL-1, as a Single Agent and in Combination with Venetoclax in Patients with Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML), Myelodysplastic Syndrome (MDS)/AML, or Chronic Myelomonocytic Leukemia (CMML)- (EU Trial Number: 2024-514356-33-00)*

1 Why is this study needed ?

This study is needed to test a new drug called S227928 alone or in combination with venetoclax in participants with the following types of blood disorders:

- Acute Myeloid Leukemia (AML): a cancer of the blood and bone marrow (the spongy tissue inside bones where blood cells are made).
- Myelodysplastic Syndrome (MDS): a disorder in which bone marrow does not make enough healthy blood cells.
- Chronic Myelomonocytic Leukemia (CMML): a rare type of blood cancer.

In leukemias, several proteins prevent cancer cells from dying when they should; two such important proteins are B-Cell Lymphoma 2 (BCL-2) and Myeloid Cell Leukemia 1 (MCL-1). Drugs that block these proteins are a good way to treat patients with leukemias.

S227928 is a new drug which blocks MCL-1 and may help in the treatment of some types of leukemias. Venetoclax is a drug that blocks the action of BCL-2, causing cancer cell death. Venetoclax is currently used to treat AML and other types of leukemia.

2 What are we mainly looking for ?

What is the main goal of the study?

The main goal of this study is to find the highest safe and most effective dose of S227928 and see how well it works when given alone and in combination with venetoclax.

What are the main study endpoints ?

A study endpoint is the criteria used to decide whether a study goal is reached or not. The main endpoints of this study are to find:

- The highest dose of S227928 that participants can take without too much risk (highest tolerated dose) and the recommended dose, which is the one that is both safe for participants and most effective against leukemias.
- Number of unwanted medical events, laboratory measurements, electrical activity of the heart, and heart function.
- If S227928 dose has to be reduced or stopped due to unwanted medical events.
- If there is a decrease or disappearance (complete remission) of leukemia in blood and bone marrow.

3 What about the other goals of the study ?

What are the other goals of this study?

The other goals of this study are to further investigate how S227928 is processed in the body (pharmacokinetics), its effects on normal and leukemic cells (pharmacodynamics), its effectiveness, and safety.

What are the other study endpoints?

The other study endpoints are to measure:

- Several pharmacokinetic evaluations of S227928 amount in blood.
- The possibility that the body's immune system may form proteins against S227928.
- Type and time of response to study treatment and continued need for transfusions.
- How long participants will live before the cancer grows back and how long they will live after treatment.

4 Who is participating in the study ?

Overall, 132 participants are expected in the study.

To take part, participants have to:

- Be at least 18 years old.
- Had received at least one prior standard treatment for AML, MDS/AML, or CMML but the disease returned after improvement or did not respond to any treatment.
- Have adequate kidney, liver and heart function.

5 How is the study carried out ?

The study is called an "open-label" study. This means that both the participants and the research doctors know which treatment is taken.

The study is split into 2 parts:

- Part 1 (Dose escalation): Different doses are tested to find the highest tolerated dose and/or the recommended dose to give to participants in Part 2.
- Part 2 (Dose expansion): The recommended dose of S227928 in combination with venetoclax will be given in a larger group of participants (to better determine the safety and effectiveness of S227928 with venetoclax).

To find the highest tolerated dose, the doctors test different doses of S227928 alone or in combination with venetoclax in small groups of participants. The first group receives the lowest dose, then each new group receives a higher dose.

For each dose, the doctors check the safety of the study drug(s). Then, the researchers decide whether it is safe to increase the dose in the next group of participants.

Once the highest tolerated dose is found, the researchers define the recommended dose to be given in part 2.

This study will have a screening period (up to 21 days), a treatment period, and a follow-up period (up to 6 months).

The total length of this study will vary depending on how long participant receive the study treatments.

6 What are the treatments and tests used in the study?

In **Part 1**, up to 76 participants will receive either:

- **S227928 (38 participants)** once every 2 weeks as infusion (an injection given slowly, usually over 30 to 60 minutes) on Days 1 and 15 during time periods called "cycles". Each cycle is 28 days.
- **S227928 in combination with venetoclax (38 participants).** S227928 is given once every 2 weeks as infusion. Participants also take venetoclax tablets for 21 days (dose range 100 to 400 mg) of each cycle of 28 days.

These 28-day cycles are repeated for as long as the disease does not progress and if the participant does not have too severe side effects. The participant can also decide to stop the treatment at any time.

In **Part 2,** up to 56 additional participants will receive the recommended dose of S227928 in combination with venetoclax. Participants will be assigned to two groups:

- Participants with AML or MDS/AML.
- Participants with CMML.

The participants will visit the clinic regularly. During the visits, the doctors will collect information about the participants' health. In order to closely monitor the efficacy and safety of the study treatments, blood samples will be collected at most clinic visits. Bone marrow samples will be collected at some visits. Electrocardiograms (ECGs: tests that record the electrical activity of the heart) or tests to take pictures of the heart will be performed in addition to the standard of care.

7 What are the possible benefits and risks?

S227928 has not yet been tested in humans, which means it may or may not improve the condition of blood disorder.

As for all drugs, the study drugs may cause some unwanted events, called side effects. Every care will be taken to avoid side effects and treat them if they occur.

Like any other medications, the study drugs may cause allergic reactions. Safety data from animal studies with S227928 suggest that the following side effects may occur: tumor lysis syndrome (rapid destruction of many tumor cells leading to organ(s) damage), infusion-related reactions (such as chills, fever, itching, wheezing), gastrointestinal symptoms (nausea, vomiting and diarrhea), increase in liver proteins, low blood cell counts, increased risk of infections, and damage to the heart.

The most common side effects associated with venetoclax are low blood cell counts, diarrhea, feeling sick, infection of the upper air passage, and tiredness.

Risks related to study procedures are manageable and include risks related to birth-control methods, bone marrow sample collection (aspirate) and blood drawing.