Protocol Summary

Of a Clinical Trial

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

A study of S095035 as a single agent and in combination in adult participants with advanced or metastatic solid tumors with deletion of MTAP

Full scientific title: *A Phase 1/2, open-label, multicenter clinical trial investigating the safety, tolerability, pharmacokinetics, and antineoplastic activity of S095035 (MAT2A inhibitor) as a single agent and in combination in adult participants with advanced or metastatic solid tumors with homozygous deletion of MTAP (EU trial number : 2025-521249-25-00)*

1 Why is this study needed?

This study aims to test a new study drug, S095035, as a single medication or in combination with another drug called TNG462. Researchers will test these new study drugs in participants with advanced solid tumors that have a specific change in a gene called *MTAP*. This specific change is the loss of the *MTAP* gene. Scientists call this a deletion. The loss of *MTAP* is thought to help tumors grow.

The *MTAP* gene makes an enzyme (MTAP) that breaks down a molecule called MTA. In patients who have cancer with an *MTAP* loss, the enzyme cannot be produced. The absence of the MTAP enzyme leads to a buildup of MTA that affects the normal function of the PRMT5 enzyme.

S095035 acts by blocking an enzyme called MAT2A. By blocking the MAT2A enzyme, S095035 indirectly prevents the PRMT5 enzyme from working, which ultimately leads to tumor cell death. TNG462 acts by directly blocking the PRMT5 enzyme.

Researchers believe that, by preventing PRMT5 from working in cancer cells without *MTAP*, S095035 alone or with TNG462 could stop these cancer cells from growing.

2 What are we mainly looking for?

What are the main goals of the study?

Study part 1:

- To look at the safety of S095035 alone and with TNG462 and whether participants tolerate them.
- To find the highest dose of S095035 alone and with TNG462 that participants can take without too much risk (highest tolerated dose).
- To find the dose of S095035 alone and with TNG462 that is both safe and effective (the recommended dose) for use in study part 2.

Study part 2:

- To see how well S095035 alone and with TNG462 work in treating the tumor.

What are the main study endpoints?

Researchers use study endpoints as measurements to decide whether a study has met its goal or not.

Study part 1:

- The number of unwanted medical events during the study and how serious they are.

Study part 2:

- The percentage of participants whose cancer shrinks or disappears during the study.

3 What about the other goals of the study ?

What are the other goals of the study?

- To understand what the body does to S095035 and TNG462. Scientists call this pharmacokinetics (PK).
- To understand the effects and mode of action of S095035 alone and with TNG462 on the tumor and the participant's body. Scientists call this pharmacodynamics (PD).
- To understand how well S095035 alone and with TNG462 work on the tumor.
- To confirm the safety of the recommended dose of S095035 alone and with TNG462.

What are the other study endpoints?

- PK and PD measurements, including the levels of S095035, TNG462, and other tumor-related substances in the blood.
- Changes in the size of the tumors, how quickly the tumor shrinks or disappears, and how long it remains small or gone.
- How long participants live after the start of the treatment and how long they live without their cancer getting worse.
- The number of unwanted medical events and how serious they are.

4 Who is participating in the study ?

To take part in the study, participants must:

- Be adults aged 18 or older.
- Have solid tumors with *MTAP* loss:
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  - that have spread to surrounding tissues or lymph nodes (known as 'advanced') or to other parts of the body (known as 'metastatic').
  - that have worsened despite treatment and with no other standard treatment available.
- Be able to provide a sample of their tumor. This involves a minor surgical procedure to remove a piece of the tumor from the body. Scientists call this a biopsy.

5 How is the study carried out ?

The study is called an "open-label" study. This means the doctors and the participants know which treatment is given. Participants will receive either S095035 alone, or in combination with TNG462. Participation in the study is completely voluntary. Participants can change their minds and withdraw from the study at any stage, for any reason.

This study has two parts. Participants will take part in either part 1 or part 2.

Study part 1: Dose Escalation

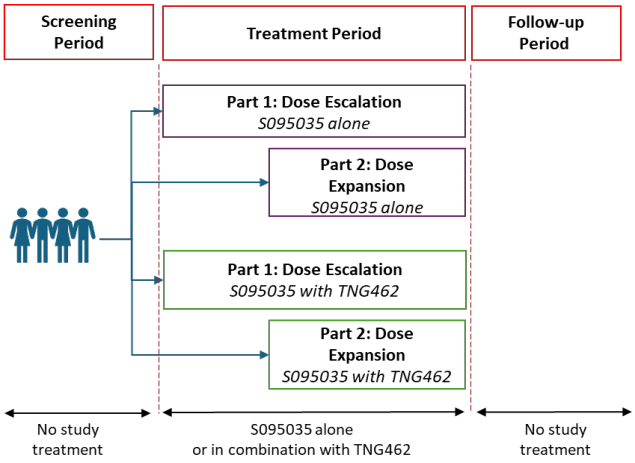
In this part, doctors will test increasing dose levels of S095035 alone or with TNG462, in small groups of participants, to find the recommended dose for study part 2.

Study part 2: Dose Expansion

In this part of the study, doctors will give the recommended dose found in study part 1 to a bigger group of participants.

Doctors will continue to monitor participants closely. This helps them to find out more information on how well S095305 alone and with TNG462 work and their side effects. Side effects are unwanted medical events which occur because of the study treatment(s).

The image below presents the study design:



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

Participants will receive S095035 alone or with TNG462, as tablets to take by mouth, once a day. Participants will take the treatments in 28-day cycles. These 28-day cycles will be repeated as long as the participant benefits from the treatment, or until the tumor gets worse, or the participant experiences severe side effects. The participant can also decide to stop the treatment at any time. The dose level and whether the participants take S095035 alone or with TNG462 depend on the group the participant is in.

Participants visit the doctors regularly for check-ups to closely monitor the safety of the study treatments and how well they work. These check-ups will include blood tests, scans to look at the tumors, and other health checks. The types of tests and exams the participants have during their visits depend on the type of cancer they have. The doctors could ask the participants to provide a biopsy.

7 What are the possible benefits and risks?

The participant's disease may or may not improve with study treatment. In any case, participants will receive close medical follow-up. The results of this study will help the researchers learn more about the study drugs. Studies such as this one could lead to better treatments for people with similar medical conditions in the future.

Researchers designed the study to be safe, with minimal risk or discomfort for participants. The study has strict safety rules and regular check-ups. As with all medicines, S095035 and TNG462 may cause side effects. The study doctors will tell the participants about the known side effects of S095035 and TNG462, and possible side effects based on human and animal studies, or knowledge of similar drugs. Every care will be taken to avoid them. If side effects occur, the study doctors will take care of the participants until they are resolved.

The informed consent document will contain detailed benefits, risks and side effects. This is a document that provides people with the information they need to decide if they want to join the study.