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.

Vorasidenib in Combination With Temozolomide (TMZ) in IDH-mutant Glioma

Full scientific title: A Phase 1b/2, multicenter study of vorasidenib in combination with temozolomide (TMZ) in participants with IDH1- or IDH2-mutant glioma (EU Trial Number: 2024-513738-39-00)

1 Why is this study needed?

This study is needed to test a drug called vorasidenib in combination with another drug, temozolomide (TMZ), in participants with glioma carrying an isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) mutation. Glioma is a type of cancer that starts in the glial cells in the brain or spinal cord.

In some types of cancers, abnormal forms of the IDH1 or IDH2 proteins are present in the cancer cells due to changes called mutations. When these proteins are present in abnormal forms, they produce too much 2-hydroxyglutarate (2-HG). This impairs normal cell functioning and may cause cells to become cancer cells.

Participants will be treated with a combination of vorasidenib and TMZ. TMZ is an approved medicine for the treatment of glioma. Vorasidenib is a drug that blocks the activity of abnormal IDH1 and IDH2 proteins and thus may reduce 2-HG levels in cancer cells. Vorasidenib is approved in some regions for the treatment of Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation.

2 What are we mainly looking for?

What is the main goal of the study?

The main goal of this study is to assess if the combination of vorasidenib and TMZ is safe, tolerable, and effective in participants with glioma carrying an IDH1 or IDH2 mutation.

What are the main study endpoint(s)?

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 number and severity of unwanted medical events.
- The recommended dose of vorasidenib and TMZ that participants can take without too much risk.
- The percentage of participants who live without the cancer getting worse after 12 months of treatment.

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 the effectiveness of vorasidenib and TMZ when given as a combination and how vorasidenib and TMZ are processed in the body (pharmacokinetics).

What are the other study endpoints?

The other study endpoints are to measure:

- How long participants live.
- How long participants live before their cancer gets worse.
- The number of participants whose cancer shrinks, disappears, or stays the same after treatment.
- How vorasidenib and TMZ move through and are processed by the body.

4 Who is participating in the study?

Overall, 39 to 45 participants are expected in the study.

To take part, participants have to:

- Be at least 12 years old.
- Have glioma with an IDH1 or IDH2 mutation and have not received treatment with an IDH inhibitor before.
- Have normal kidney, liver, and bone marrow (the spongy tissue inside bones that makes blood cells) 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 being taken.

The study is to be conducted in 2 parts:

- **Phase 1b** to test if the combination of vorasidenib with TMZ is safe and well-tolerated and to find the recommended dose of this combination.
- **Phase 2** to test if the recommended dose found in Phase 1b is safe and effective in a larger group of participants.

To find the recommended dose, the doctors may test different doses of vorasidenib in combination with TMZ in small groups of participants. Participants will start with a specific dose of vorasidenib and TMZ.

For each dose, the doctors check the safety of the study drugs. If this dose is safe, more people may be added to confirm. If not, the dose will be adjusted for the next group of participants. Once the safe dose is found, the researchers define the recommended dose of vorasidenib in combination with TMZ to be given in Phase 2.

This study will have a screening period (up to 28 days), a treatment period, a follow-up period (a visit about 30 days after ending treatment and survival follow-up every 3 months).

The total length of this study will vary for each participant, depending on how long they remain on the study treatments.

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

The participants will take the study drugs during time periods called "cycles." One cycle last 28 days.

In **Phase 1b**, 6 to 12 participants will receive:

- **Vorasidenib** tablet(s) at a starting dose of 40 mg to be taken by mouth every day of each 28-day cycle.
- **TMZ** capsules by mouth once a day at a dose of 150 mg/m² for the first 5 consecutive days of Cycle 1, with no TMZ intake for the remaining 23 days of the cycle. For Cycles 2 to 12, the TMZ dose may increase to 200 mg/m², following the same 5-day regimen. Participants can receive TMZ for up to 12 cycles.

These 28-day cycles are repeated for as long as the cancer does not progress, if the participant does not have too severe side effects, and if the participant is not discontinued from the study for other reasons.

In **Phase 2**, about 35 participants will receive the recommended dose of vorasidenib in combination with TMZ.

The participants visit the doctors regularly. During the visits, the doctors collect information about the participants' health. In order to closely monitor the efficacy and safety of the study treatment, blood samples will be taken at most clinic visits. To monitor the progression or regression of glioma, imaging tests called magnetic resonance imaging (MRI) scans will be done at certain visits. Additionally, electrocardiograms (ECGs: tests that record the electrical activity of the heart) will also be performed.

7 What are the possible benefits and risks?

Glioma may or may not improve with the study drugs. Vorasidenib has been tested at different doses and in many clinical conditions.

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

Like any other medications, the study drugs may cause allergic reactions. Safety data from other studies with vorasidenib suggest that the following side effects may occur: abnormal liver function test (which may indicate possible liver damage), feeling tired, fatigue, weakness, headache, COVID-19 (coronavirus disease 2019), nausea, diarrhea, seizure, dizziness, constipation, vomiting, cough, difficulty falling asleep, staying asleep, or getting good quality sleep.

TMZ can cause side effects, including a condition in which the bone marrow cannot make enough blood cells, liver damage, fungal infection in the lungs, and chances of developing other types of cancer later on. The most common side effects people experience with TMZ include loss of appetite, difficulty speaking, headache, vomiting, nausea, diarrhea, constipation, rash, hair loss, and tiredness.

Participants will receive more detailed information when they take part in the study.

Risks related to study procedures are manageable and include risks related to birth-control methods, and blood drawing.