# 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.*

## *Study of AG-881 in Participants with Residual or Recurrent Grade 2 Glioma with an IDH1 or IDH2 Mutation*

**Full scientific title:** *A Phase 3, Multicentre, Randomised, Double-blind, Placebo-Controlled Study of AG-881 in Subjects With Residual or Recurrent Grade 2 Glioma With an IDH1 or IDH2 Mutation*
*EU registration ID: 2024-512961-15-00*

## 1 Why is this study needed?

This study is looking into a new treatment for a type of brain tumour called Grade 2 glioma. These tumours may come back or continue to grow even after surgery. Researchers have discovered that many of these tumours have mutations (changes) in specific genes called IDH1 or IDH2. These mutations result in abnormal IDH proteins in the cancer cells that can help the tumour. Vorasidenib (also called AG-881) is a drug that is designed to block the abnormal IDH1 and IDH2 proteins in cancer cells. The aim of the study is to see if vorasidenib is safe and effective in stopping these tumours from growing.

This research is important because, currently, there are limited treatment options for patients with this type of tumour who have already had surgery.

## 2 What are we mainly looking for?

### What is the main goal of the study?

The main goal of this study is to test how vorasidenib works compared to a placebo in participants who have Grade 2 glioma with IDH1 or IDH2 mutations. The placebo looks like vorasidenib but does not have any medicine in it.

### What is the main study endpoint ?

The main endpoint the researchers will look at, called the primary study endpoint, is "progression-free survival" (PFS). This means they will measure how long the participants live without the tumour growing or worsening, using special brain scans. These scans will be done regularly throughout the study.

## 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 understand how long it takes before participants need another treatment.
- To understand how well vorasidenib works in stopping or slowing tumour growth.
- To check how safe vorasidenib is.
- To see how taking vorasidenib affects the daily lives and well-being of participants.
- To see how vorasidenib moves through and gets processed in the body.

### What are the other study endpoints?

The other study endpoints are:

- The time from when the patient is assigned to study treatment until they need a new cancer therapy, called the Time to Next Intervention (TTNI).
- The number of unwanted medical events and how serious they are, also known as Safety and Tolerability.
- How the size of the tumour changes over time, called Tumour Growth Rate (TGR).
- The percentage of participants whose tumours shrink or disappear, called Objective Response Rate (ORR).

- How quickly the tumour shrinks or disappears (called Time to Response) and how long it remains small or gone (called Duration of Response).
- How long participants live from the beginning of the study, called Overall Survival (OS).
- Results from questionnaires about how participants feel and their ability to do daily activities, known as Quality of Life (QoL).
- How much of the vorasidenib and its breakdown product is present in the blood at different times, known as Pharmacokinetics.

## 4 Who is participating in the study?

The study plans to include about 340 participants with Grade 2 glioma that has returned or isn't completely gone after surgery.

To take part of the study, participants have to:

- be at least 12 years old (or 18 years old in Germany) and weigh at least 40 kg.
- have had surgery to remove the tumour at least one year ago but not more than five years ago.
- have a specific gene mutation (IDH1 or IDH2) in their tumour, confirmed through special tests.
- not have had any other cancer treatments like chemotherapy (treatment with medicines) or radiotherapy (treatment with radiations).
- not have an immediate need for chemotherapy or radiotherapy.
- be generally healthy with well-functioning bone marrow (the spongy tissue inside bones where blood cells are made), liver and kidneys.

## 5 How is the study carried out?

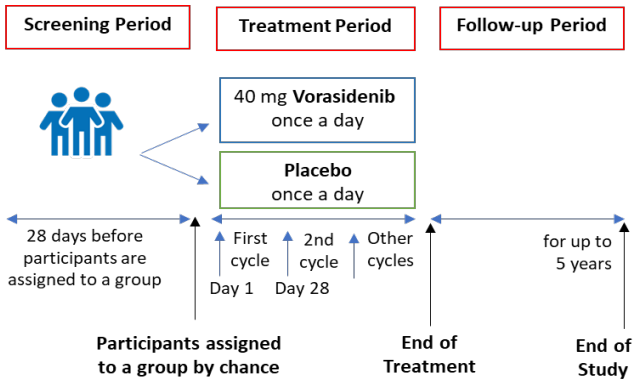
The study is a "double-blind" and "randomised" trial. "Double-blind" means neither the participant nor the doctors know who is getting vorasidenib or placebo to avoid any influence on the results. "Randomised" means that participants are chosen at random to receive either vorasidenib or placebo.

The doctors will check for IDH mutations in the participants' tumour before the screening period. During the screening period, doctors will check whether the potential participants can take part in this study.

Then, participants will take either vorasidenib or placebo according to their treatment group. Participants in the placebo group will be allowed to switch to vorasidenib if their glioma gets worse and if they meet certain criteria.

After stopping treatment, doctors will check on participants to see how their disease progresses and how they are doing for up to 5 years.

The participants will visit the doctors regularly. During the visits, the doctors will collect information about the participants' health.
The study design is presented in the image below:




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

Participants will receive either vorasidenib 40 milligrams (mg) or a placebo, as tablets. Both are taken by mouth once a day during time periods called "cycles". One cycle lasts 28 days. These 28-day cycles will be repeated until the tumour gets worse (called progression), the patient needs another treatment, experiences severe side effects, becomes pregnant, or chooses to stop.

Participants will take their medication daily at home but will visit the doctors regularly for monitoring. These visits will ensure the participants' safety and check if the treatment is working. These will include physical examinations, blood tests, and brain scans to check the tumour's size and growth. The doctors will also collect information about any unwanted medical events and the participants' overall health.

## 7 What are the possible benefits and risks?

Participating in this study may benefit participants with glioma because vorasidenib might stop or slow the tumour's growth. The main benefit is contributing to scientific research, which could lead to better treatments for gliomas in the future.

Like all medicines, vorasidenib might cause side effects. During the study, participants will be closely monitored, so any side effects can be quickly identified and treated. This study has a

group of experts, separate from the researchers, who oversee the benefits and risks. If they decide that the study treatment is not safe or doesn't show any benefit, the study can be stopped.

Some discomfort may be felt during lumbar puncture (if any), blood tests or brain scans. A lumbar puncture involves inserting a needle into the lower spine to collect fluid for tests.

More information about the possible benefits and risks is in the protocol and in the informed consent form.