Clinical Trial Summary

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, multicenter, randomized, double-blind, placebo-controlled study of AG-881 in subjects with residual or recurrent grade 2 glioma with an IDH1 or IDH2 mutation

We thank all the participants who took part in the study. Clinical study participants are very important for making progress in science, for the benefit of patients.
This document is a summary of the study. It is written for a general audience.

Researchers need many studies to decide which medicines work the best and are the safest for patients. For medical science to progress, many studies involving patients are running all around the world. This summary only shows the results from this one study. Other studies, evaluating the same drug, may find different results. You should not change your current treatment based on the results of this single study. If you have any questions about this study, please talk to your doctor.

Therapeutic area:
Oncology

Disease:
Glioma (Oligodendroglioma or Astrocytoma)

Study phase:
Phase 3

Final version
05/01/2024

In this summary:

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1 Why was this study done?

This study was done to test a new cancer drug called vorasidenib (also called AG-881) in patients with Grade 2 gliomas, which are types of brain cancer. Grade 2 gliomas are serious diseases with limited treatment options.

A protein called IDH (isocitrate dehydrogenase) is found inside cells that take part in providing energy to other cells in the body. Two types of IDH proteins are found in cells: IDH1 and IDH2. Changes in these proteins (called mutations) are found in several types of cancer, notably Grade 2 gliomas. These abnormal proteins make chemicals that cause gliomas to grow and spread.

Vorasidenib blocks the activity of abnormal IDH proteins. This drug is yet to be approved by regulatory agencies to treat patients who have gliomas with changes in the IDH1 or IDH2 proteins.

The main goal of this study was to test how vorasidenib works compared to a placebo in patients who have Grade 2 glioma with changes in the IDH1 or IDH2 proteins. A placebo looks like vorasidenib but does not have any medicine in it.

2 When and where did this study take place?

When did the study take place?

- This study started in January 2020.
- The study is still on-going. Participant inclusions in the study are now complete.

This summary only includes information collected up to 06 September 2022.

Where did the study take place?

The study took place in the following countries:

Country	Number of participants
United States	177
Israel	41
France	32
United Kingdom	17
Canada	16
Italy	10
Netherlands	10
Spain	10
Switzerland	9
Germany	9

3 Who participated in the study?

Which participants were included in the study?

To take part, participants had to:

- Be at least 12 years old.
- Have glioma with changes in the IDH1 or IDH2 proteins.
- Have Grade 2 glioma that stays (residual) or comes back after treatment (recurrent).
- Have had at least one prior surgery for removal of the glioma.
- Have not received any cancer treatment other than surgery.

How many participants took part in the study?

A total of 331 participants took part in the study: 144 women and 187 men.

How old were the participants?

The average age of the participants was 40 years. The youngest participant was 16 years old and the oldest was 71 years old.

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4 Which treatments did the participants receive?

Participants received one of the following treatments daily:

- Vorasidenib tablets taken by mouth at a dose of 40 milligrams (mg), or
- Placebo tablets taken by mouth.

The participants took the drugs during time periods called "cycles". One cycle lasted 28 days. These 28-day cycles were repeated for as long as:

- Participant's glioma did not get worse,
- Participant did not have too severe side effects, or
- Participant did not need other glioma treatment options.

The participant could also decide to stop the treatment at any time.

5 How was the study carried out?

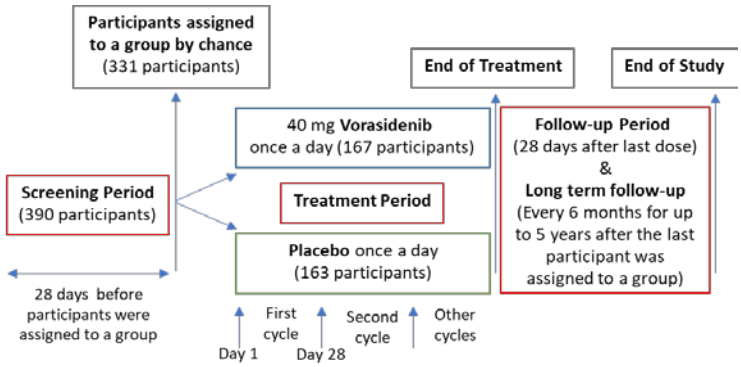
The study is called a "randomised" study. This means that the participants were put by chance into one of the 2 groups of treatment.

Among the 331 participants included in the study:

- 167 participants took vorasidenib.
- 163 participants took placebo.
- 1 participant in the vorasidenib group decided not to take part in the study before taking the treatment.

The study is called a "double-blind" study. This means that neither the participants nor the research doctors knew which treatment was taken. This was to avoid any influence on the results.

The study design is presented in the image below.



The doctors checked IDH mutations in the participants' cancer before the screening period. During the screening period, doctors checked if the participants could take part in this study. Then, participants took either vorasidenib or placebo according to their treatment group.

Participants who took vorasidenib continued their treatment for about 13 months. Participants who took placebo continued their treatment for about 11 months.

A group of independent specialists checked the participant's brain scans to confirm if their glioma got worse without knowing which treatment they took. The doctors were allowed to check which treatment participants were taking if independent specialists confirmed that their glioma got worse.

If the participant was taking placebo, then the participant was allowed to change to take vorasidenib. This was done to allow these participants to receive vorasidenib since their cancer had gotten worse. This type of change is called a "crossover".

Overall, 52 participants from the placebo group changed to receive vorasidenib.

The participants visited the doctors regularly. During the visits, the doctors collected information about the participants' health.

6 What were the side effects?

Side effects are unwanted medical events that the doctors think may be caused by the treatments in the study.

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The results may be presented differently in other documents related to the study.

The table below shows the number of participants who had side effects.

	Vorasidenib (out of 167 participants)	Placebo (out of 163 participants)
Participants who had side effect(s)	109 (65%)	95 (58%)
Participants who had serious* side effect(s)	3 (2%)	0
Participants who stopped the treatment because of side effect(s)	6 (4%)	1 (below 1%)

**See definition of serious side effects below*

What were the types of side effects?

The table below shows the most common side effects reported in the study (reported by at least 10% of participants in either of the treatment groups).

	Vorasidenib (out of 167 participants)	Placebo (out of 163 participants)
Increase in liver enzyme called ALT	61 (37%)	18 (11%)
Increase in liver enzyme called AST	41 (25%)	9 (6%)
Tiredness	35 (21%)	29 (18%)
Feeling sick	25 (15%)	26 (16%)
Increase in liver enzyme called GGT	22 (13%)	5 (3%)
Diarrhoea	20 (12%)	16 (10%)
Headache	12 (7%)	17 (10%)

= participants

What were the serious side effects?

A side effect is considered serious when:

- the participant needs to be hospitalised,
- it causes lasting damage or death,
- the participant's life is in danger or,
- it is medically important in the doctor's opinion.

In this study, 3 participants had serious side effects (serious unwanted medical events thought to be caused by the treatments in the study). All of them were in the vorasidenib group.

The table below shows all the serious side effects reported in the study.

	Vorasidenib (out of 167 participants)	Placebo (out of 163 participants)
Inflammation of the liver caused by overactivity of the immune system (the body system and its cells that fight diseases)	1 (below 1%)	0
Liver failure	1 (below 1%)	0
Increase in liver enzyme called ALT	1 (below 1%)	0

= participants

In the study, no participants were dead up to 06 September 2022.

7 What were the study results?

This summary includes information collected up to 06 September 2022.

This document presents only the results for the main goal of the study. Other results are available in other documents listed in section 10.

The study is still on-going. Further calculations will be done when the study is complete.

To test the effectiveness, the researchers measured the time from starting the treatment until the cancer got worse or the participant died. This is called "progression-free survival".

The average progression-free survival time was 28 months for participants who took vorasidenib and 11 months for those who took placebo. This means that participants treated with vorasidenib lived longer without the cancer getting worse.

8 How has this study helped research?

The study found that "progression-free survival" was longer with vorasidenib than with placebo in participants with Grade 2 gliomas who had changes in the IDH1 or IDH2 proteins.

Findings from this study will be used to get approvals for vorasidenib to treat participants with Grade 2 gliomas with changes in the IDH1 or IDH2 proteins.

This summary shows only the main results from this one study. Other studies, evaluating the same drug, may find different results.

9 Are there plans for further studies?

Clinical studies with vorasidenib are on-going and further studies are planned.

10 Further information

What are the identification numbers of the study?

- Protocol code: AG881-C-004
- EudraCT number: 2019-002481-13
- US NCT number: NCT04164901

Who did the study?

The company that organised and funded the research, called the "sponsor", is the Institut de Recherches Internationales Servier based in Gif-Sur-Yvette, France.

How can you contact the sponsor?

Contact us on the Servier website https://servier.com/en/

Where can you learn more about this study?

You can find more information about this study on these websites:

- https://clinicaltrials.servier.com/find-clinical-trials
- www.clinicaltrialsregister.eu/ctr-search
- https://www.clinicaltrials.gov/

In this document we translated medical terms into lay terms. You can find the corresponding medical terms in the Servier glossary at https://clinicaltrials.servier.com/glossary/

You can find general information about clinical trials on https://clinicaltrials.servier.com/