SERVIER

Clinical Trial Summary

A Phase 3 study to test for efficacy of an oral investigational drug, AG-120, in patients with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation

Full scientific title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-controlled Study of AG-120 in Previously-treated Subjects with Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 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:
Cancers

Disease:
Cholangiocarcinoma

Study phase:
Phase 3

16 December 2022
Final version

In this summary:

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1 Why was this study done?

The study was done to test if ivosidenib (also called AG-120 or TIBSOVO) is an effective treatment in patients with a type of severe bile duct cancer.

Bile duct cancer (cholangiocarcinoma) is a serious and rare disease with few effective treatment options. Some cancer cells have changes called mutations in their IDH1 (isocitrate dehydrogenase 1) genes. Genes carry instructions that tell our cells how to build proteins. Cells with changes in their IDH1 genes make abnormal IDH1 proteins. The abnormal proteins make a chemical that causes cancer cells to grow and spread throughout the body. Abnormal IDH1 proteins are found in many different types of cancer.

Ivosidenib is a drug that blocks the activity of abnormal IDH1 proteins. It has already been approved in the United States to treat people who have acute myeloid leukaemia, a type of cancer in the blood and bone marrow.

The main goal of this Phase 3 study was to test how ivosidenib works compared to placebo in patients who have severe bile duct cancer with changes in the IDH1 gene. A placebo looks like ivosidenib but does not have any medicine in it.

2 When and where did this study take place?

When did the study take place?

- The study started in February 2017.
- The study ended in May 2021.

Where did the study take place?

The study took place in the following countries:

Country	Number of participants
United States	125
Spain	27
South Korea	12
United Kingdom	11
Italy	6
France	6

3 Who participated in the study?

Which participants were included in the study?

Study participants had to:

- Be at least 18 years old
- Be diagnosed with severe bile duct cancer that could not be treated with surgery
- Have cancer cells with changes in the IDH1 gene
- Have taken 1-2 different anticancer medicines before that did not work

How many participants took part in the study?

A total of 187 participants, 119 women and 68 men, joined the study.

How old were the participants?

The youngest participant was 33 years old. The oldest was 83 years old. The average age was 61 years old.

4 Which treatments did the participants receive?

The study drug was ivosidenib. Not everyone in the study was given the drug. Some received a placebo, which looks like the study drug but does not contain any medicine.
Every day, participants received either

- ivosidenib tablets taken by mouth at a total dose of 500 milligrams, or
- placebo tablets taken by mouth.

Each participant also continued receiving their usual medical care for bile duct cancer.

The participants took the ivosidenib or placebo every day during set lengths of time called “cycles”. Each cycle lasted 28 days. These cycles continued one after another as long as:

- the cancer did not get worse and
- the participant did not have side effects that were too severe.

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

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5 How was the study carried out?

The study is called a "randomised" study. This means that a computer program put the participants into one of the two groups by chance (2 in 3 chances of being in the ivosidenib group and 1 in 3 chances of being in the placebo group).

In this study:

- 126 participants were put in the ivosidenib group.
- 61 participants were put in the placebo group.
- 3 participants from the ivosidenib group and 2 participants from the placebo group stopped the study before receiving the treatment.

After the treatment began, 43 participants from the placebo group were allowed to join the group taking ivosidenib. This was done to give them any chance of benefit from the drug since their cancer had gotten worse. This is called a "crossover". Since the crossover participants had been taking the placebo before they started taking ivosidenib, they are counted in both the placebo and ivosidenib groups. By the end of the study, a total of:

- 166 participants had taken ivosidenib and
- 59 participants had taken the placebo.

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. For the 43 crossover participants (and not the others), the study was "open-label" because both the participants and the research doctors knew they were moving to the ivosidenib group.

Participants who received ivosidenib continued the treatment for an average of 6 months, and participants who received the placebo continued the treatment for an average of 2 months. While participants were receiving their treatments, they visited the doctors regularly. During the visits, the doctors collected information about the participants' health.

6 What were the side effects?

Like all treatments, ivosidenib can cause side effects, although not everybody gets them.

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

The table below shows the number of participants who had side effects. The results may be presented differently in other documents related to the study.

	Ivosidenib Treatment Group (of 166 participants)	Placebo Group (of 59 participants)
Participants who had side effect(s)	104 (62.7%)	23 (39.0%)
Participants who had serious* side effect(s)	3 (1.8%)	0
Participants who stopped the treatment because of side effect(s)	2 (1.2%)	0

**See definition of serious side effects below*

What were the type of side effects?

The table below shows the most common side effects reported in the study (in at least 10% of the participants in one group).

	Ivosidenib Treatment Group (of 166 participants)	Placebo Group (of 59 participants)
Diarrhoea	35 (21.1%)	5 (8.5%)
Feeling sick	34 (20.5%)	9 (15.3%)
Vomiting	14 (8.4%)	7 (11.9%)
Tiredness	28 (16.9%)	4 (6.8%)

= *participants*

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What were the serious side effects?

A side effect is considered serious when:

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

In this study, 3 of 166 participants who received the study drug had 4 serious side effects (serious unwanted medical events thought to be caused by the treatments in the study). All the serious side effects are described in the table below.

	Ivosidenib Treatment Group (of 166 participants)	Placebo Group (of 59 participants)
Yellowing of the skin and eyes (also called jaundice) caused by liver problems	1 (0.6%)	0
Increase in liver blood test called bilirubin (hyperbilirubinaemia)	1 (0.6%)	0
Abnormal electrical activity of the heart that affects its rhythm (QT prolonged)	1 (0.6%)	0
Fluid around the lungs	1 (0.6%)	0

= *participant(s)*

In the study, no participants died because of an unwanted event thought to be caused by the ivosidenib treatment.

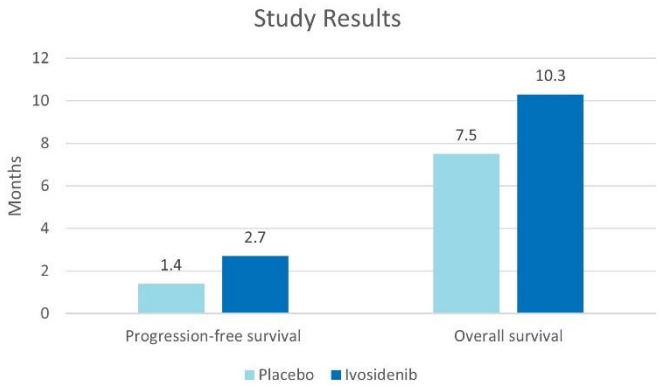
7 What were the study results?

The study was completed as planned.

This document presents below the results for the main goal of the study.

To test if ivosidenib was effective, the researchers measured the time from the start of the treatment until the cancer got worse. This is called "progression-free survival". This average time was 2.7 months for those who got ivosidenib and 1.4 months for those who got placebo. That means that in this study, the time from the start of treatment until the cancer got worse was longer with ivosidenib than with placebo.

The researchers also measured the time from starting the treatment until the participant died. This is called "overall survival". The average time was 10.3 months for the ivosidenib group and 7.5 months for the placebo group. Even though overall survival was longer in the ivosidenib group, this result was not so large that it could not have been due to chance alone.



Other results can be found in the scientific study summary at https://clinicaltrials.servier.com

8 How has this study helped research?

The study found that "progression-free survival" was longer with ivosidenib than with placebo in patients with previously treated, severe bile duct cancer with changes in the IDH1 gene. Overall, side effects caused by ivosidenib were manageable.

Findings from this study will be used to get approvals for using ivosidenib to treat patients with severe bile duct cancer.

9 Are there plans for further studies?

There are many other clinical studies right now on ivosidenib. These studies test if ivosidenib works in other types of cancer with changes in the IDH1 gene. These include leukaemia and a type of brain cancer called glioma. In the future, we plan to test ivosidenib in other diseases, too.

10 Further information

What are the identification numbers of the study?

- Protocol code: AG120-C-005
- EudraCT number: 2015-005117-72
- US NCT number: NCT02989857

Who did the study?

The Institut de Recherches Internationales Servier (the "sponsor") based in Suresnes, France organised and funded the research.

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 the study on these websites:

- https://clinicaltrials.servier.com
- https://www.clinicaltrialsregister.eu
- https://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/

In accordance with the recommendations of the French National Cancer Plan III (Measure 5.4), this document was submitted for review and guidance to the Clinical Cancer Research Patients Committee of La Ligue Nationale contre le Cancer.