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Clinical·Trial·Summary¶

A Phase 3 study to test the AG-120 in combination with Azacitidine in comparison with the use of Azacitidine alone in patients ≥ 18 Years of Age with previously untreated Acute Myeloid Leukemia with an IDH1 Mutation.

Full scientific title: A phase 3, multicenter, double-blind, randomized, placebo-controlled study of AG-120 in combination with azacitidine in subjects ≥18 years of age with previously untreated acute myeloid leukemia with an IDH1 mutation (AGILE study).

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:
Acute myeloid leukemia

Study phase:
Phase 3

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Final version

In this summary:

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1 Why was this study done?

The study was done to test if AG-120 (study drug) is an effective treatment, when combined with another drug used to treat patients with acute myeloid leukaemia (AML).

AML is a type of cancer in the blood and bone marrow. 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.

AG-120 (also called ivosidenib or TIBSOVO) 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 AML and people who have bile duct cancer.

In this study, AG-120 was combined with a drug called azacitidine that blocks the growth of cancer cells. Azacitidine has been approved in several countries. It is recommended for patients with AML who cannot receive strong chemotherapy, called intensive chemotherapy.

The main goal of this study was to test how AG-120 in combination with azacitidine worked compared to placebo with azacitidine in patients who have AML with changes in the IDH1 gene. A placebo looks like AG-120 but does not contain any real medicine.

2 When and where did this study take place?

When did the study take place?

- This study started in March 2018.
- Participant enrollment is now complete.
- The study is still ongoing. The end of the study will be when the last participant has stopped participating in the study for any reason.

This summary only includes information collected up to 18 March 2021.

Where did the study take place?

The study took place in the following countries:

Country	Number of participants
France	23
Spain	20
Germany	12
China	12
Taiwan	11
Italy	10
Poland	9
Brazil	8
Australia	6
Japan	6
South Korea	5
Russia	5
Israel	4
Netherlands	4
Canada	3
Austria	2
United Kingdom	2
United States	2
Czech Republic	1
Mexico	1

3 Who participated in the study?

Which participants were included in the study?

To take part, participants had to:

- Be at least 18 years old
- Have previously untreated AML
- Have cancer cells with changes in the IDH1 gene
- Be too frail for intensive chemotherapy

How many participants took part in the study?

A total of 146 participants took part in the study: 66 women and 80 men.

How old were the participants?

The average age of the participants was 75 years. The youngest participant was 45 years old and the oldest was 94 years old.

4 Which treatments did the participants receive?

The participants took the drugs during time periods called "cycles". They received one of the following combination treatments:

- AG-120 (study drug) + azacitidine:
  Participants took the study drug orally every day, at a total dose of 500 milligrams, for 28 days, over 28-day cycles. They also received azacitidine into a vein or under the skin for 7 days, over the same 28-day cycles.
- Placebo + azacitidine:
  A placebo looks like AG-120 but does not contain any real medicine.
  Participants took placebo orally every day, for 28 days, over 28 day-cycles. They also received azacitidine into a vein or under the skin for 7 days, over the same 28 day-cycles.

These 28-day cycles were repeated for as long as the cancer did not progress and if the participant did not have too severe side effects. The participant could also decide to stop the treatment at any time.

5 How was the study carried out?

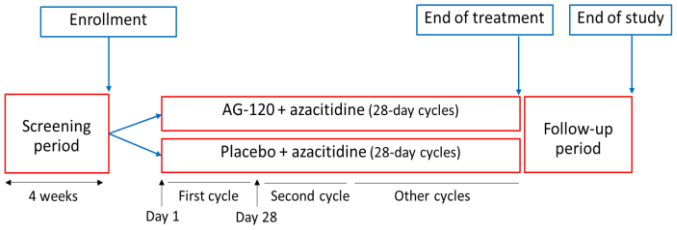
The study is called a "randomised" study. This means that the participants were put by chance into one of the two treatment groups.

Among the 146 participants included in the study:

- 71 participants took AG-120 with azacitidine
- 73 participants took placebo with azacitidine
- 2 participants died before receiving 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 personal influence on the results.

The study design is presented in the image below.



The participants started with a first period called a screening period. This period allowed doctors to decide if the participant could receive the study treatment.

Then, the participants were enrolled in the study and visited the doctors regularly. During the visits, the doctors collected information about the participants' health.

Participants who received AG-120 with azacitidine continued the treatment for an average of 9 months. Participants who received the placebo with azacitidine continued the treatment for an average of 5 months.

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.

In this summary, we describe unwanted medical events thought to be caused by AG-120 and azacitidine in one group and placebo and azacitidine in the other group.
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.

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	AG-120 with azacitidine (out of 71 participants)	Placebo with azacitidine (out of 73 participants)
Participants who had side effect(s)	42 (59%)	36 (49%)
Participants who had serious* side effect(s)	16 (23%)	9 (12%)

**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 (by at least 5% of the participants in either group).

	AG-120 with azacitidine (out of 71 participants)	Placebo with azacitidine (out of 73 participants)
Feeling sick	17 (24%)	12 (16%)
Vomiting	14 (20%)	8 (11%)
Lack of white blood cells called neutrophils	10 (14%)	4 (5%)
Decrease in the number of red blood cells	7 (10%)	5 (7%)
Constipation	6 (8%)	4 (5%)
Diarrhoea	6 (8%)	5 (7%)
Fever with lack of white blood cells called neutrophils	6 (8%)	5 (7%)
Lack of platelets, cells that help the blood to clot	6 (8%)	5 (7%)
Lower appetite	6 (8%)	2 (3%)
Decrease in number of platelets, cells that help the blood to clot	4 (6%)	2 (3%)
Unusual weakness	4 (6%)	5 (7%)
Tiredness	4 (6%)	2 (3%)
Fever	4 (6%)	5 (7%)
Weight decreased	1 (1%)	4 (5%)

= *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.

The table below shows the serious side effect reported by more than 2% of the participants in either group.

	AG-120 with azacitidine (out of 71 participants)	Placebo with azacitidine (out of 73 participants)
Fever with lack of white blood cells called neutrophils	5 (7%)	5 (7%)

In the study, no participant died because of an unwanted event thought to be caused by the AG-120 treatment.

7 What were the study results?

The results included in the summary include information collected up to 18 March 2021.

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

To test if AG-120 with azacitidine was effective, the researchers measured the time from the start of the treatment until a disease event appeared. Disease events were: treatment failure, or the cancer got worse, or the participant died. Treatment failure means that the cancer did not completely disappeared by 6 months.

The results showed that AG-120 in combination with azacitidine reduced the risk of disease event by 67% compared to placebo with azacitidine.

This means that the number of patients who remained event-free was higher with AG-120 with azacitidine than with placebo with azacitidine.

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

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

8 How has this study helped research?

This study found that there were fewer disease events with AG-120 and azacitidine than with placebo and azacitidine in patients who have AML with changes in the IDH1 gene.

Findings from this study were used to get approval in the United States for using AG-120 in combination with azacitidine to treat patients who have AML. It will also be used to obtain approvals in other countries.

9 Are there plans for further studies?

There are many other clinical studies right now on AG-120. These studies test if AG-120 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 AG-120 in other diseases, too.

10 Further information

What are the identification numbers of the study?

- Protocol code: AG120-C-009
- EudraCT number: 2016-004907-30
- US NCT number: NCT03173248

Who did the study?

The company that organised and funded the research, called the "sponsor", is the Institut de Recherches Internationales Servier based in Suresnes, 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://clinical trials.servier.com/trials
- 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/