Protocol Summary

Of a Clinical Trial

The protocol of a clinical study is a document that explains why and how a study will be carried out.

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 (EU-CT number: 2024-514309-73-00).*

1 Why is this study needed ?

The study is needed to test if AG-120 (study drug) is an effective and safe treatment when combined with another drug called azacitidine, used to treat patients with acute myeloid leukaemia (AML). AML is a type of cancer of the blood and bone marrow.

In 6 to 10% of cases of AML, an abnormal form of a protein called isocitrate dehydrogenase 1 (IDH1) is present in the cancer cells due to changes called mutations. When IDH1 is present in this abnormal form, it produces too much 2-hydroxyglutarate (2-HG). This impairs normal cell functioning and may cause cells to become cancer cells.

AG-120 is a drug that blocks the activity of abnormal IDH1 proteins and thus may reduce 2-HG levels in cancer cells to normal levels. It has already been approved in several countries to treat AML and bile duct cancer in patients with IDH1 mutation.

In this study, AG-120 is combined with azacitidine which 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.

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 well AG-120 in combination with azacitidine works 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.

What is the main study endpoint?

A study endpoint is the measurement used to decide whether a study goal is reached or not. The main endpoint of this study is to measure Event-Free Survival. This means the time from when participants start their treatment until one of three things happens: their treatment stops working, their disease comes back after getting better, or they pass away from any cause. If the treatment does not make the disease go away by Week 24, it is considered a treatment failure.

3 What about the other key goals of the study ?

What are the other key goals of this study?

The other key goals are:

- To see how many participants have complete remission with AG-120 plus azacitidine compared to those treated with placebo plus azacitidine.

Complete remission means the disease has completely gone away, with no sign of cancer, and all other blood cell counts have returned to normal levels.

- To see how long participants live from the beginning of the study with AG-120 plus azacitidine compared to those treated with placebo plus azacitidine. This is called overall survival.
- To see how many participants have complete remission or complete remission with incomplete recovery of blood cells with AG-120 plus azacitidine compared to those treated with placebo plus azacitidine. Complete remission with incomplete recovery of blood cells means the disease has completely gone away, with no sign of cancer, but some of the healthy blood cells haven't fully returned to normal levels yet.
- To see the overall response rate in participants treated with AG-120 plus azacitidine compared to those treated with placebo plus azacitidine. The overall response rate is the percentage of participants whose cancer shrinks or disappears with treatment.

What are the other key study endpoints?

The other key study endpoints are:

- How many participants have complete remission.
- How long participants live from the beginning of the study (overall survival).
- How many participants have either complete remission or complete remission with incomplete recovery of blood cells.
- The percentage of participants whose cancer shrinks or disappears (overall response rate).

4 Who is participating in the study ?

Overall, 200 participants are expected in the study.

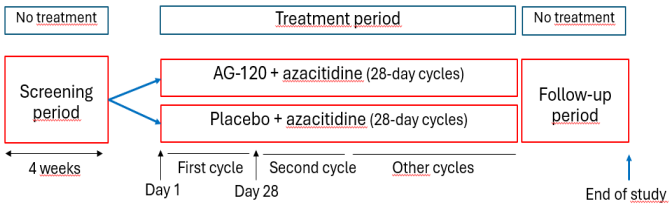
To take part, participants have to:

- 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.

5 How is the study carried out ?

The study is called a "double-blind" and "randomised" study. "Double-blind" means that neither the participants nor the research doctors know which treatment is taken. This is to avoid any influence on the results. "Randomised" means that the participants are put into one of the two treatment groups by chance.

The study design is presented in the image below:



6 What are the treatment(s) and tests used in the study?

The participants take the study treatments during time periods called "cycles". They receive one of the following combination treatments:

- AG-120 + azacitidine: participants take AG-120 (500 miligrams) orally every day, over 28-day cycles. They also receive azacitidine into a vein or under the skin for 7 days, over the same 28-day cycles.
- Placebo + azacitidine: participants take placebo orally every day, over 28 day-cycles. They also receive azacitidine into a vein or under the skin for 7 days, over the same 28 day-cycles.

These 28-day cycles are repeated for as long as the cancer does not progress and the participant does not have too severe side effects. The participant can decide to stop the treatment at any time.

The participants visit the doctors regularly. During the visits, the doctors collect information about the participants' health. These regular check-ups include blood tests, bone marrow tests, and possibly scans to monitor the disease and check for side effects. The bone marrow tests involve taking a sample (fluid or solid tissue) of the bone marrow from the hip or chest.

7 What are the possible benefits and risks?

The participants' AML may or may not improve with the study drug. The study will help doctors learn more about treating AML, which can benefit others in the future.

As with all drugs, the study drug may cause some unwanted events, called side effects. Every care will be taken to avoid side effects and treat them if they occur. Like any medicine, the study drugs may cause allergic reactions.

The main risks known to be caused by the use of AG-120 in blood cancers are QT prolongation, IDH

differentiation syndrome, and tumour lysis syndrome. QT prolongation is abnormal electrical activity of heart. IDH differentiation syndrome is a condition that has only been reported in patients with blood cancers. It causes an abnormal amount of immune proteins (cytokines) in the blood and may be life-threatening. Tumour lysis syndrome is a condition which happens when a lot of tumour cells die. This causes changes in the blood that may cause damage to organs. Risks are considered low and manageable based on available safety data for AG-120.

Some exams, like bone marrow sampling and blood drawing, might cause discomfort.

Doctors will monitor participants closely to manage any side effects and ensure their safety.