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.

Ivosidenib (IVO) monotherapy and azacitidine (AZA) monotherapy in patients with hypomethylating agent (HMA) naive myelodysplastic syndromes (MDS) with an IDH1 mutation

Full scientific title: A Phase 3, multicenter, open label, randomized, non-comparative two-arm study of ivosidenib (IVO) monotherapy and azacitidine (AZA) monotherapy in adult patients with hypomethylating agent (HMA) naive myelodysplastic syndromes (MDS) with an isocitrate dehydrogenase-1 (IDH1) mutation (PyramIDH study) (2023-510155-37-00)

1 Why is this study needed ?

This study is done to test a drug called ivosidenib in adults with myelodysplastic syndromes (MDS) never treated by a class of drugs called hypomethylating agent (HMA) and carrying an isocitrate dehydrogenase-1 (IDH1) mutation. MDS are a group of disorders in which bone marrow (the spongy tissue inside the bones) does not make enough healthy blood cells or platelets. MDS leads to low blood cell count that can increase the risk of infections, blood transfusion and progression to Acute Myeloid Leukemia (AML). AML is an aggressive form of white blood cells cancer.

In several types of cancers, an abnormal form of a protein called IDH1 is present in the cancer cells due to changes called mutations. When IDH1 is present in abnormal form, it produces too much 2-hydroxyglutarate (2-HG). This impairs normal cell functioning and may cause cells to become cancer cells.

Participants will be treated with ivosidenib or with azacitidine. Azacitidine belongs to HMA, which is standard treatment for MDS. Ivosidenib is a drug that blocks the activity of abnormal IDH1 proteins and thus may reduce 2-HG levels in cancer cells to normal levels.

2 What are we mainly looking for ?

What is the main goal of the study ?

The main goal of this study is to assess if ivosidenib is effective in participants with MDS never treated by HMA and carrying an IDH1 mutation.

What is (are) the main study endpoint(s) ?

A study endpoint is the criteria used to decide whether a study goal is reached or not. The main endpoint of this study is to see if there is a decrease in or disappearance of signs and symptoms of MDS (complete remission) or if some (but not all) signs and symptoms of cancer disappear (partial remission), after CCI [redacted]. The doctor evaluates the signs and symptoms of MDS using International Working Group 2006 criteria (response criteria for MDS).

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 further investigate the effectiveness and the safety of ivosidenib.

What are the other study endpoints?

The other study endpoints are:

- Duration from remission until return of cancer or death
- Time from drug assignment to the date of first remission
- Number of participants with no blood transfusion during 56 consecutive days during treatment
- Number of participants whose disease progress to AML

- Number of participants who can receive bone marrow transplant
- Number of medical events, laboratory measurements, vital signs (such as heart rate) and other observations related to safety

4 Who is participating in the study ?

Overall, 48 participants are expected in the study.

To take part, participants have to:

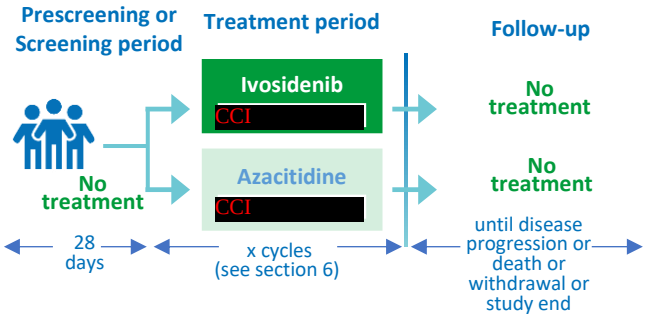
- Be at least 18 years old.
- Have MDS with IDH1 mutation and have not received treatment with HMA.
- Have adequate kidney, liver and heart function.

5 How is the study carried out ?

The study is called an "open label" study. This means that both the participants and the research doctors know which treatment is being taken.

The study is called a "randomised" study. This means that the participants are put by chance into 1 of the 2 groups of treatment. CCI [redacted]

The study design is presented in the image below:



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

The participants receive either:

- Ivosidenib: 2 tablets of 250 mg once daily, every day during time periods called "cycles". Each cycle will be of 28 days.
- Azacitidine: 1 injection (75 mg/m^2) under the skin or into a vein every day for 7 days of each cycle of 28 days.

These 28-day cycles are repeated for as long as the cancer does not progress and if the participant does not have too severe of side effects. The treatment can be stopped if participant proceed to stem cell transplant, become pregnant, or decide to stop the treatment.

The participants visit the doctors regularly. During the visits, the doctors collect information about the participants' health. In order to closely monitor the efficacy and safety of the study treatment, blood samples are collected at most of the clinic visits. Bone marrow sample will be collected at some visits. Electrocardiograms (ECGs: tests that record the electrical activity of the heart) or echocardiogram (ECHO: test to take pictures of the heart) will be performed in addition to the standard of care.

7 What are the possible benefits and risks?

The MDS may or may not improve with the study drug. As there are high chances that participants with MDS carrying IDH1 mutation progresses to AML, treatment with ivosidenib may benefit these participants as there is no specific targeted drug for this condition.

As for 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. Three risks are known to be caused by the use of ivosidenib in blood cancers: change in the electrical activity of heart, abnormal amount of immune proteins (cytokine) in the blood that may be life-threatening, and elevation of white blood cells count. Risks are considered low and manageable based on available safety data for ivosidenib.

Identified risks associated with azacitidine are manageable and include: low blood cells count, kidney and liver damage, tumour lysis syndrome (a condition which occurs when a lot of cancer cells die; this causes changes in the blood that may cause damage to organs) and harmful effects on unborn baby.

Risks related to study procedures are manageable and include risks related to birth-control methods, bone marrow sample collection (aspirate) and blood drawing.

The available safety and efficacy data support a favourable benefit/risk balance for the use of ivosidenib in MDS participants.