A RANDOMIZED, DOUBLE-BLINDED, DOUBLE-DUMMY, PLACEBO-CONTROLLED THOROUGH QTC STUDY WITH SINGLE ORAL DOSES OF CEDAZURIDINE IN HEALTHY SUBJECTS

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Ethical review	Approved WMO
Status	Completed
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON50873

Source
ToetsingOnline

Brief title
Thorough QT Assessment of Cedazuridine in Healthy Subjects

Condition

- Leukaemias

Synonym
Leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Astex Pharmaceuticals, Inc
Source(s) of monetary or material Support: Pharmaceutical industry.

Intervention

Keyword: Cancer, Cedazuridine, ECG, Moxifloxacin

Outcome measures

Primary outcome

To evaluate the effect of a single therapeutic and supratherapeutic dose of

cedazuridine on QTcF in healthy volunteers.

Secondary outcome

To evaluate the effect of cedazuridine-epimer on QTcF in healthy volunteers

To confirm the effect of moxifloxacin on QTcF in healthy subjects for

comparison to cedazuridine

To evaluate the safety and tolerability of therapeutic and supratherapeutic

doses of cedazuridine in healthy subjects

To evaluate the effects of a single therapeutic and supratherapeutic dose of

cedazuridine on heart rate (HR), PR, QRS intervals, and T-wave morphology.

To evaluate the pharmacokinetics (PK) of cedazuridine and the

cedazuridine-epimer

Study description

Background summary

Cedazuridine is a compound that could possibly be used in combination with other agents to enable their oral administration. These agents include hypomethylating agents (HMAs, a type of anticancer agent), such as decitabine,

for the treatment of a number of cancers, including acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and chronic myelomonocytic leukemia (CMML). In these cancers, white blood cells in the bone marrow do not mature and therefore do not become healthy blood cells.
When HMAs are administered orally, they do not work because HMAs are broken down in the gut and liver, specifically by the enzyme called cytidine deaminase (CDA). Cedazuridine is a new compound which slows down how fast HMAs disappear in the body, especially in the stomach, intestine and the liver, which could help HMAs be better absorbed in the body. At this moment, one of the combinations with cedazuridine (INQOVI® [decitabine and cedazuridine] tablets) has been approved for the treatment of MDS and CMML in the United States, Canada, and Australia.

Study objective

The purpose of the study is to investigate the effect of cedazuridine on the values of specific electrocardiogram (ECG) parameters. One of these parameters is the QT -interval. The QT -interval indicates the recovery time of the heart muscle cells after they have been electrically stimulated. Importantly, the study will assess whether there is a prolongation of the QT interval following cedazuridine treatment. When the QT interval is prolonged, repolarization (return to resting state) of the heart is delayed. This means that cardiac (heart) cells need more time to prepare for the next beat. When a new heartbeat is about to start and not all cardiac cells are ready for repolarization, arrhythmias (abnormal heartbeat) could develop. For this study the expected small changes to your ECG recordings are considered to be relatively safe.

In this study we will also investigate how safe the compound cedazuridine is and how well it is tolerated when it is used by healthy participants. We also investigate how quickly and to what extent cedazuridine is absorbed, transported, and eliminated from the body (this is called pharmacokinetics).

Moxifloxacin is used as a control during this study. Moxifloxacin is known to prolong the QT- interval and is therefore a suitable compound to monitor the proper conduct of the study. In addition, moxifloxacine has a favorable safety profile. Therefore, it is often used as a positive control in similar QT-interval studies. Moxifloxacin is on the market as an antibiotic and has been available in the European Union for more than 10 years. You will receive a patient information leaflet for more information on this compound
.
We compare the effects of cedazuridine and moxifloxacin also with the effects of a placebo. A placebo is a compound without any active ingredient. Please note that when the term *study compound* is used in this document, we mean cedazuridine, moxifloxacin, or placebo.
Cedazuridine has been used by humans before. In addition, it has been extensively tested in the laboratory and on animals.

Study design

The study requires that the volunteers stay in the study center for 4 consecutive periods of 5 days (a total of 21 days and 20 nights).

Day 1 is the first day on which the research drug is given. Volunteers are expected the day prior to the first study drug administration at the study center. In that case, one must report at 14:00 o'clock in the afternoon. The entry time can be adjusted. Leave the study center on Day 5 of study treatment period 4 (19 days after the first study drug administration).

One receives cedazuridine, moxifloxacin, or placebo after an overnight fast (at least 10 hours without food and drink) as oral capsules with 240 milliliters (mL) of tap water.

After taking the research drug, one of the researchers will inspect the hands and mouth. This is to check whether the study drug has been taken.

During each treatment period, fasting is continued for up to 4 hours after study drug administration. Then they get lunch. During the fast one may drink water with the exception of 2 hours before to 2 hours after administration of the study drug.

Intervention

Treatment A: once 100 mg cedazuridine
Treatment B: once 400 mg cedazuridine
Treatment C: once placebo
Treatment D: once 400 mg moxifloxacin

Study burden and risks

Blood draw
Drawing blood may be painful or cause some bruising. The use of the indwelling cannula can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and bleeding in the environment of the puncture site. In some individuals, a blood draw can sometimes cause pallor, nausea, sweating, low heart rate, or drop in blood pressure with dizziness or fainting.
In total, we will take about 130 mL of blood. This amount does not cause any problems in adults.

Heart tracing (ECG)
To make a heart tracing, electrodes will be placed at specific locations on the arms, chest and legs. To monitor the heart rate, electrodes will be placed on the chest and abdomen. Prolonged use of these electrodes can cause skin irritation.

Holter (monitoring heart rate)
The heart rate will be monitored continuously from 1 hour before administration of the study compound until 24 hours thereafter. As long as the volunteers are connected to the device they cannot take a shower, they have to behave as relaxed as possible and prevent from sweating. As soon as hey are connected, they cannot use electric devices (razor, electric toothbrush, hairdryer) anymore. They may not wear jewelry or a watch. At certain time-points they will be asked to remain lying down for 15 minutes without moving, talking or sleeping. During these moments they may not listen to music, watch television or use a laptop, media player or phone.

Fasting
If the volunteer has to fast for a prolonged time during the study, this may lead to symptoms such as dizziness, headache, stomach upset, or fainting.

Coronavirus test
Samples for the coronavirus test will be taken from the back of the nose and throat using swabs. Taking the samples only takes a few seconds, but can cause discomfort and can give an unpleasant feeling. Taking a sample from the back of the throat may cause the volunteer to gag. When the sample is taken from the back of the nose, they may experience a stinging sensation and the eyes may become watery.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Sex : male or female; females of nonchildbearing potential, or postmenopausal.
2. Age : 18 to 55 years, inclusive, at screening.
3. Body mass index (BMI) : 18.0 to 32.0 kg/m2, inclusive.
4. Weight : >=50 kg, inclusive.
5. Status : healthy subjects.

Exclusion criteria

1. Employee of PRA or the Sponsor.
2. History of relevant drug and/or food allergies.
3. History of alcohol abuse or drug addiction (including soft drugs like cannabis products).
4. History or presence of atrioventricular block (any degree) or sick sinus syndrome.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-06-2021
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Moxifloxacin
Generic name:	n.a.
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-05-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-06-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-004773-45-NL
CCMO	NL77573.056.21

Study results

Date completed: 16-11-2021

Results posted: 27-06-2022

First publication
14-06-2022