A first-in-human, participant and investigator-blinded, randomized, placebo-controlled, single and multiple-ascending dose study with drug-drug interaction, to investigate the safety,
tolerability, and pharmacokinetic profile of AB521, in healthy volunteers.

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

Summary

ID

NL-OMON51736

Source
ToetsingOnline

Brief title
Safety, PK and PD of AB521 in healthy volunteers

Condition

- Other condition

Synonym
cancer, Renal cell carcinoma

Health condition

Renal cell carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Arcus Biosciences, Inc.
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: AB521, PD, PK

Outcome measures

Primary outcome

- To assess the safety and tolerability of AB521 after single- and multiple

oral doses.

- To characterize the PK profile of AB521 after single- and multiple oral

doses.

Secondary outcome

- To evaluate the effect of multiple oral doses of AB521 on the PK of midazolam

when midazolam is administered as a single dose

Exploratory:

- To assess the potential PD effects of AB521

- To characterize AB521 excretion in urine

- To characterize potential metabolite(s) of AB521 in plasma and urine

Study description

Background summary

AB521 is a new compound that may potentially be used for the treatment of cancer. Cells of solid tumors (tumors that don't contain any liquid or cysts) are frequently exposed to low oxygen conditions. In order to survive in these conditions, tumor cells make use of specific proteins, including *Hypoxia-Inducible Factor-2α* (HIF-2α). AB521 has been shown to be able to inhibit the HIF-2α protein. Treatment with AB521 is expected to prevent the growth and spread of these tumor cells.

*For part 3 only:
This study evaluates how AB521 affects the body, in particular the enzymes in the liver that are important in the breakdown of other medication such as midazolam. Laboratory studies have shown that this may be the case. Midazolam is a substance processed by enzymes in the liver and is recommended by the European Medicines Agency (the agency that approves drugs for use in Europe) to study the effects on these enzymes. This could alter the amount of midazolam in the body when given at the same time as AB521.*

Study objective

In this study, we will investigate how safe the new compound AB521 is and how well it is tolerated when it is used by healthy participants. We will also investigate how quickly and to what extent AB521 is absorbed and eliminated from the body. In addition, we will look at the effect of AB521 on a certain blood marker.

AB521 has been administered to 32 healthy participant in Part 1 of this study. It has also been tested in the laboratory and on animals. AB521 will be tested at various dose levels.

We will compare the effects of AB521 with the effects of a placebo. A placebo is a compound without any active ingredient.

*For part 3 only:
Furthermore, we will evaluate a possible interaction between AB521 and midazolam. We will do this by investigating the effect of AB521 on the pharmacokinetics of midazolam. Both these compounds will be administered in this study.

Midazolam is a sedative and sleep-inducing agent that is registered as a sleep aid for oral administration and as a short-acting sedative before or during a medical examination or surgery for other forms of administration. The dose of midazolam used in the current study is well below the dose levels achieved for these purposes.*

Study design

For part 1:
It is necessary that the volunteer stays in the research center for 1 period of 9 days (8 nights). This will be followed by 3 short visits to the research center, including a follow-up visit at the end of the study. These short visits will take place on Day 10, Day 13, and between Day 21 and Day 28.

Day 1 is the day when the volunteer receives the study compound. The volunteer is expected at the research center 2 days before the day of administration of the study compound (Day -2). He/she will leave the research center on Day 7 of the study.

The volunteer will be given AB521 or placebo as oral capsules with 240 milliliters (mL) of (tap) water.

Whether the volunteer will receive AB521 or placebo will be determined by chance. Per group, 6 participants will receive AB521 and 2 participants will receive placebo.

For part 2:
It is necessary that the volunteer stays in the research center for 1 period of 10 days (9 nights). This will be followed by 3 short visits to the research center and a follow-up visit at the end of the study. These short visits will take place on Day 11, Day 14, and day 17.

Day 1 is the first day that the volunteer receives the study compound. The volunteer is expected at the research center 2 days before the day of administration of the study compound. The volunteer will leave the research center on Day 8 of the study.

The volunteer will be given AB521 or placebo as oral capsules with 240 milliliters (mL) of (tap) water.

Whether the volunteer will receive AB521 or placebo will be determined by chance. Per group, 6 participants will receive AB521 and 2 participants will receive placebo.

For part 3:
It is necessary that the volunteer stays in the research center for 1 period of 10 days (9 nights). This will be followed by 1 short visit to the research

center and a follow-up visit at the end of the study. This short visit will take place on Day 13.

Day 1 is the first day that the volunteer receives the study compound. The volunteer is expected at the research center 2 days before the day of administration of the study compound. The volunteer will leave the research center on Day 9 of the study.

The volunteer will be given AB521 or placebo as oral capsules with 240 milliliters (mL) of (tap) water. The volunteer will also receive midazolam as a drink containing 2 mg compound.

Intervention

Part 1:
The volunteer will be given AB521 or placebo as oral capsules with 240 milliliters (mL) of (tap) water.

Part 2:
If the volunteer participates in group 1 it will receive on day 1 to 7 AB521 15 mg or placebo once daily
If the volunteer participates in group 2 it will receive on day 1 to 7 AB521 50 mg or placebo once daily

Part 3:
The volunteer will receive AB521 from day 2-7, dose between 15 mg and 50 mg based on Part 2.
The volunteer will receive AB521 on day 8, dose between 15 mg and 50 mg based on Part 2.
The volunteer will receive Midazolam on day 1 and day 8, dose 2 mg once daily.

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, seating, low heart rate, or drop in blood pressure with dizziness or fainting.

In total, we will take about 215 mL (Part 1), 221 mL (Part 2) or 161 mL (Part 3) of blood from the volunteer. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time.

Heart tracing (holter monitoring)

To make a heart tracing, electrodes will be placed on the arms, chest and legs. To monitor your heart rate, electrodes will be placed on the chest and abdomen. Prolonged use (3 day period) of these electrodes can cause skin irritation.

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, the volunteer may experience a stinging sensation and the eyes may become watery.

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.

Contacts

Public
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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Inclusion criteria

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. Participant must be at least 18 to 55 years of age inclusive, at the time of signing the informed consent.
3. Participants who are healthy volunteers (in the opinion of the investigator) as determined by pre-study medical history, physical examination, vital signs, and 12-lead ECG.
4. Participants must have clinical laboratory tests within the reference range for age and gender at screening and baseline.
5. Screening and randomization hemoglobin for males and females is as follows:
a) SAD: male and female hemoglobin level >= 12.5 g/dL (7.7 mmol/L)
b) MAD and DDI: male hemoglobin level >= 14.2 g/dL (8.8 mmol/L) and female hemoglobin level >= 12.5 g/dL (7.7 mmol/L).

Further criteria apply

Exclusion criteria

1. Has any (acute or chronic [including SARS-CoV-2 infection]) medical or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the study participant*s ability to participate in this study.
2. Has history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, cerebrovascular, neurological, or other major disorders capable of significantly altering the absorption, metabolism, or elimination of IMP; constituting a risk when taking the study intervention; or interfering with the interpretation of data in the opinion of the investigator.
3. Abnormal blood pressure (BP) or pulse measurements at the Screening Visit or Day -2/-1 (Admission) in a supine position after 5 minutes of rest as follows: mean systolic BP >= 139 mm Hg or mean diastolic BP >= 89 mm Hg; mean pulse < 40 bpm or > 100 bpm. Study participants with a BP within normal range but who, in the opinion of the investigator, have a high risk for cardiovascular accident based on, eg, family history, smoking, BMI, or lipid spectrum can be excluded. Results that are outside the specified ranges and are deemed clinically non-significant will be allowed at the discretion of the investigator, after discussion with the Sponsor Medical Monitor (or designee). If a study participant has a test result outside the normal range that is deemed potentially clinically significant, repeat of the investigation may be allowed once at the discretion of the investigator, after discussion with the Sponsor

Medical Monitor (or designee).
4. The following liver enzyme test results:
a) Alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, or alkaline phosphatase (ALP) >1.0× upper limit of normal (ULN).
• Tests that result in ALT, AST, bilirubin, or ALP up to 25% above the exclusion limit may be repeated once for confirmation.
b) Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of asymptomatic gallstones).
5. Has 12-lead ECG with changes considered to be clinically significant (eg, QTcF > 450 msec for males and > 470 msec for females, left bundle branch block, or evidence of myocardial ischemia) at the Screening Visit or Day -2/-1 (Admission).

Further criteria apply

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	09-11-2021
Enrollment:	68
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Midazolam
Generic name:	N/A

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-10-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-11-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-06-2022
Application type:	Amendment
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	EUCTR2021-003856-17-NL
CCMO	NL79307.056.21

Study results

Date completed: 17-02-2023

Results posted: 06-11-2023

First publication
18-09-2023