An alternating panel, single ascending dose trial to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, relative bioavailability, and food effect of orally administered AS-1763 in healthy subjects

Published: 12-01-2021
Last updated: 17-01-2025

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Ethical review	Approved WMO
Status	Completed
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON51167

Source
ToetsingOnline

Brief title
SAD study investigating safety, tolerability, PK and PD of AS-1763

Condition

- Autoimmune disorders
- Leukaemias

Synonym
Chronic Leukemia, Inflammatory Diseases

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AS-1763, Safety, Tolerability

Outcome measures

Primary outcome

• To investigate the safety and tolerability of AS-1763 following single-dose oral administration in healthy subjects.

Secondary outcome

• To investigate the pharmacokinetics (PK) of AS-1763 (in plasma) following single-dose oral administration in healthy subjects.

• To investigate the pharmacodynamics (PD) of AS-1763 (in blood) following single-dose oral administration in healthy subjects.

• To investigate potential QT effects of AS-1763 following single-dose oral administration in healthy subjects, using serial electrocardiograms (ECGs) extracted from continuous recordings (Holter) combined with AS-1763 plasma concentration: QT interval corrected for heart rate (QTc) analysis.

Study description

Background summary

AS-1763 is a new compound that may potentially be used for the treatment of diseases of the immune system. More specifically for the treatment of immune

system diseases that are caused by a type of immune cell that is called a B-cell. This includes diseases such as leukemia and other types of cancer (B-cell lymphoma). B-cells play a central role in the immune system and your body*s ability to defend itself against pathogens. In certain types of diseases of the immune system, the B-cells may not be working properly or they may be overactive. AS-1763 is intended to slow down the B-cell activity and may therefore potentially be used for the treatment of these diseases. In addition to B-cell diseases, the study compound is also being developed for the treatment of inflammatory and autoimmune disorders such as rheumatoid arthritis.

Study objective

In this study we will investigate how safe the new compound AS-1763 is and how well it is tolerated when it is used by healthy participants.

We also investigate how quickly and to what extent AS-1763 is absorbed, transported, and eliminated from the body.

We will compare AS 1763 as a drink (Group A and B) to AS 1763 as a tablet (Group C).

In Group A and B, we also look at the effect of AS 1763 on cells in your blood (this is called pharmacodynamics). We compare the effects of AS 1763 as a drink 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 AS 1763, placebo, or both.

In Group C, we also investigate if food has an effect on how the body handles the AS 1763 tablet.

This is the first study where AS 1763 is given to humans. It has been extensively tested in the laboratory and on animals. In this study, AS 1763 will be tested at various dose levels.

Study design

For the study it is necessary that you stay in the research center for 4 periods (Group A), 3 periods (Group B), or 2 periods (Group C) of 5 days (4 nights).

Day 1 is the day when subjects receive the study compound AS-1763. Subjects will leave the research center on Day 4 of each period.

Group A and B
Subjects will be given AS-1763 or placebo as a drink. After administration of

the study compound, the vial will be rinsed twice with 20 mL solution, which subjects will also be required to drink. This will be followed by drinking an additional amount of water so that in total subject ingested 200 milliliters (mL).

The study compound will be given after subjects have been fasting for 10 hours.

Whether subjects will receive AS-1763 or placebo will be determined by chance. Per group, 6 participants will receive AS-1763 and 2 participants will receive placebo. This study will be done double-blinded. In each period, different participants will receive placebo.

Group C
The volunteer will be given AS-1763 as a tablet with a maximum of 200 milliliters (mL) of water.

All participants will receive the study compound once with a breakfast and once without breakfast. The order in which this will occur will be determined by drawing lots. In each period the volunteer must fast for at least 10 hours overnight before intake of AS 1763 or before the start of breakfast (as applicable). In one period, the volunteer will receive a high-fat breakfast with a standard composition, which must be started exactly on time and must be finished in 30 minutes or less. The entire breakfast must be consumed.

Participants will be divided in two three groups: Group A, Group B, and Group C. In total the volunteer will receive the study compound 4 times (Group A), 3 times (Group B) or 2 times (Group C). There will be at least 28 days between consecutive study compound intakes (between treatment periods) in Group A and B and at least 7 days between dosings in Group C.

Intervention

Group A and B:
The table below shows the planned dose levels for each group. The doses after treatment period 1 can be adjusted. For example because the study compound had more or less effect than was expected. However, the dose will not be lower than 5 milligram (mg). The dose for the next group will only be increased if the lower dose of the previous group was found to be well tolerated and in case of no objection by the Medical Research Ethics Committee. The study will be discontinued if, in the opinion of the investigators, unacceptable side effects appear.

The planned dose levels for each group is as follows:

Treatment period* 1A 1B 2A 2B 3A 3B
4A
Group A 5mg 100mg 600mg 1000mg

Group B 25mg 300 mg
800mg

* From treatment period 1B onwards, the dose that subjects will receive will be based on the results of the previous groups. The dose may therefore be different from what is mentioned in the table. Subjects will be informed verbally about the dose that subjects will receive.

Group C
Participants in Group C will receive 100 mg AS 1763 in each period (twice in total). Please refer to the table below for an overview of the possible treatments per period.

Group C Period 1 Period 2
Sequence AB 100 mg after fasting 100 mg after food
Sequence BA 100 mg after food 100 mg after fasting

Study burden and risks

Blood draw
Drawing blood may be painful or cause some bruising. The use of the indwelling canula can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and bleeding in the environment (bruising) 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.

The total amount of blood collected in the entire study will not exceed 500 milliliters (mL). This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time. If the investigator thinks it is necessary for the safety of a participant, extra samples might be taken for possible additional testing. If this happens, the total amount of blood drawn will be more than the amount indicated above.

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

Meals/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.

For Group C: The high-fat breakfast is a big breakfast containing eg, 2 fried eggs, fried potatoes and bacon. The volunteer must consume the whole breakfast in 30 minutes or less. It can be difficult to consume the entire breakfast, particularly for light eaters.

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 subject to gag. When the sample is taken from the back of the nose, subject 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. Must have signed an ICF prior to screening, indicating that he/she understands the purpose of, and procedures required for, the trial and are willing to participate in the trial.
2. Healthy males or females of non-childbearing potential, between 18 and 64

years of age, inclusive, at screening.
3. Body Mass Index (BMI; weight in kg divided by length in square meters) between 18.0 and 30.0 kg/m2, inclusive, at screening.
4. Good physical and mental health as established by medical history, physical examination, electrocardiogram (ECG) and vital signs (including temporal body temperature) recording, and results of biochemistry, hematology, and urinalysis tests during screening as judged by the investigator.
5. Non-smoker/non-user of nicotine-containing products for at least 3 months prior to screening, as confirmed by a urine cotinine test at screening and on Day -1 of the first treatment period of each cohort.

Exclusion criteria

1. History of or current clinically significant medical illness including (but not limited to) gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, endocrinologic, genitourinary, renal, hepatic, respiratory, inflammatory, neoplastic, or infectious disease, or any other illness that the investigator considers should exclude the subject or that could interfere with the interpretation of the trial results.
2. Clinically relevant abnormal laboratory, ECG recordings, vital signs or physical findings at screening or on Day -1 of the first treatment period, as judged by the investigator.
3. Values of hepatic aminotransferase (ALT and/or AST) > 1.5 × the upper limit of normal range (ULN) at screening or on Day -1 of the first treatment period.
4. Values of GGT and/or ALP > 1.25 x ULN at screening or on Day -1 of the first treatment period.
5. Values of total bilirubin > ULN at screening or on Day -1 of the first treatment period.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	31-03-2021
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO Date:	12-01-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-02-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-08-2021

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-11-2021
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	EUCTR2020-005599-37-NL
CCMO	NL76291.056.21

Study results

Date completed:	17-12-2021
Results posted:	15-09-2022

First publication
11-05-2022