A randomized, double-blind, placebo-controlled, safety, tolerability, pharmacokinetic, and pharmacodynamic study of MET409 after single and multiple ascending oral dose administration in healthy male subjects

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON45980

Source
ToetsingOnline

Brief title
MET409 SAD and MAD study

Condition

- Hepatic and hepatobiliary disorders

Synonym
Non-alcoholic steatohepatitis [NASH])

Research involving

Human

Sponsors and support

Primary sponsor: Metacrine, Inc.
Source(s) of monetary or material Support: Metacrine;Inc.

Intervention

Keyword: MAD, MET409, NASH, SAD

Outcome measures

Primary outcome

-To assess the safety and tolerability of single and multiple oral doses of

MET409.

-To characterize the pharmacokinetics (PK) of single and multiple oral doses of

MET409.

Secondary outcome

-To characterize the pharmacodynamics (PD) of single and multiple oral doses of

MET409.

-To identify the recommended multiple oral dose level(s) of MET409 for future

studies in patients.

Study description

Background summary

MET409 is a new compound that may eventually be used for the treatment of non-alcoholic steatohepatitis (NASH). NASH is a chronic liver disease which is characterized by inflammation and the build-up of fat in the liver. The

farnesoid X receptor (FXR) is a protein that is present at high levels in the liver and intestine where it has an important role in various metabolic functions (i.e., bile acid synthesis, carbohydrate and lipid metabolism). MET409 is a FXR agonist, so it binds to FXR and then activates the receptor. By activating FXR, the inflammation and the build-up of fat in the liver may be reduced in patients with NASH.

Study objective

This study will be performed in 124 healthy male volunteers. The study will be performed in 2 parts, Part A and Part B.

Part A will be performed in 64 healthy male volunteers divided over 8 groups of 8 volunteers each.
Part B will be performed in 60 healthy male volunteers divided over 6 groups of 10 volunteers each.

The purpose of this study is to investigate how safe the new compound MET409 is and how well it is tolerated when it is administered to healthy volunteers. MET409 has not been administered to humans before. It has been previously tested in the laboratory and on animals. MET409 will be tested at various dose levels.

It will also be investigated how quickly and to what extent MET409 is absorbed by and eliminated from the body (pharmacokinetics). In addition, the effect of MET409 on certain blood markers will be investigated (pharmacodynamics).

MET409 will be compared with a placebo.

Study design

Part A:
The study will consist of 1 period during which the volunteer will stay in the research center UMCG location for 5 days (4 nights).

Day 1 is the day of administration of the study compound. the volunteer is expected at the research center at 14:00 h in the afternoon prior to the day of administration of the study compound (Day -1). The volunteer will leave the research center on Day 4 of the study.

On 7 - 14 days after the end of the study the health of the volunteer will be checked for the last time.

Part B:
The study will consist of 1 period during which the volunteer will stay in the research center UMCG location (Group B1) or Martini Hospital location (Groups

B2-B6) for 18 days (17 nights).

Day 1 is the first day of administration of the study compound. The volunteer is expected at the research center at 14:00 h in the afternoon prior to the first day of administration of the study compound (Day -1). The volunteer will leave the research center on Day 17 of the study.

On 7 - 14 days after the end of the study the health of the volunteer will be checked for the last time.

Intervention

Part A:
The study will consist of 1 period during which you will receive MET409 or placebo as a single dose. MET409 and placebo will be given as oral tablets with 240 mL of tap water (or up to 480 mL of tap water, if needed, for Groups A7 and A8 [400 and 800 mg MET409] because of the large amount of tablets the volunteers need to swallow).

When MET409 or placebo is administered, the volunteer should have fasted for at least 10 hours (no eating and drinking). Also, after administration of the study compound, the volunteer will be required to fast for 4 additional hours on Day 1. Then the volunteer will be served lunch. During fasting the volunteer is allowed to drink water, except during 2 hours before and 1 hour after administration of the study compound.

One of the investigators will inspect volunteers hands and mouth after the study compound intake.

Whether the volunteer will receive MET409 or placebo will be determined by chance (randomized study). Per group, 6 volunteers will receive MET409 and 2 volunteers will receive placebo. Neither the volunteer nor the responsible doctor knows if MET409 or placebo will be administered (double-blinded study). However, if it is important for volunteers health, for example in case of a serious side effect, this information will be looked up during the study.

For safety reasons, initially 2 volunteers will receive the study compound in Group A1. One volunteer will receive MET409, and 1 will receive placebo. After administration, the safety and tolerability of the study compound in these 2 volunteers will be closely monitored. If there are no concerns about the safety and tolerability 24 hours after administration, then the remaining 6 volunteers (5 will receive MET409 and 1 will receive placebo) will receive the study compound.

We refer to the table below to see the planned dose levels for the groups.

Group Day Treatment How often

A1 1 20 mg MET409 or placebo Once
A2 1 30 mg MET409 or placebo Once
A3 1 50 mg MET409 or placebo Once
A4 1 100 mg MET409 or placebo Once
A5 1 150 mg MET409 or placebo Once
A6 1 200 mg MET409 or placebo Once
A7 1 400 mg MET409 or placebo Once
A8 1 800 mg MET409 or placebo Once

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 responsible doctor, unacceptable side effects appear.

Part B:
The study will consist of 1 period during which you will receive MET409 or placebo once daily for 14 consecutive days (Day 1 to Day 14). MET409 and placebo will be given as oral tablets with 240 mL of tap water (or up to 480 mL of tap water, if needed, for Groups B5 and B6 [up to 400 and 800 mg MET409] because of the large amount of tablets the volunteers need to swallow).

When MET409 or placebo is administered, the volunteer should have fasted for at least 10 hours (no eating and drinking). Also, after administration of the study compound, the volunteer will be required to fast for 4 additional hours on Day 1 and on Day 14. Then the volunteer will be served lunch. On all other dosing days (Days 2 to 13) the volunteer will receive a standard breakfast 1 hour after administration of the study compound. During fasting the volunteer is allowed to drink water, except during 2 hours before and 1 hour after administration of the study compound.

One of the investigators will inspect volunteers hands and mouth after the study compound intake.

Whether the volunteer will receive MET409 or placebo will be determined by chance (randomized study). Per group, 8 volunteers will receive MET409 and 2 volunteers will receive placebo. Neither the volunteer, nor the responsible doctor knows if MET409 or placebo will be administered (double-blinded study). However, if it is important for the health of the volunteer, for example in case of a serious side effect, this information will be looked up during the study.

We refer to the table below to see the planned dose levels for the groups.

Group Days Treatment How often
B1 1 to 14 20 mg MET409 or placebo Once daily
B2 1 to 14 50 mg MET409 or placebo Once daily
B3 1 to 14 100 mg MET409 or placebo Once daily

B4 1 to 14 200 mg MET409 or placebo Once daily
B5 1 to 14 400 mg MET409 or placebo Once daily
B6 1 to 14 800 mg MET409 or placebo Once daily

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 responsible doctor, unacceptable side effects appear.

Study burden and risks

All potential drugs cause side effects; the extent to which this occurs differs. Since MET409 will be administered in humans for the first time, side effects of MET409 in humans are currently not known. MET409 has been investigated in animals. In monkeys and rats, MET409 was well tolerated and a few side effects were seen. There were no safety concerns and in particular no effects on cardiac, pulmonary and neurologic function.

There is limited information on other FXR agonists that are under development: it is known that up to now they have generally shown to be safe. However, the occurrence of pruritus has been reported in several FXR agonists, e.g. with the registered drug Ocaliva®.

The volunteer should be aware that the aforementioned side effect and possibly other, still unknown side effects, may occur during the study. However, with the doses used in this study no serious side effects are expected. The volunteer will be immediately informed if relevant safety and tolerability information of the study compound becomes available during the conduct of the study.

Tests
Drawing blood and/or insertion of the indwelling cannula may be painful or cause some bruising. In total, we will take about 200 milliliters (part A) and 435 milliliters (part B) of blood from the volunteer. This amount does not cause any problems in adults. To compare: a blood donation involves 500 milliliters of blood being taken each time.

To monitor the heart rate, electrodes (small, plastic patches) will be pasted at specific locations on the chest and arms and legs. Prolonged use of these electrodes can cause skin irritation (rash and itching).

Procedures: pain, minor bleeding, bruising, possible infection.

Contacts

Public
Metacrine, Inc.

Sorrento Valley Blvd, Suite C 3985
San Diego CA 92121
US
Scientific
Metacrine, Inc.

Sorrento Valley Blvd, Suite C 3985
San Diego CA 92121
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-Healthy male subjects
-18-65 years, inclusive, at screening
-BMI 18.0-30.0 kg/m2, inclusive, at screening
-Weight >=60 kg

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. In case of participation in another drug study within 90 days before the start of this study or being a blood donor within 60 days from the start of the study. In case of donating more than 1.5 liters of blood in the 10 months prior the start of this study.

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:	Recruitment stopped
Start date (anticipated):	17-05-2018
Enrollment:	124
Type:	Actual

Ethics review

Approved WMO Date:	16-04-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-04-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	23-07-2018
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	EUCTR2018-000857-38-NL
CCMO	NL65693.056.18