# An open-label, fixed sequence, crossover, 1-way drug-drug-interaction study between IMB-1018972 and each of repaglinide, midazolam, paroxetine, and fluvoxamine in healthy subjects

Published: 20-08-2019
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The purpose of Part 1 is to investigate the effect of multiple doses of IMB-1018972 on the absorption, distribution and elimination of single doses of repaglinide and metformin and thereby understand to what extent IMB-1018972 may possibly change...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON48361

**Source**
ToetsingOnline

**Brief title**
IMB-1018972 DDI study

### Condition

- Other condition

**Synonym**
Ischemic cardiovascular disease

**Health condition**

Ischemic cardiovascular disease

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** DDI, IMB-1018972

## Outcome measures

### Primary outcome

- To assess the effects of multiple-dose IMB-1018972 on the single-dose pharmacokinetics (PK) of repaglinide and midazolam when coadministered in healthy subjects (Part 1)

- To assess the effects of multiple-dose paroxetine on the single-dose PK of IMB1018972 when coadministered in healthy subjects (Part 2)

- To assess the effects of multiple-dose fluvoxamine on the single-dose PK of IMB-1018972 when coadministered in healthy subjects (Part 3)

### Secondary outcome

- To assess the safety and tolerability of IMB-1018972 when coadministered with repaglinide, midazolam, paroxetine, or fluvoxamine in healthy subjects (Parts 1, 2, and 3)

# Study description

### Background summary

IMB-1018972 is a new compound that may eventually be used for the treatment of patients with angina, a medical term for chest pain or discomfort due to

coronary heart disease (also called ischemic heart disease). It occurs when the heart muscle doesn't get as much blood as it needs. This usually happens because one or more of the heart's arteries are narrowed or blocked, also called ischemia. Angina often occurs with physical exertion, like climbing stairs, when the heart works harder and needs more oxygen.

Under normal conditions, the heart muscle uses fatty acids to generate energy that is required to pump blood and this process requires oxygen. However, when heart muscle doesn't get as much blood as it needs, glucose metabolism produces more energy per oxygen molecule than fatty acid metabolism. IMB-1018972 shifts the production of energy in the heart muscle from fatty acids toward glucose.

The other medications administered in this study are repaglinide, midazolam, paroxetine and fluvoxamine.

Repaglinide and midazolam are approved drugs and already available on the market under several dosages and formulations. Repaglinide is a drug that lowers the blood glucose levels and is being used in the treatment of diabetes mellitus type 2. Midazolam is a short-acting sedative used prior to invasive diagnostic or surgical procedures.

Paroxetine is an approved drug and already available on the market under several dosages and formulations. Paroxetine is a so-called selective serotonin reuptake inhibitor (SSRI) and is being used in the treatment of depression, anxiety, obsessive-compulsive disorder, panic disorder, and posttraumatic stress disorder.

Fluvoxamine is an approved drug and already available on the market under several dosages and formulations. Fluvoxamine is a so-called selective serotonin reuptake inhibitor (SSRI) and is being used in the treatment of depression and obsessive-compulsive disorder.

**Study objective**

The purpose of Part 1 is to investigate the effect of multiple doses of IMB-1018972 on the absorption, distribution and elimination of single doses of repaglinide and metformin and thereby understand to what extent IMB-1018972 may possibly change the absorption, distribution and elimination of other drugs.

The purpose of Part 2 is to investigate the effect of multiple doses of paroxetine on the absorption, distribution and elimination of single doses of IMB-1018972 and thereby understand to what extent other drugs may possibly change the absorption, distribution and elimination of IMB-1018972.

The purpose of Part 3 is to investigate the effect of multiple doses of fluvoxamine on the absorption, distribution and elimination of single doses of IMB-1018972 and thereby understand to what extent other drugs may possibly

change the absorption, distribution and elimination of IMB-1018972.

It will also be investigated in Parts 1, 2 and 3 to what extent IMB-1018972 is tolerated by volunteers when it is administered in combination with other medications: repaglinide (Part 1), midazolam (Part 1), paroxetine (Part 2) and fluvoxamine (Part 3).

**Study design**

Part 1:
This part will consist of 1 period during which the volunteer will stay in the research center for 9 days (8 nights). The volunteer is expected at the research center at 14:00 h in the afternoon on Day -1, the day prior to Day 1 (Day 1 is the day of administration of repaglinide). The volunteer will leave the research center on Day 8.

During the study the volunteer will receive multiple doses of IMB-1018972 and 2 single doses each of repaglinide and midazolam. IMB-1018972 will be given as an oral capsule formulation. Repaglinide will be given as an oral tablet formulation. Midazolam will be given as an oral solution and, because of the small volume, this will be squirted in the mouth using a syringe (without a needle).

Please see below an overview of the planned treatments:

Day 1: a single dose of 0.5 milligrams repaglinide (1 tablet) in the morning under fasted conditions,
Day 2: a single dose of 2 mg midazolam in the morning under fasted conditions,
Day 3 to Day 5: 2 doses of 150 mg IMB-1018972 each day (3 capsules per dose) for 3 days under fed conditions (each day in the morning and in the evening),
Days 6 and 7: 2 doses of 150 mg IMB-1018972 each day (3 capsules per dose) under fasted conditions in the morning and under fed conditions in the evening,
Day 6: a single dose of 0.5 mg repaglinide (1 tablet) will be administered together with the morning dose of 150 mg IMB-1018972 (3 capsules) under fasted conditions,
Day 7: a single dose of 2 mg midazolam will be administered together with the morning dose of 150 mg IMB-1018972 (3 capsules) under fasted conditions.

Part 2:
This part will consist of 1 period during which the volunteer will stay in the research center for 16 days (15 nights). The volunteer is expected at the research center at 14:00 h in the afternoon on Day -1, the day prior to Day 1 (Day 1 is the day of administration of IMB-1018972). The volunteer will leave the research center on Day 15.

During the study the volunteer will receive 2 single doses of IMB-1018972 and multiple doses of paroxetine. IMB-1018972 will be given as an oral capsule

formulation. Paroxetine will be given as an oral tablet formulation.

Please see below an overview of the planned treatments:

Day 1: a single dose of 50 milligrams (mg) IMB-1018972 (2 capsules) in the morning under fasted conditions,
Day 3 to Day 7: a single dose of 20 mg paroxetine (1 tablet per dose) each day for 5 days in the morning under fed conditions,
Day 8 to Day 12: a single dose of 30 mg paroxetine (1 tablet per dose) each day for 5 days in the morning under fed conditions,
Day 13: a single dose of 50 mg IMB-1018972 (2 capsules) will be administered together with a single dose of 30 mg paroxetine (1 tablet) in the morning under fasted conditions,
Day 14: a single dose of 30 mg paroxetine (1 tablet) in the morning under fed conditions.

Part 3:
This part will consist of 1 period during which the volunteer will stay in the research center for 13 days (12 nights). The volunteer is expected at the research center at 14:00 h in the afternoon on Day -1, the day prior to Day 1 (Day 1 is the day of administration of IMB-1018972). The volunteer will leave the research center on Day 12.

During the study the volunteer will receive 2 single doses of IMB-1018972 and multiple doses of fluvoxamine. IMB-1018972 will be given as an oral capsule formulation. Fluvoxamine will be given as an oral tablet formulation.

Please see below an overview of the planned treatments:

Day 1: a single dose of 50 milligrams (mg) IMB-1018972 (2 capsules) in the morning under fasted conditions,
Day 3 to Day 5: a single dose of 50 mg fluvoxamine each day (1 tablet per dose) for 3 days in the morning under fed conditions,
Day 6 to Day 9: a single dose of 100 mg fluvoxamine each day (2 tablets per dose) for 4 days in the morning under fed conditions,
Day 10: a single dose of 50 mg IMB-1018972 (2 capsules) will be administered together with a single dose of 100 mg fluvoxamine (2 tablets) in the morning under fasted conditions,
Day 11: a single dose of 50 mg fluvoxamine (1 tablet) in the morning under fed conditions.

**Intervention**

Part 1:
During the study the volunteer will receive multiple doses of IMB-1018972 and 2 single doses each of repaglinide and midazolam. IMB-1018972 will be given as an oral capsule formulation. Repaglinide will be given as an oral tablet

formulation. Midazolam will be given as an oral solution and, because of the small volume, this will be squirted in the mouth using a syringe (without a needle).

Please see below an overview of the planned treatments:

Day 1: a single dose of 0.5 milligrams repaglinide (1 tablet) in the morning under fasted conditions,
Day 2: a single dose of 2 mg midazolam in the morning under fasted conditions,
Day 3 to Day 5: 2 doses of 150 mg IMB-1018972 each day (3 capsules per dose) for 3 days under fed conditions (each day in the morning and in the evening),
Days 6 and 7: 2 doses of 150 mg IMB-1018972 each day (3 capsules per dose) under fasted conditions in the morning and under fed conditions in the evening,
Day 6: a single dose of 0.5 mg repaglinide (1 tablet) will be administered together with the morning dose of 150 mg IMB-1018972 (3 capsules) under fasted conditions,
Day 7: a single dose of 2 mg midazolam will be administered together with the morning dose of 150 mg IMB-1018972 (3 capsules) under fasted conditions.

Part 2:
During the study the volunteer will receive 2 single doses of IMB-1018972 and multiple doses of paroxetine. IMB-1018972 will be given as an oral capsule formulation. Paroxetine will be given as an oral tablet formulation.

Please see below an overview of the planned treatments:

Day 1: a single dose of 50 milligrams (mg) IMB-1018972 (2 capsules) in the morning under fasted conditions,
Day 3 to Day 7: a single dose of 20 mg paroxetine (1 tablet per dose) each day for 5 days in the morning under fed conditions,
Day 8 to Day 12: a single dose of 30 mg paroxetine (1 tablet per dose) each day for 5 days in the morning under fed conditions,
Day 13: a single dose of 50 mg IMB-1018972 (2 capsules) will be administered together with a single dose of 30 mg paroxetine (1 tablet) in the morning under fasted conditions,
Day 14: a single dose of 30 mg paroxetine (1 tablet) in the morning under fed conditions.

Part 3:
During the study the volunteer will receive 2 single doses of IMB-1018972 and multiple doses of fluvoxamine. IMB-1018972 will be given as an oral capsule formulation. Fluvoxamine will be given as an oral tablet formulation.

Please see below an overview of the planned treatments:

Day 1: a single dose of 50 milligrams (mg) IMB-1018972 (2 capsules) in the morning under fasted conditions,

Day 3 to Day 5: a single dose of 50 mg fluvoxamine each day (1 tablet per dose) for 3 days in the morning under fed conditions,
Day 6 to Day 9: a single dose of 100 mg fluvoxamine each day (2 tablets per dose) for 4 days in the morning under fed conditions,
Day 10: a single dose of 50 mg IMB-1018972 (2 capsules) will be administered together with a single dose of 100 mg fluvoxamine (2 tablets) in the morning under fasted conditions,
Day 11: a single dose of 50 mg fluvoxamine (1 tablet) in the morning under fed conditions.

**Study burden and risks**

IMB-1018972 has been administered to man in a prior clinical study. Single doses of 50 mg, 150 mg, 200 mg and 400 mg IMB-1018972 or placebo were given to healthy volunteers with or without food. Multiple doses at 50 mg or 150 mg IMB-1018972 or placebo were given twice a day for 14 days with food to healthy volunteers. In total, 54 volunteers have received IMB-1018972 so far. All doses were safe and only mild side effects appeared. One particular side effect was seen at increasing dose levels. After a single dose of 400 mg IMB-1018972 or placebo, about a third of the volunteers reported flushing of the skin which can be unpleasant but is harmless and short-lived. Skin flushing develops as the result of a transitory widening of the blood vessels in the skin and is associated with intense sensations of tingling or burning on the skin, and a feeling of warmth and reddening of the skin. The skin flushing goes away on its own. The flushing was also seen in a few volunteers at lower doses but was milder and occurred in fewer volunteers, especially when the study compound was taken with food.

IMB-1018972 has also been studied extensively in the laboratory and in animals. Animal studies are required to be performed before an investigational compound is given to humans. In these animal studies, a range of doses are tested, including doses that are much higher than those that are expected to be used in humans in this study. At very high doses of IMB-1018972 (doses much higher than planned for this study), several effects were seen including salivation, convulsions, vomiting, loose stools, reduced activity, and various organ abnormalities.

Based on the animal research, knowledge about the mechanism of action of IMB-1018972, and the previous clinical study, no specific side effects are anticipated. However, there may be (possibly serious) side effects that have not previously emerged from the animal research or the clinical study.

A metabolite of IMB-1018972 is trimetazidine, which, in much higher doses, is an approved drug for the treatment of angina in some European countries (not in The Netherlands). Trimetazidine has been associated with a rare side effect which is not expected with IMB-1018972.

Drawing blood and/or insertion of an indwelling cannula may be painful or cause some bruising.

To make a heart tracing, electrodes will be pasted at specific locations on the volunteer arms, chest and legs. Prolonged use of these electrodes can cause skin irritation.

# Contacts

**Public**
Imbria Pharmaceuticals, Inc.

Park Plaza #439 20
Boston MA 02116
US
**Scientific**
Imbria Pharmaceuticals, Inc.

Park Plaza #439 20
Boston MA 02116
US

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

1. Gender : male or female.
2. Age :
Part 1: 18 to 65 years, inclusive, at screening;
Parts 2 and 3: 25 to 65 years, inclusive, at screening.

3. Body mass index : 18.0 to 32.0 kg/m2, inclusive, at screening.
4. Status : healthy subjects.
5. Race :
Part 1: all races;
Parts 2 and 3: Caucasian only

### Exclusion criteria

1. Previous participation in the current study.
2. Employee of PRA or the Sponsor.
3. History of relevant drug and/or food allergies.
4. Smoking more than 5 cigarettes, 1 cigar, or 1 pipe daily; the use of tobacco products within 48 hours prior to admission to the clinical research center is not allowed.
5. History of alcohol abuse or drug addiction (including soft drugs like cannabis products).

## Study design

### Design

| | |
|---|---|
| Study type: | Interventional |
| Intervention model: | Crossover |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 30-08-2019 |
| Enrollment: | 58 |
| Type: | Actual |

### Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Fluvoxamine |

| | |
|---|---|
| Generic name: | N/A |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Midazolam |
| Generic name: | N/A |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Paroxetine |
| Generic name: | N/A |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Repaglidine |
| Generic name: | N/A |
| Registration: | Yes - NL intended use |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 20-08-2019 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 29-08-2019 |
| 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 | EUCTR2019-002887-29-NL |
| CCMO | NL71106.056.19 |