An open-label, 4-arms study to assess the drug-drug interaction of PXL770 with repaglinide, tolbutamide, midazolam, and caffeine in healthy subjects

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In this study we will investigate how quickly and to what extend the approved compounds repaglinide, tolbutamide, midazolam or caffeine are absorbed and eliminated from the body when it is given together with PXL770. This study is a drug-drug...

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

Summary

ID

NL-OMON50829

Source
ToetsingOnline

Brief title
DDI study PXL770 with repaglinide, tolbutamide, midazolam, and caffeine

Condition

- Other condition
- Hepatic and hepatobiliary disorders

Synonym
Non-alcoholic steatohepatitis

Health condition

NASH

Research involving
Human

Sponsors and support

Primary sponsor: Poxel SA
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: drug-drug interaction, open-label, PXL770

Outcome measures

Primary outcome

To assess the effect of repeated doses of PXL770 on the primary pharmacokinetics (PK) parameters of repaglinide, tolbutamide, midazolam, and caffeine in healthy subjects.

Secondary outcome

To assess the safety and tolerability of PXL770 with and without coadministration of repaglinide, tolbutamide, midazolam, and caffeine in healthy subjects.

To assess the effect of repeated doses of PXL770 on the secondary PK parameters of repaglinide, tolbutamide, midazolam, and caffeine in healthy subjects.

To assess PK parameters of PXL770 after repeated dosing.

To assess the effect of repeated doses of PXL770 on the PK parameters of midazolam*s metabolite 1* hydroxymidazolam in healthy subjects.

To assess the effect of repeated doses of PXL770 on the PK parameters of

caffeine*s metabolite paraxanthine in healthy subjects.

Study description

Background summary

Non-alcoholic fatty liver disease (NAFLD) is the accumulation of fat in the liver which is not caused by excessive alcohol consumption. Some NAFLD patients also develop inflammation in the liver, this is called non-alcoholic steatohepatitis (NASH). The inflammation leads to damage and scar tissue (fibrosis) in the liver. This can lead to liver cirrhosis, cancer and eventually liver failure. PXL770 is a new compound that may eventually be used for the treatment of NASH. PXL770 works by activating a protein (AMPK) that results, among other things, in a decrease in the uptake of fat by the liver, which can be beneficial for patients that suffer from NASH.

The study compound will be administered in combination with the compounds repaglinide, tolbutamide, midazolam, or caffeine. Repaglinide, tolbutamide, midazolam and caffeine are approved drugs and available in the Netherlands under several dosages and formulations. Which compound subjects will receive depends on the group in which they will participate. Repaglinide is a drug that lowers the blood glucose levels and is being used in the treatment of diabetes mellitus type 2. Tolbutamide is a medication used for the treatment of diabetes type 2 because it stimulates the release of insulin. Midazolam is a short acting sedative used prior to invasive diagnostic or surgical procedures. Caffeine is a stimulant and is given in combination with pain medication (such as paracetamol) for the treatment of headache and migraine.

Study objective

In this study we will investigate how quickly and to what extend the approved compounds repaglinide, tolbutamide, midazolam or caffeine are absorbed and eliminated from the body when it is given together with PXL770. This study is a drug-drug interaction study.

Repaglinide, tolbutamide, midazolam and caffeine have been chosen because they are known to be broken down by certain enzymes in the liver. By looking at the effect of PXL770 on these compounds, something can also be said about whether PXL770 has an influence on these enzymes. This is important to know when PXL770 is given in the future along with compounds that are also broken down by these enzymes.

We also investigate how safe the new compound PXL770 is and how well it is tolerated when it is administered to healthy volunteers. In addition, we also investigate the pharmacokinetics of PXL770 itself.

PXL770 has been administered to humans before. It has previously also extensively been tested in the laboratory and on animals. PXL770 will be tested at a fixed dose of 500 mg. Repaglinide, tolbutamide, midazolam and caffeine are no new compounds; they are already available on the market in several dosages and formulations.

Study design

The study will take a maximum of 6 weeks (Groups 1, 2 and 3) or 7 weeks (Group 4) from the screening until the follow-up visit.

Group 1, 2 and 3:

For the study it is necessary that you stay in the research center for 1 period of 12 days (11 nights). Day 1 is the first day when subjects receive the study compound. Subjects will leave the research center on Day 11 of the study.

Screening Between Day -21 and Day -2
Entry Day -1
Stay Day -1 to 11
Leave Day 11
Follow-up Day 17 ± 1

Group 4

For the study it is necessary that you stay in the research center for 1 period of 20 days (19 nights). Day 1 is the first day when subjects receive the study compound. Subjects will leave the research center on Day 19 of the study.

Screening Between Day -21 and Day -2
Entry Day -1
Stay Day -1 to 19
Leave Day 19
Follow-up Day 25 ± 1

Intervention

Subjects will be given PXL770 and repaglinide (Group 1), PXL770 and tolbutamide (Group 2), PXL770 and midazolam (Group 3), or PXL770 and caffeine (Group 4). On the day that both PXL770 and repaglinide, tolbutamide, midazolam or caffeine will be administered (Day 9 or Day 17), subjects will be given PXL770 first,

followed within 10 minutes by the second study compound.

Group 1
PXL770 will be given as 2 oral tablets (2x 250 mg) and repaglinide will be given as 1 oral tablet (0.5mg). These will be given with 240 milliliters (mL) of (tap) water. Subject will be given PXL770 once daily for 8 days on Day 3 to Day 10, and repaglinide on Day 1 and Day 9 (once each day).

Group 2
PXL770 will be given as 2 oral tablets (2x 250 mg) and tolbutamide will be given as an oral tablet (500mg). These will be given with 240 mL of (tap) water. Subjects will be given PXL770 once daily for 8 days on Day 3 to Day 10, and tolbutamide on Day 1 and Day 9 (once each day).

Group 3
PXL770 will be given as 2 oral tablets (2x 250 mg) with 240 milliliters (mL) of (tap) water, and midazolam will be given as an oral solution (2mg). Because of the small volume of the oral solution, this will be squirted in the mouth using a syringe (without a needle). Subjects will be given PXL770 once daily for 8 days on Day 3 to Day 10, and midazolam on Day 1 and Day 9 (once each day).

Group 4
PXL770 will be given as 2 oral tablets (2x 250mg), and caffeine will be given as 4 oral tablets (200 mg). These will be given with 240 milliliters (mL) of (tap) water. Subjects will be given PXL770 once daily for 16 days on Day 3 to Day 18, and caffeine on Day 1 and Day 17 (once each day).

After intake of the study compounds one of the investigators will inspect hands and mouth. This it to check if subjects have taken the study compound.

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

In total, we will take less than 500 milliliters (mL) of blood. 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 at specific locations on arms, chest and legs. Prolonged use of these electrodes can cause skin irritation.

Finger prick
For measuring the blood sugar levels, we will take blood samples on multiple days via finger prick.

Coronavirus test
A sample for the coronavirus test will be taken from the back of the nose and throat using a swab. Taking the sample 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 subjects to gag. When the sample is taken from the back of the nose, subjects 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)
Elderly (65 years and older)

Inclusion criteria

1. Gender: male or female.
2. Age: 18 to 55 years, inclusive, at screening.
3. Body mass index (BMI): 18.0 to 30.0 kg/m2, inclusive. at screening.
4. Weight: >=50 kg at screening.
5. Status: healthy subjects.
6. Race: Caucasian.

Exclusion criteria

1. Previous participation in any clinical study with PXL770 (only if subject received study drug).
2. Employee of PRA or the Sponsor.
3. Mental handicap, legal incapacity, or any history of clinically important emotional and/or psychiatric illness.
4. Vulnerable subjects (eg, persons kept in detention).
5. History of relevant drug and/or food allergies.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	06-04-2021
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Midazolam
Generic name:	Midazolam
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NovoNorm
Generic name:	Repaglinide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tolbutamide
Generic name:	Tolbutamide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-02-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-03-2021
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	EUCTR2019-004915-30-NL
CCMO	NL76722.056.21

Study results

Date completed: 20-07-2021

Results posted: 24-03-2022

First publication
27-01-2022