A Phase 1 Study to Evaluate the Potential Drug-Drug Interaction between GS-4224 and Probe Inhibitors, Inducers and Substrates in Healthy Subjects

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The purpose of this study is to investigate how quickly and to what extent GS-4224 is absorbed and eliminated from the body. We study this when the study compound is administered alone and together with compounds that influence the activity of a...

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

Summary

ID

NL-OMON49788

Source
ToetsingOnline

Brief title
GS-US-439-5302 DDI study in healthy subjects

Condition

- Hepatic and hepatobiliary disorders

Synonym
Hepatitis B, viral infection

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences, Inc.

Source(s) of monetary or material Support: Pharmaceutical/Biotechnological Industry.

Intervention

Keyword: Chronic Hepatitis B, GS-4224

Outcome measures

Primary outcome

• To evaluate the effect of CYP3A/P-gp/BCRP inhibition on the pharmacokinetics

(PK) of GS-4224

• To evaluate the effect of CYP3A/P-gp/BCRP induction on the PK of GS-4224

• To evaluate the effect of GS-4224 on the PK of CYP3A substrates

Secondary outcome

• To evaluate the effect of GS-4224 on GS-9688 PK

• To evaluate the safety and tolerability of GS-4224 alone or in combination

with probe drugs or GS-9688

Study description

Background summary

GS-4224 is an experimental compound that may eventually be used for the treatment of chronic hepatitis B (CHB). Hepatitis B is a viral infection that affects the liver and can lead to cirrhosis and liver cancer. After an infection with the hepatitis B virus not all patients have a strong enough immune reaction to completely clear the virus from the body. Between 5% and 10% of adults and up to 90% of children with a hepatitis B virus infection develop CHB as a result. CHB can lead to liver diseases including cirrhosis and liver cancer. GS-4224 reacts with a protein on the cell surface (programmed cell death-ligand 1 or PD-L1) that decreases the activity of a specific type of immune cells (cytotoxic T-cells) in the body. By blocking this protein, the activity of the specific immune cells increases, and the body can better fight the infection with the hepatitis B virus increasing the chance to clear the infection with the hepatitis B virus, even if this is a chronic infection.

Group 1:
Voriconazole is a medication used to treat fungal infections. In this study it is used because it decreases the activity of CYP3A4, an enzyme that helps to break down chemicals in the body.
Itraconazole is a medication that is also used to treat fungal infections. In this study it is used because it decreases the activity of CYP3A4 and P-gp, enzymes that either speed up the breakdown or decrease the intestinal absorption of compounds like GS-4224.
Group 2:
Rifampin, also known as rifampicin, is a medication used to treat bacterial infections such as tuberculosis. In this study it is used because it strongly increases the activity of the following proteins:
• CYP3A4: an enzyme that helps to break down chemicals in the body
• P-gp: a protein that acts as a pump to remove damaging materials from the cell
• BCRP: transports chemicals from inside the cell to the outside
Group 3:
Rifabutin is an antibiotic medication used to treat bacterial infections such as tuberculosis. In this study it is used because it increases the activity of the following proteins:
• CYP3A4: an enzyme that helps to break down chemicals in the body
• P-gp: a protein that acts as a pump to remove damaging materials from the cell
• BCRP: transports chemicals from inside the cell to the outside
Group 4:
Midazolam is a medication used to treat sleep disorders and is also used for anesthesia. In this study it is used as a model to measure the activity of CYP3A4, an enzyme that helps to break down chemicals in the body. First, we will examine how fast your body breaks down midazolam. Second, we will measure to what extent GS-4224 can slow down this break down process.
Group 5:
GS-9688 is another new compound that is under investigation and can potentially be used to treat CHB. GS-9688 can bind to a cell receptor (TLR8) that plays an important role in the immune response. By binding to this receptor, GS-9688 can stimulate the production of proteins that influence the communication between immune cells (interleukins). This can result in the activation of immune cells (natural killer cells) that can then attack the invading viruses.

Study objective

The purpose of this study is to investigate how quickly and to what extent GS-4224 is absorbed and eliminated from the body. We study this when the study compound is administered alone and together with compounds that influence the activity of a specific group of enzymes (CYP3A4, Pgp, and BCRP). In Group 1 these compounds are voriconazole and itraconazole. GS-4224 was administered to healthy human subjects in a study before but is not currently approved by any health authorities for use in any indications. Voriconazole and itraconazole are not new compounds; they are already available on the market in several dosages and formulations.

We will also investigate how safe the experimental compound GS-4224 (alone and combined with voriconazole and with itraconazole) is and how well it is tolerated when it is administered to healthy volunteers.

We will also investigate how safe the experimental compound GS-4224 (alone and combined with rifampin) is and how well it is tolerated when it is administered to healthy volunteers.

We will also investigate how safe the experimental compound GS-4224 (alone and combined with rifabutin) is and how well it is tolerated when it is administered to healthy volunteers.

We will also investigate how safe the experimental compound GS-4224 (alone and combined with midazolam) is and how well it is tolerated when it is administered to healthy volunteers.

We will also investigate how safe the experimental compound GS-4224 (alone and combined with GS-9688) is and how well it is tolerated when it is administered to healthy volunteers. In addition, we will study if administration of these compounds has an effect on several (immunological) processes.

This study will be performed in approximately 94 healthy male and nonpregnant, nonlactating female volunteers. The study will be performed in up to 5 parts, Group 1 to Group 5. Whether all five groups will be performed will be decided based on the results from the previous groups.

Group 1 consists of 2 subgroups of 9 volunteers each.
Group 2 consists of 2 subgroups of 9 volunteers each.
Group 3 consists of 18 volunteers. There will be 2 subgroups of 9 volunteers each.
Group 4 consists of two subgroups with in total 15 volunteers.
Group 5 consists of 4 subgroups with 25 volunteers in total.

Study design

Group 1:
GS-4224, voriconazole and itraconazole are given as tablets and capsules by mouth with 240 milliliters (mL) of water.
The actual research consists of 1 period during which volunteers will stay in the research center for 24 days (23 nights).
Group 2:
GS-4224 and rifampicin are given as tablets and capsules by mouth with 240 milliliters (mL) of water.
The actual research consists of 1 period during which volunteers will stay in the research center for 18 days (17 nights).
Group 3:
GS-4224 and rifabutin are given as tablets and capsules by mouth with 240

milliliters (mL) of water.
The actual research consists of 1 period during which volunteers will stay in the research center for 18 days (17 nights).
Group 4:
GS-4224 and midazolam are given as tablets and capsules by mouth with 240 milliliters (mL) of water.
The actual research consists of 1 period during which volunteers will stay in the research center for 13 days (12 nights).
Group 5:
GS-4224 and GS-9688 are given as tablets and capsules by mouth with 240 milliliters (mL) of water.
The actual research consists of 1 period during which volunteers will stay in the research center for 17 days (16 nights).

Intervention

See Protocol and ICF's.

Study burden and risks

Drawing blood and/or insertion of the indwelling cannula (tube in an arm vein) may be painful or cause some bruising, lightheadedness, fainting, and very rarely, infection at the site of the needle stick.

This study includes periods of fasting. Fasting could cause dizziness, headache, stomach discomfort, and/or fainting.

In total, there will be taken no more than 500 mL of blood. This amount does not cause any problems in adults.

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

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) Have the ability to understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of study procedures
2) Be aged 18 through 45 years of age, inclusive at screening
3) Be a nonsmoker. The use of nicotine or nicotine-containing products must be discontinued 90 days prior to the first dose of study drug.
4) Have a calculated body mass index (BMI) of >= 19.0 and <= 30.0 kg/m2 at screening
Further criteria apply.

Exclusion criteria

1) Pregnant or lactating female
2) Received any study drug within 60 days prior to study dosing
3) Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance or subject safety, or a positive drug or alcohol test at screening or baseline
4) A positive test result for human immunodeficiency virus type 1 (HIV-1) antibody, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibody at screening
a) Subjects who are HCV Ab positive, but have a documented negative HCV RNA, are eligible
5) Have a positive test result for autoantibodies (ANA >1:80 and/or SMA >1:80 and/or AMA>1:40 and/or anti-TPO >1:40; or lab equivalent for positivity)

Further criteria apply.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-12-2019
Enrollment:	94
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n.a.
Generic name:	Itraconazole
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	n.a.
Generic name:	Midazolam
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	n.a.
Generic name:	Rifabutin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-10-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-11-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2021
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	EUCTR2019-003353-28-NL
CCMO	NL71694.056.19