A single-center, open-label, fixed-sequence Phase 1 trial to evaluate the effect of multiple doses of pritelivir on the pharmacokinetics of substrates for CYP2C9, CYP2B6, CYP3A4 and OATP2B1

Published: 22-09-2021
Last updated: 05-04-2024

In this study, we will investigate how quickly and to what extent the investigational medicinal product pritelivir is absorbed, transported, and eliminated from the body (this is called pharmacokinetics). In addition, we will evaluate a possible...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON50697

Source
ToetsingOnline

Brief title
Pritelivir DDI study with celiprolol, flurbiprofen, bupropion and midazolam

Condition

- Viral infectious disorders

Synonym
Herpes Simplex Virus, HSV

Research involving
Human

Sponsors and support

Primary sponsor: AiCuris Anti-infective Cures AG
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: DDI, Multiple dose, Pharmacokinetics, Pritelivir

Outcome measures

Primary outcome

* AUC0-*, AUC0-last, Cmax of celiprolol, flurbiprofen, bupropion and midazolam

• Hydroxy-bupropion to bupropion AUC0-* and AUC0-last ratios and

hydroxy-flurbiprofen to flurbiprofen AUC0-* and AUC0-last ratios

Secondary outcome

• tmax, tlag, t1/2, CL/F, Vd/F, MRT of celiprolol, flurbiprofen, bupropion and

midazolam in plasma

• AUC0-*, AUC0-last, Cmax, , tmax, tlag, t1/2 of hydroxy-flurbiprofen and

hydroxy-bupropion

• Trough concentrations (C0h) of pritelivir and its metabolites AIC090015 and

AIC090105 in plasma

• AUC0-24h, Cmax,ss, Cmin, tmax, tlag, CL/F, Vd,ss/F, MRT of pritelivir in

plasma

• AUC0-24h, Cmax,ss, Cmin, tmax, tlag, CL/F, Vd,ss/F, MRT of pritelivir in

blood

• AUC0-24h, Cmax,ss, Cmin, tmax, tlag, MRT of metabolites AIC090015 and

AIC090105 in plasma

• AUC0-24h, Cmax,ss, Cmin, tmax, tlag, MRT of metabolites AIC090015 and AIC090105 in blood

• The ratio between each of the metabolites AIC090015 and AIC090105 versus pritelivir

• The blood/plasma ratio for pritelivir, AIC090015 and AIC090105

• The blood/plasma ratio for AUC0-*, AUC0-last, Cmax of pritelivir, AIC090015 and AIC090105

Study description

Background summary

Pritelivir is a new compound that may potentially be used for the treatment of skin infections caused by viruses such as the herpes simplex virus (HSV). Infections with HSV are lifelong, with frequent and sometimes painful recurrences, and carry the risk of serious complications in patients with a weak immune system. Pritelivir can inhibit the replication of HSV and can protect uninfected cells. It is being developed to treat patients with weak immune systems where other treatments of HSV do not work.

In this study, the effect of pritelivir on various existing medications (celiprolol, flurbiprofen, bupropion, and midazolam) will be evaluated. They are substances that are acted upon by particular liver enzymes and transporters. Based on earlier experiments, pritelivir may impact the activity of these enzymes and transporters and as such may influence the presence of these medications in the body when given simultaneously

Celiprolol is a beta-blocker and is used to treat high blood pressure. Flurbiprofen is a drug that is used to reduce pain, swelling, and joint stiffness in arthritis. Bupropion is an anti-depressant medication and is used to treat major depressive disorders and to help people quit smoking. Midazolam is a short-acting sedative used prior to a medical examination or procedure. The dose levels of flurbiprofen, bupropion, and midazolam used in the current study are far below the marketed dose levels. The dose level of celiprolol used in the current study is similar to the marketed dose level.

Study objective

In this study, we will investigate how quickly and to what extent the investigational medicinal product pritelivir is absorbed, transported, and eliminated from the body (this is called pharmacokinetics). In addition, we will evaluate a possible interaction between pritelivir and various existing medications. We will do this by investigating the effect of pritelivir on the pharmacokinetics of celiprolol, flurbiprofen, bupropion, and midazolam. All these compounds will be administered in this study.

We will also investigate how safe pritelivir is and how well it is tolerated when it is used by healthy participants.

At last, we will look at the effect of your genetic information on the body*s response to pritelivir (this is called pharmacogenetics)

Study design

For the study, it is necessary that the volunteers stays in the research center for 1 period of 26 days (25 nights). Day 1 is the day when the volunteer receive one of the study compounds (celiprolol) for the first time. The volunteer is expected at the research center the day before the day of first administration of the study compound, so on Day -1. The volunteers have to be at the research center at approximately 6:00 pm. The time of entry may be changed. If this happens, the volunteer will be informed about it in advance. The volunteer will leave the research center on Day 25 of the study.

Below is an overview of the days you stay at the research center, or when you visit the research center.
Screening 1 short visit between Day -28 and Day -2
In-house Period Day -1 up to Day 25
Follow-up 1 short visit between Day 28 and Day 35

The volunteer will be given pritelivir and celiprolol as tablets, flurbiprofen and midazolam as a small drink, and bupropion as capsules via the mouth. The volunteer will also be given 240 milliliters (mL) of water after each administration.
One of the investigators will inspect the hands and mouth after administration of the study compound. This it to check if the volunteers have taken the study compound.

Intervention

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In the table below the planned study compound administrations.
Day Study compound How much How often
1 Celiprolol 200
mg Once
2 -
- -
3 Flurbiprofen 10
mg Once
Bupropion 20
mg Once
Midazolam 1
mg Once
4 and 5 -
- -
6 Pritelivir 400
mg Once
7 Pritelivir 100
mg Once
8 Celiprolol 200
mg Once
Pritelivir 100
mg Once
9 to 18 Pritelivir 100
mg Once daily
19 Flurbiprofen 10
mg Once
Bupropion 20
mg Once
Midazolam 1
mg Once
Pritelivir 100
mg Once
20 and 21 Pritelivir 100
mg Once daily
22 to 25 -
- -

Study burden and risks

Pritelivir has been investigated in studies with healthy subjects receiving single doses between 5 mg and 600 mg, and multiple doses between 5 mg/day and 400 mg/day for up to 21 days. A total of 202 patients with HSV infections with recurrent genital herpes were treated with pritelivir up to 100 mg/day or 400

mg/week for up to 4 weeks.

The volunteer may experience none, some, or all of the adverse events described below which have been reported as possibly being caused by pritelivir.

In Phase 1 single dose studies, 110 healthy subjects receiving pritelivir reported 149 adverse events associated with pritelivir administration.
Reported adverse events considered to be commonly [>=1/100 and <1/10 (>=1% and <10%)] related to pritelivir after single dose treatments were:
• increased liver functions tests in 7 subjects (6%), and
• headache in 4 subjects (4%).

In 68 healthy subjects receiving multiple doses between 5 mg/day and 400 mg/day of pritelivir in Phase 1 studies for up to 21 days, a total of 267 adverse events were reported.
Reported adverse events considered to be very commonly (>=1/10 [>=10%]) related to pritelivir were:
• headache (26%),
• itching (19%),
• reddening of the skin (16%),
• rash (13%), and
• fatigue (12%).
Reported adverse events considered to be commonly [>=1/100 and <1/10 (>=1% and <10%)] related to pritelivir were:
• increased liver functions tests (7%), and
• dry skin (4%).

These adverse events were mainly reported with multiple daily doses of 400 mg pritelivir and were possibly observed as a result of a viral infection, but an effect of treatment with pritelivir could also not be excluded.

In two Phase 2 studies, a total of 202 subjects were treated with pritelivir.

In the first Phase 2 study (AIC316-01-II-01), 103 subjects of the 125 treated with pritelivir reported adverse events associated with pritelivir administration. Those subjects were treated with 5 mg/day, 25 mg/day, 75 mg/day, or 400 mg/week. Treatment lasted for 4 weeks.
Very commonly reported adverse events were:
• headache (18%), and
• nausea (17%).
Commonly reported adverse events were:
• abdominal pain and -discomfort (8%),
• dizziness (6%),
• fatigue (5%), and
• rash (5%).

The incidence (how often an adverse event occurs) of the reported adverse

events in this study appeared to be comparable across treatment (= dose) groups.

In the second Phase 2 study (AIC316-01-II-02), 20 of the 77 subjects treated with pritelivir 100 mg/day for 28 days reported adverse events associated with pritelivir administration.
A very commonly reported adverse event was:
• headache (10%).
Commonly reported adverse events were:
• diarrhea (4%),
• nausea (4%),
• fatigue (4%),
• dizziness (3%) and
• vaginal itching (3%).

The incidence of the reported adverse events was comparable to valacyclovir, a drug approved for this indication.

Pritelivir is inhibiting an enzyme called carbonic anhydrase, which may lead to a number of adverse events including but not limited to urinary urgency (sudden urge to urinate), deterioration of performance, hearing impairment, depression, and hepatic impairment when used in therapeutic amounts. Increased liver functions tests (hepatic impairment) and fatigue (deterioration of performance) were detected in pritelivir Phase 1 trials as adverse reactions. However, it is unclear whether these side effects were caused by an inhibition of the enzyme carbonic anhydrase.

Study treatment related effects on male fertility were detected in rats after several weeks of pritelivir dosing and also after higher doses compared to the human dose. These effects were fully reversible after a period of several weeks without treatment. These effects did not occur with chronic use of pritelivir in monkeys at very high doses. Therefore, these findings are considered unlikely to be relevant to humans.

Very common, common, and uncommon side effects of celiprolol, flurbiprofen, bupropion, and midazolam are described below.

The following side effects have been reported for celiprolol.
Common Side Effects
• (Severe) depression
• Trembling, tingling, headache, weakness, drowsiness, dizziness
• Hot flashes, paleness of fingers or toes
• Vomiting, nausea, upper abdominal pain, dry mouth
• Excessive sweating, skin redness, rash, itching
• Impotence
Uncommon Side effects
• Insomnia
• Dry eyes, visual disturbances

• Palpitations
• Low blood pressure, cold blue limbs
• Shortness of breath
• Muscle cramp
Flurbiprofen

The following side effects have been reported for flurbiprofen.
Common
• Dizziness, headache
• Throat irritation
• Mouth ulcers, pain or numbness in the mouth
• A sore throat
• Discomfort (warm or burning sensation or tingling) in the mouth
• Nausea, diarrhoea
• Prickling and itching of the skin
Uncommon Side effects
• Drowsiness
• Blistering in the mouth or throat, numbness in the throat
• Stomach bloating, abdominal pain, flatulence, constipation, indigestion, vomiting
• Dry mouth
• Burning sensation in the mouth, altered sense of taste
• Drowsiness or difficulty falling asleep
• Worsening of asthma, wheezing, shortness of breath
• Less sensation in the throat

The following side effects have been reported for bupropion.
Very Common Side Effects
• Sleeping problems
• Headache
• Dry mouth
• Nausea, vomiting
Common Side Effects
• Fever, dizziness, itching, sweating and rash
• Trembling, trembling, weakness, fatigue, chest pain
• Feeling anxious or restless
• Abdominal pain or other problems (constipation), changes in the taste of food, loss of appetite (anorexia)
• Increased blood pressure (sometimes severe), sudden redness of the face and neck
• Ringing in the ears, visual disturbances
Uncommon Side Effect
• Feeling depressed
• Feeling confused
• Concentration problems
• Elevated heart rate
• Weight loss

Midazolam
For the side effects of midazolam, it is not possible to determine the frequency of occurrence with the available data. The following side effects have been reported for midazolam.
Immune system disorders:
• General allergic reactions (skin reactions, heart and blood system reactions, wheezing)
Mental disorders:
• Confusion
• Euphoria (excessive feeling of well-being or excitement)
• Hallucinations (seeing and possibly hearing things that are not there)
• Excitement (restlessness)
• Restlessness
• Hostility, anger or aggression
• Excitement (happiness)
Nervous system disorders:
• Drowsiness and prolonged sedation
• Decreased alertness
• Headache
• Dizziness
• Difficulty with muscle coordination
• Temporary amnesia
Cardiac and blood vessel disorders:
• Low blood pressure
• Slow heart rate
• Redness of the face and neck (flushing), fainting or headache
Gastrointestinal disorders:
• Nausea
• Vomit
• Blockage
• Dry mouth
Skin and subcutaneous tissue disorders:
• Result
• Hives with a rash
• Itch
Musculoskeletal and connective tissue disorders:
• Muscle spasms and tremors (muscle trembling without you being able to do anything about it)
General disorders and administration site conditions:
• Fatigue
• Redness
• Swelling of the skin
Injuries, poisoning and procedural complications:
• There is a risk of falling and breaking bones in patients taking benzodiazepine-type medicines. This risk is higher in the elderly and people who also use other anesthetics (including alcohol)

Blood draw
Drawing blood may be painful or cause some bruising. On Days 1, 3, 8, 17, and 19, blood will be sampled very frequently using an indwelling cannula (a tube in a vein in the arm) to determine the course of the concentration of the study compounds in the blood over time. The use of the indwelling cannula can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and/or bruising around the puncture site. In some individuals, a blood draw can sometimes cause pallor, nausea, sweating, low heart rate, and/or a drop in blood pressure with dizziness or fainting.

Heart tracing
To make a heart tracing, electrodes (small, plastic patches) will be placed on the arms, chest, and legs. Prolonged use of these electrodes can cause skin irritation (rash and itching).

Fasting
The volunteers have to fast for a prolonged time during the study, this may lead to symptoms such as dizziness, headache, stomach upset, or fainting.

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 your throat may cause the volunteer to gag. When the sample is taken from the back of your nose, the volunteer may experience a stinging sensation and the eyes may become watery.

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Subject has been informed both verbally and in writing about the objectives of the clinical trial, the methods, and the potential risks and the discomfort to which he/she may be exposed and has given written consent to participation in the trial prior to trial start and any trial related procedure.
- Healthy male and female subjects of any ethnic origin, aged between 18 and 55 years (inclusive). Assessed as healthy based on a pre-trial examination including medical history,
physical examination, blood pressure, pulse rate, body temperature, ECG assessment, and clinical laboratory results.
- In women negative serum β-HCG (beta-human chorionic gonadotropin) test at screening and
negative urine β-HCG test on Day -1.
- Subject agrees to pharmacogenetic blood sampling.
- Normal body weight as evidenced by a Body Mass Index (BMI) >=18.0 and <=30.0 kg/m2, and a body weight >=50.0 kg at Screening.
More criteria apply

Exclusion criteria

1. History or current evidence of clinically relevant allergies or idiosyncrasy to drugs or food.
2. History of allergic reactions to any active or inactive ingredient(s) of the Investigational Medicinal Products (IMPs).
3. History or current evidence of any clinically relevant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, hematological, endocrinological, metabolic, neurological, psychiatric, or other disease suspected to influence pharmacokinetics or safety of the IMPs.
4. History of malignancy within 5 years, unless one of the following, treated

and considered cured: basal cell carcinoma, in situ cervical cancer, or breast ductal carcinoma in situ.
5. Resting pulse rate after 5 minutes in supine position at Screening and Day -1: <45 or >100 beats per minute (bpm), if out of range, up to one repeat assessment is allowed.
More 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):	18-10-2021
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pritelivir
Generic name:	n.a.

Ethics review

Approved WMO

Date:	22-09-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	14-10-2021
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	EUCTR2021□004263□27-NL
CCMO	NL79024.056.21

Study results