A phase I, open-label, randomized, 4-way crossover study in subjects with chronic Hepatitis B virus infection to assess pharmacokinetics (fasted/fed), safety, tolerability and pharmacodynamics of single oral doses of Farnesoid X receptor agonist EYP001a.

Published: 04-01-2017
Last updated: 11-04-2024

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

Summary

ID

NL-OMON45541

Source
ToetsingOnline

Brief title
EYP001 study in subjects with chronic hepatitis B virus (HBV) infection

Condition

- Other condition
- Hepatic and hepatobiliary disorders

Synonym

Hepatitis B, viral infection of the liver

Health condition

Hepatitis B

Research involving
Human

Sponsors and support

Primary sponsor: ENYO Pharma SA
Source(s) of monetary or material Support: Farmaceutische industrue

Intervention

Keyword: EYP001a, HBV

Outcome measures

Primary outcome

Pharmacokinetics:

- Plasma EYP001a concentrations

- Plasma PK parameters estimated using non compartmental analysis, as

appropriate: Cmax, tmax, tlag, kel, t*, AUC0-24, AUC0-t, AUC0-inf and tlast

Secondary outcome

Safety:

- Adverse events (AEs), clinical laboratory, vital signs, 12-lead

electrocardiogram (ECG), liver ultrasound

Pharmacodynamics:

Bile metabolism related: plasma levels of total bile acids; chenodeoxycholic

acid (CDCA), deoxycholic acid (DCA) and lithocholic acid (LCA); primary and

secondary bile acids; bile acid precursor C4 (7α hydroxy-4-cholesten-3-one) and bile regulating fibroblast growth factor 19 (FGF-19); plasma levels of FXR mRNA profile

HBV virology related: Quantitative levels of hepatitis B surface antigen (HBsAg), hepatitis Be antigen (HBeAg), HBV DNA and HBV RNA; levels of hepatitis Be antibody (anti HBe) and hepatitis B surface antibodies (anti-HBs)

Glucose and lipid metabolism related: homeostatic model assessment of insulin resistance (HOMA-IR), β cell function (HOMA-%B) and insulin sensitivity (HOMA-%S); lipid panel: cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, apolipoprotein (Apo) A1 and ApoB

Study description

Background summary

EYP001a is a new investigational compound that may eventually be used for the treatment of chronic hepatitis B. Hepatitis B is a worldwide common infection of the liver caused by a virus.

If it does not heal spontaneously and evolves into chronic hepatitis, there is no effective treatment. If the infection has not healed spontaneously after 6 months, it is a chronic hepatitis B virus infection. Currently, there is no treatment to cure chronic hepatitis B virus infection. However, the virus can be suppressed with drugs currently available.

EYP001a is a 'farnesoid X receptor (FXR) agonist (stimulator). The FXR receptor is a protein located on the cell nucleus mainly in liver cells. Its function is being regulated by bile acids. The FXR receptor plays a role in the production of bile acids and cholesterol, and in various metabolic processes, including

fat and carbohydrate metabolism. For its multiplication, the hepatitis B virus is dependent on the action of this FXR receptor: when the FXR receptor is stimulated, the hepatitis B virus will be inhibited. Therefore, the compound does not act directly on the virus but on a certain function of the host which the virus depends upon. In the future, the combination of an FXR agonist (stimulator) with drugs that inhibit the virus directly may possibly cure a chronic hepatitis B virus infection.

EYP001a is not registered as a drug but has been administered to healthy volunteers before in a clinical study at PRA. Several FXR agonists are under development for other, non-viral, liver disease including non-alcoholic fatty liver disease. However, the use of an FXR agonist as a possible drug for the treatment of hepatitis B is new. To date, one FXR agonist has been registered: Ocaliva®.

Study objective

The purpose of the study is to investigate how quickly and to what extent EYP001a is absorbed into, distributed in and eliminated from the body (this is called pharmacokinetics) when EYP001a is administered with and without food. It will also be investigated how safe EYP001a is and how well EYP001a is tolerated. In addition, the effect of EYP001a on certain blood markers, including the virus concentration, will be investigated; this is called pharmacodynamics. Because bile acids are subject to a distinct variation during the day, the study compound will be given in the morning and in the evening, both with and without food.

This study will be performed in a maximum of 14 subjects with a chronic hepatitis B virus infection.

Study design

The screening visit will take place at the AMC, at the UMCG or at PRA. The follow-up visit will take place at the AMC for subjects who have been screened at the AMC and at PRA for subjects who have been screened at the UMCG and at PRA. For all subjects, the study itself will take place at the PRA clinical research center in Groningen.

The actual study will consist of 2 periods; the volunteer will not leave the clinical research center between the 2 periods. The volunteer will stay in the clinical research center for 13 days (12 nights): this will be from the afternoon of Day -1 (1 day before first administration of the study compound; also called admission) to the morning of Day 12. Period 1 will start at admission on Day -1 and will end just before the first dose on Day 8 in Period 2. Period 2 will start just before the first dose on Day 8 in Period 2 and will end at discharge from the clinical research center on Day 12.

Each dose of 300 mg EYP001a will be administered as oral capsules with 240 milliliters of tap water.

Intervention

The study will consist of 2 periods during each of which the volunteer will be administered 2 single doses of 300 milligrams (mg) EYP001a. Thus the volunteer will receive a total of 4 single doses of 300 mg EYP001a each. EYP001a will be given in the form of oral capsules: 3 capsules with 100 mg EYP001a each will have to be swallowed per dose.

Study burden and risks

All potential drugs cause adverse effects; the extent to which this occurs differs. EYP001a has been investigated in animals. In rats and dogs EPY001a was well tolerated and few side effects were seen: in dogs, hypersalivation (excessive production of saliva) and vomiting were observed. No effects were seen on the nervous system, lung function and heart function. Some slight changes were seen in blood results that usually quickly returned to normal.

EYP001a has also been administered to healthy men before in a clinical study that is currently ongoing at PRA. No complaints considered to be related to the study compound were observed at single doses of 30, 60, 120 and 250 mg EYP001a. At a single dose of 500 and 800 mg EYP001a, several volunteers reported short-lasting light nausea or dyspepsia, and at a single dose of 800 mg EYP001a, 1 volunteer reported diarrhea, these side effects occurred shortly after dosing.

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

Procedures: pain, minor bleeding, bruising, possible infection

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

- Has documented chronic HBV infection
- Gender : male or female
- Age : 18-65 years, inclusive, at screening
- Body mass index (BMI) : 17.0-35.0 kg/m2 inclusive, at screening

Exclusion criteria

Suffering from hepatitis C, cancer or HIV/AIDS. Previous participation in the current study. In case of donating more than 100 milliliters of blood in the 60 days prior the start of this study.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover

Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-01-2018
Enrollment:	14
Type:	Actual

Ethics review

Approved WMO Date:	04-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-04-2017

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	EUCTR2016-004713-27-NL
CCMO	NL60228.056.16