A randomized, double-blind, placebo-controlled study to determine the safety, tolerability, pharmacokinetics and pharmacodynamics of the FXR-agonist EYP001a in chronically HBV infected subjects.

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

Summary

ID

NL-OMON46529

Source
ToetsingOnline

Brief title
EYP001-003

Condition

- Other condition
- Hepatic and hepatobiliary disorders

Synonym
Chronic HBV

Health condition

Hepatitis B

Research involving
Human

Sponsors and support

Primary sponsor: Enyo Pharma, SA
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Chronical, EYP001a, FXR-agonist, HBV

Outcome measures

Primary outcome

Safety endpoint: evaluations will include the following:

* Incidence and severity of AEs;

* Vital signs parameters;

* Physical examination findings;

* ECG parameters;

* Clinical laboratory parameters (serum chemistry, hematology, coagulation,

urinalysis).

Pharmacokinetic endpoints:EYP001a PK parameters to be calculated include:

* Maximum concentration (Cmax);

* Time to maximum concentration (Tmax);

* Area under the concentration-time curve from time 0 to last measurable

concentration (AUC0-6h);

* Lag time (tlag);

* Average plasma drug concentration at steady state (Cavg,ss);

* Time to steady state (Tss).

Secondary outcome

PD markers:

The following markers will be measured:

-Bile acids: Bile acid precursor C4 (7*hydroxy-4-cholesten-3-one) and fibroblast growth factor 19 (FGF19)

-Lipid metabolism: Total plasma cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, apolipoprotein (Apo) A1 and ApoB.

-HBV virology: hepatitis B surface antigen (HBsAg), HBV core-related antigen (HBcrAg), hepatitis B envelope antigen (HBeAg), HBV DNA (viral load) and HBV pgRNA.

Study description

Background summary

Chronic hepatitis B (CHB) remains a public health problem despite the fact that an efficient and safe vaccine exists. One third of the world*s population has been infected by HBV and 240 million individuals are chronically infected with the inherent risk of progression to cirrhosis and hepatocellular carcinoma. Available treatments often fail to induce functional cure. Treatment with multiple drugs having different mechanisms of action may be needed to improve

viral clearance. More effective and better tolerated therapies without the need for lifelong medication should therefore be developed.

EYP001a is a novel synthetic agonist (stimulator) of the nuclear hepatocyte farnesoid X receptor (FXR) which plays a pivotal role in regulating bile acids (BA) biosynthesis. FXRs are expressed in high amounts in the liver, intestines and kidney. One of the primary functions of FXR activation is the suppression of cholesterol 7 alpha-hydroxylase (CYP7A1), the rate-limiting enzyme in bile acid synthesis from cholesterol.

Hepatitis B virus and bile salt mechanism seem tightly interdependent. Given the interdependence of HBV and FXR, and the fact that FXR agonist EYP001a showed consistent anti-HBV in vitro activity, the compound was selected to be developed as an oral HBV therapy aiming for a functional cure of chronic infection.

EYP001a is not registered as a drug but has been administered to healthy male subjects before in a clinical study. In addition a phase 1 clinical study has been conducted in subjects with chronic HBV infection to determine the effect of food on the PK. The overall clinical development goal is to achieve a safe and tolerable dose or doses of EYP001a that would result in the same or greater level of antiviral efficacy compared to the existing marketed drug for hepatitis B.

Study objective

The primary objective of the study is to determine the safety and tolerability of 4 week oral administration of EYP001a in subjects with Chronic Hepatitis B Virus Infection (CHBV) when given as monotherapy or in combination with Pegylated interferon alpha 2a (Peg-IFN*2a) (Part B only).

The secondary objectives of the study are to:
* Evaluate the pharmacodynamics (PD) of bile acid and lipid metabolism of EYP001a in CHBV subjects;
* Evaluate the pharmacokinetics (PK) of EYP001a in CHBV subjects;
* Evaluate viral PD markers of EYP001 in CHBV against standard of care entecavir (ETV);
* Evaluate viral PD markers of EYP001 in combination with standard of care Peg-IFN*2a against EYP001a monotherapy.

Study design

This study is designed as a multicenter, randomized, double-blind, placebo-controlled two-part trial. Part A and part B. The visits to the hospital consist of outpatient visits.

The design incorporates 29 days monotherapy (6 parallel treatment arms in Part A) and 29 days combination therapy (3 parallel treatment arms in Part B). Three dose-levels and 2 dosing regimens of EYP001a will be explored.

The design also includes an open-label standard of care ETV monotherapy arm in Part A and an open-label standard of care Peg-IFN*2a co-treatment arms in Part B.

Each treatment group will consist of six subjects (n=6).

Intervention

The study will consist of Part A and Part B. Subjects who have completed Part A and new CHBV subjects who meet study entry criteria are eligible for Part B.

Part A:
The subjects will be randomly assigned to receive 1 of the following 6 treatments for a period of 29 days:
* Treatment A: oral EYP001a (1x100 mg/day; n=6)
* Treatment B: oral EYP001a (1x200 mg/day; n=6)
* Treatment C: oral EYP001a (1x400 mg/day; n=6)
* Treatment D: oral EYP001a (2x200 mg/day; n=6)
* Treatment E: oral placebo (n=6) or
* Treatment F: oral ETV (open-label 0.5 mg/day) (n=6)

An external, independent Data Safety Monitoring Committee (DSMC) will review all available unblinded preliminary safety, PK and PD results after 18 subjects have completed study visit Day 15 across all treatment groups in Part A. Following review of the available data the DSMC will advise any amendments that are necessary for safety or methodological reasons or will recommend continuation of the study according to this protocol. The DSMC may also recommend accrual of up to 12 additional subjects to compensate for any subjects dropping out of the study prior to completing 29 days of treatment. Patient accrual will continue throughout the period of DSMC review.

Part B:
Following review of the available data from the first 18 subjects in Part A, the DSMC will identify and recommend two dose levels of EYP001a to be evaluated in Part B of this study. The a priori dose levels for Part B will be 300 mg/day (morning dose only) and 150 mg 2x/day (morning and evening doses). These dose levels can be modified by the DSMC. Alternative dose levels selected by the DSMC will not be lower than a total dose of 100mg/day and will not exceed a total dose of 500 mg/day.
In addition to selecting dose levels for Part B, the DSMC will also determine whether dosing in Part B will be once a day or twice a day. This selection will be based on safety, tolerability, PK and PD data obtained from the first 18 subjects who have been assessed at Day 15 study visit

across all treatment groups in Part A.

Adults with CHBV infection will be assigned randomly to receive 1 of the following 3 treatment regimens:
* Treatment G: oral EYP001a (1x300 mg/day) plus open label Peg-INF*2a (n=6)
* Treatment H: oral EYP001a (2x150 mg/day plus open label Peg-INF*2a (n=6)
* Treatment I: oral placebo plus open label Peg-INF*2a (n=6)

EYP001a will be self-administered in the form of oral capsules from 50 mg or 100 mg capsule sizes. ETV will be self- administered in the form of film-coated tablet and Peg-INF*2a will be administered subcutaneous.

The DSMC will review all available preliminary safety, PK and PD results after 9 subjects across the 3 treatment arms have completed study visit Day 15. Following review of the available data, the DSMC will advise on any amendments that are necessary for safety or methodological reasons or will recommend continuation of the study according to this protocol.. The DSMC may also recommend accrual of up to 6 additional subjects to compensate for any subjects dropping out of the study prior to completing 29 days of treatment in Part B. Patient accrual will continue throughout the period of DSMC review.

Study burden and risks

Preliminary experience from EYP001a in healthy subjects shows that single and multiple oral doses are well tolerated. Short- lasting gastrointestinal events (nausea, dyspepsia, loose stools and vomiting) of mild or moderate intensity were seen mostly at the 500 mg (single and repeated) and 800 mg (single only) dose levels.

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 given voluntary written informed consent;
2. Have documented medical history of chronic HBV infection (defined as HBsAg positivity lasting for at least 6 months at whatever point in time) and have recent, documented, laboratory tests at the screening visit with the following results:
* Documented positive hepatitis B surface antigen (HBsAg) and
* Documented HBV DNA > 1000 IU/mL (HBV DNA load values of 750-1000 IU/mL may be allowed following consultation with the sponsor. Subjects with recent (within 12 months) documented HBV DNA >1000 IU/mL but with HBV DNA values below 750 at screening can be discussed with sponsor for inclusion);
Note: subject can be either hepatitis Be antigen (HBeAg) negative or positive, this test result is not required for randomization and if not available can be established during the Day 1 visit with baseline PD virology assessments.
3. Is anti-HBV treatment naive or treatment experienced (see also exclusion criterion #3).
4. Gender: male or female.
5. Age: 18 to 65 years inclusive.
6. Body mass index (BMI): 17.0-35.0 kg/m2 inclusive.
7. Has clinical chemistry, hematology, coagulation and urinalysis tests within normal, allowable limits (with the exception of alanine aminotransferase [ALT]); see inclusion criterion #10); if there is an out of range value, the result must be considered clinically non-significant by the investigator in order to be eligible.
8. Vital signs after at least 5 minutes resting in supine position at screening within the following ranges:
* systolic blood pressure: between 90 mm Hg and 145 mm Hg
* diastolic blood pressure: between 45 mm Hg and 90 mm Hg
* heart rate: between 40 bpm and 100 bpm
9. Have no clinically significant abnormal 12-lead automatic electrocardiogram (ECG) (incomplete right bundle branch block can be accepted) at screening: PR interval * 210 ms, QRS-duration < 120 ms, QTc-interval (Fridericia*s) * 450 msec.

10. ALT at screening * 5 x upper limit of normal (ULN).
11. Agrees to abstain from all medication, including non-prescription and prescription medication for 28 days prior to the Day 1 study visit, except for authorized medications (such as hormonal contraceptives for females, vitamins prescribed per label dosages and paracetamol). On a case-by-case basis, regular co-medication either as defined on the medication exception list or as documented by written approval from the sponsor as acceptable prior to randomization, will not be considered as a deviation from this criterion.
12. At screening, females must be non-pregnant and non-lactating, or of non-childbearing potential (documented tubal ligation, bilateral oophorectomy or hysterectomy or physiologically incapable of becoming pregnant, or at least 1 year post-menopausal [amenorrhea duration of 12 consecutive months); non pregnancy will be confirmed for all females of child bearing potential by a pregnancy test conducted at screening, during the treatment period and at the EOS/ET visit.
13. Female subjects of child-bearing potential, with a fertile male sexual partner, should be willing to use adequate contraception from screening until 90 days after the EOS/ET visit. Adequate contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm or cervical cap, or a condom. Also, total abstinence, in accordance with the lifestyle of the subject, is acceptable.
14. Male subjects, if not surgically sterilized, should be willing to use adequate contraception and not donate sperm from the Day 1 visit to the clinical research centre until 90 days after the EOS/ET visit. Adequate contraception for the male subject (and his female partner) is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm or cervical cap, or a condom. Also, total abstinence, in accordance with the lifestyle of the subject is acceptable.
15. At screening, has no recent (<3 months) history of any clinically significant conditions, which, in the opinion of the investigator, would jeopardize the safety of the subject or impact the validity of the study results.
16. Willingness to abstain from alcohol from 24 hours prior to each study visit to the clinical research centre.

Exclusion criteria

1. Employee of a CRO participating in this study or the sponsor.
2. Has certain or probable compensated liver cirrhosis documented by at least 2 of the following:
a. Optional assessment: has documented liver histology Metavir score (F4), Ishak >5 or Scheuer (F4)
b. Mandatory assessment: has presence or history of ascites, spontaneous bacterial peritonitis, esophageal varices, hepatic encephalopathy
c. Mandatory assessment: platelet count below 90,000/uL within 12 months of screening visit
d. Optional assessment: positive indirect blood test of APRI or FIB4 or positive direct blood test Fibrosure, Fibrotest, or FibroSpect within 12 months of screening visit
e. Optional assessment: has positive elastography within 6 months of screening visit

(Fibroscan or Shearwave Aixplorer)
f. Optional assessment: has abnormal liver imaging (CT/US/MRI) consistent with a lobular/nodular liver and cirrhosis or indirect signs of portal hypertension.
3. Subject is HBV treatment experienced AND currently on anti-HBV treatment during the 30 days (or 5 half-lives of the considered anti-HBV drug, whichever is longer) before the first investigational product administration and until the last study visit.
4. Co-infection with active hepatitis C virus (HCV, except for patients with sustained viral response SVR, who can be included).
5. Co-infection with human immunodeficiency virus (HIV). Note: hepatitis D virus (HDV) status is not required for randomization and if not available can be established during the Day 1 visit with baseline PD virology assessments.
6. Receives or plans to receive systemic immunosuppressive or immunomodulating medications (e.g. IFN) during the study or * 4 months prior to the first investigational product administration.
7. Has clinically relevant immunosuppression from, but not limited to immunodeficiency conditions such as common variable hypogammaglobulinemia.
8. Clinical diagnosis of substance abuse during * 12 months prior to screening with narcotics or cocaine or with alcohol (regular consumption > 21 units/week [men] and > 14 units/week [women]; 1 unit = 1*2 pint of beer, 25 mL shot of 40% spirit or a 125 mL glass of wine. Expressed in g/day: > 30 g/day [men] and > 20 g/day [women]).
9. Has a positive drug urine screen (cocaine, phencyclidine, amphetamines (incl. methamphetamines), opiates (incl. heroin, codeine and morphine), benzodiazepines, barbiturates, methadone or alcohol screen. Subjects who
admit the occasional use of cannabis will not be excluded as long as they are able to abstain from cannabis when they are assessed at study visits.
10. Has any known pre-existing medical or psychiatric condition that could interfere with the subject*s ability to provide informed consent or participate in study conduct, or that may confound study findings.
11. Has been diagnosed with hepatocellular carcinoma (HCC).
12. Has a history of long QT syndrome.
13. Has a history of clinically significant gastrointestinal disease, especially peptic ulcerations,
gastrointestinal bleeding, ulcerative colitis, Crohn*s disease or Inflammatory Bowel Syndrome, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, or cardiovascular disease or any other condition which, in the opinion of the investigator, would jeopardize the safety of the subject or impact the validity of the study results.
14. Has participated in any drug study within 90 days prior to the first drug administration in the current study. Note: Part A participation to this study is acceptable and not an exclusion criteria when considering eligibility for Part B, under the condition that EOS visit of Part A has been completed and no investigational product related SAEs have occurred during Part A.
15. Has an uncontrolled ongoing illness at screening (e.g., active viral infection).
16. Has had major surgery within 30 days prior to the first drug administration, or within 6 months for gastrointestinal surgery prior to the first drug administration.
17. Has a history of relevant drug and/or food allergies.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-09-2017
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Baraclude
Generic name:	Entecavir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	PEGASYS
Generic name:	peginterferon alfa 2a
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	03-08-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	05-09-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-07-2018
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	EUCTR2017-002211-33-NL
ClinicalTrials.gov	NCT03272009
CCMO	NL62263.056.17